By Adam Hollingworth

Pharmacology Notes

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Pharmacodynamics

- = what the drug does to the body
- = study of intrinsic sensitivity or responsiveness of (usually) receptors to a drug & mechanisms by which these effects occur
- magnitude of pharm effect depends on its concentration at molecular target
  ↳depends on:
  - absorption
  - distribution
  - metabolism
  - excretion of drug

  } = pharmacokinetics
- binding of drug to receptor ⇒ functional response
- amount of functional response determined by
  - affinity of drug for the receptor as determined by chemical forces which cause binding
- dose response curve = relationship of concentration & response
- full agonist
  - = binds & occupies the receptor ⇒ activation
  - can produce max effect
  - produces same response as endogenous ligand
  - eg endogenouse ligand = oestrogen, neurotransmitters, catecholamines
- partial agonists = produce less than maximal effect even when all receptors are occupied (lower intrinsic activity)
- antagonist
  - = binds to receptor without activating it
  - blocks access of agonist/endogenous ligand ⇒ ↓normal response
  - competitive (reversible) or irreversible
- hyperactive = unusually low dose produces expected pharmacologic effect
- hypersensitivity = allergy to a drug
- hyporeactivity = unsually large dose required to give expected effect
- tolerance = hyporeactivity due to chronic exposure to drug
- cross-tolerance = common between drugs which produce similar effects eg alcohol & volatiles
- tachyphylaxis =
  - tolerance that develops acutely
  - reflects cellular tolerance

  ↳tolerance/tachyphylaxis may be due to pharmacokinetic & pharmacodynamics causes
- additive = 2 drugs which interact to produce an affect equal to the algebraic summation eg LA's, volatiles = 1+1=2
- synergistic = 2 drugs interact to produce an effect greater than algebraic summation eg 1+1=4
- potency = ability of drug to produce certain effect
- efficacy =
  - relates to intrinsic activity of a drug
  - determines max effect attainable by a drug
  - dose response curves demonstrate difference between
    - potency & efficacy,
    - affinity & intrinsic activity
- receptor = component of a cell (usually a protein) that interacts selectively with an extracellular compound to initiate a cascade of biochemical events that result in observed effects of the compound

Molecular Targets for Drug Action

- Drugs only modify existing physiological, biochemical or biophysical functions
- 3 ways drugs have action:
  - physic-chemical interactions – eg antacids, possibly volatile GAs
  - on DNA directly
  - binding to a protein – the molecular target (see below)
- drugs action on 4 types of proteins:
  - receptors
  - carriers
  - enzymes
  - ion channels

- complete specifity = drug interact with only one molecular target, at one site and have only one effect
  ↳no drugs have this but instead have selectivity
- selectivity:
  - = preference to molecular target
  - depends on:
    - chemical structure
    - molecular size
    - electrical charge

    ↳changes cause dramatic ↑↓binding to target ⇒ alter therapeutic efficacy or toxicity
  - can have:
    - receptor selectivity eg salbutamol B2 agonist at therapeutic doses
    - tissue selectivity eg – salbutamol at high doses effects lung & skeletal mm
    - non selective drug eg isoprenaline: heart B1 tachycardia & lungs B2 bronchodilation
- types of drug binding include multiple or single interactions:
  - hydrogen bonds
  - ionic or hydrophobic interactions
  - van der Waals forces = between molecules of non polar compounds
  - covalent interactions
- strength of interaction between drug & molecular target = affinity
  ↳measured by dissociation constant K_s in enzyme kinetics

Physico-Chemical Interaction

- chemical properties:
  - antacids & chelating agents
  - eg desferrioxamine, tetracyclines etc
- physicochemical properties:
  - eg LA's & volatiles work by producing non specific changes in lipid or proteins components ⇒ changes diameter of ion channels in neuronal membrane
  - BUT:
    - is some evidence that LA's work via receptor interaction at internal aspect of Na channel ⇒ ↓channel diameter ⇒ ↓Na conductance
    - volatiles may affect neuronal proteins in brain in selective way

Action via Proteins

Carriers

- move ions & small molecules across cell membrane
  ↳lack lipid solubility to allow free movement
- symporter = movement of molecules in same direction eg Na/K/Cl transporter in loop of Henle
- antiporter = movement in opposite directions eg Na/H exchanger in prox tubule

Enzymes

- drugs alter these indispensible biological catalysts
- eg neostigmine: inhibits acetylcholinesterase at neuromuscular junction in Myasthenia Gravis
- antimetabolites:
  - drugs interact with enzyme by mimicking structure of enzymes substrate molecule ⇒ enzyme acts on drug instead of substrate
  - 2 outcomes:
    - block normal enzyme action
      ↳eg statins – simvastatin resembles HMG-CoA & thus HMG-CoA reductase works on this instead inhibiting its intended action
    - production of different end product with diff properties
      ↳eg methotrexate

Ion Channels

- drugs target ion channel in cell membranes
- eg
  - amiloride – blocks entry of Na into renal tubular cells
  - diltiazem, verapamil - Ca channel blockers

Receptors

- structural specificity is essential to receptor theory of drug action
- certain portion of drug molecule selectively combines with receptor ⇒ pharmacological effect
- complementary spatial relationship between portion of drug molecule & receptor site

Families of Receptors

	Type 1 Ligand-gated ion ch's (ionotropic)	**Type2** G-prot coupled (metabotropic)	**Type3** Kinase-linked	**Type4** Nuclear
Location	membrane	membrane	membrane	intracellular
Effector	ion channel	Ch or enzyme	enzyme	gene transcription
2nd msgr	--	c-AMP/c-GMP IP3 / DAG	--	--
Coupling	direct	G-prot	direct	via DNA
E.g.'s	n-AchR GABA$_A$ NMDA	m-AchR adrenoceptors opiod R	Insulin growth factor Cytokine r's	steroid , thyroid H receptors
Time	millisec's (fast synaptic)	seconds	hrs	hrs
Structure	oligomeric assembly of subunits around central pore	Monomeric with 7 transmembrane helices	Single trans-membr helix linking EC R domain to IC kinase domain	Monomeric str with separate R and DNA binding domains.

- 4 types:
  - type 1 = transmitter gated ion channels
  - type 2 = G protein coupled receptors (GPCRs)
    - slightly slower response time (seconds) – associated transduction mechanisms
  - type 3 = kinase linked (catalytic) receptors

        - similar to G proteins but diff transduction mechanisms
        - alter gene transcription ∴ protein synthesis
    - type 4 = nuclear receptors
        - eg steroid hormone receptors, retinoic receptors
        - often located in cytoplasm & require binding before moving to nucleus
- type 1-3 on cell membrane
- type 4 in cytoplasm

G Protein Coupled Receptors (GPCR) (type 2)

- one of largest families
- extracellular amino terminus, intracellular carboxyl terminus
- 7 membrane spanning helices
- ligand binds to either:
    - cleft in within membrane spanning regions
    - binding domain in amino terminus
- has 3 subunits: α,β,γ which essential for normal function:
    - ligands bind to α subunit
    - β & γ remain together as a complex
- agonist binds to binding site ⇒ bound GDP (inactive receptor) is exchanged for GTP on α subunit (active)
- α-GTP dissociates from both receptor & βγ subunit
- α-GTP moves to interact with effector protein eg ion channel or adenyly cyclase
    ↳βγ can also interact with effector protein
- G protein remains active until GTP is hydrolysed by intrinsic activity of GTPase ⇒ GDP
- Cells express > G protein coupled receptors

Second Messangers

- Enable communication of signal from exterior of cell to response elements in cell
- 2nd messengers intial signals through biochemical pathway

cAMP

- most studies 2nd messengers
- membrane bound adenylyl cyclase synthesises cAMP (cyclic adenosine monophosphate) under control of GPCRs
- causes a series of protein kinases to phosphorylate proteins
    ↳add phosphate gps to proteins
- phosphodiesterase terminates its action by breaking down cAMP
- linked to action of B arenoceptors & many other receptors
- eg caffeine ⇒ inhibition of phosphodiesterase ⇒↑cAMP ⇒ ↑Ca [in] ⇒ cardiac effects

PIP_2, DAG & IP_3

- common 2nd messenger system
- hydrolysis of minor component of cell membranes
- GPCR effects phospholipase C to hydrolyse PIP2 into 2 second messenger proteins:
    - Diacyclglycerol (DAG):
        - Confined to cell membrane where activates protein kinase C
        - PKC moves into cell effecting functional response
    - Inositol triphosphate (IP3)
        - Can move into cytoplasm
        - Causes release of Ca from intracellular storage sites
- Eg important in α-adrenoceptors & muscarinic receptors

cGMP

- involved in control of
    - smooth mm
    - nerve cells

  - monocytes
  - platelets
- 2 distinct forms of guanylyl cyclase ⇒ cGMP:
  - soluble form - NO activates
    ↳impt in CVS, ANS, CNS systems
  - membrane bound form – natriuretic peptides
- cGMP is terminated by phosphodiesterase enzymes (as cAMP)
  ↳eg sildenafil – inhibits phosphodiesterase 5 (PDE IV) ⇒ ↑conc of NO ⇒ ↑action on penis smooth mm

'Simple' Drug-Receptor Interaction

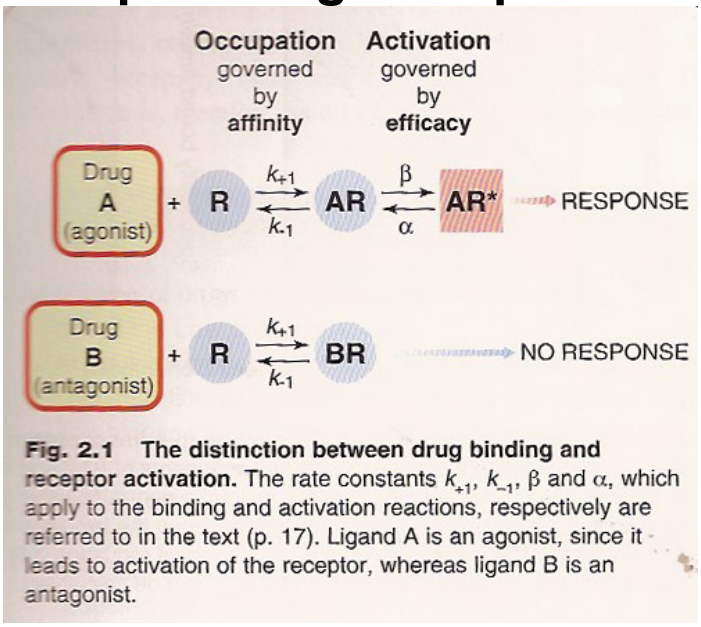

Fig. 2.1 The distinction between drug binding and receptor activation. The rate constants k_{+1}, k_{-1}, β and α, which apply to the binding and activation reactions, respectively are referred to in the text (p. 17). Ligand A is an agonist, since it leads to activation of the receptor, whereas ligand B is an antagonist.

- binding & activation = 2 distinct steps in generation of a receptor mediated response from an agonist
- drug can bind but not activate = antagonist
- affinity = tendency of drug to bind to R
  ↳drugs with high potency will tend to have high affinity (other factors exist)
- efficacy = tendancy once drug bound to cause activation
  ↳∴
    - true antagonist = zero efficacy
    - full agonist = max response with full R occupancy
    - partial agonist = submaximal response even with 100% R occupancy
- use dose response curves to differentiate affinity & efficacy
- a partial agonist might have higher affinity for R than full agonist (ie more potent) but can never reach max effect eg buprenorphine vs morphine
- receptor states:
  - receptor in resting state = R
  - activated receptor = R*
  - occupied receptor = AR
  - occupied activated receptor = AR*
- tendancy for AR ⇒ AR* will depend on equilibrium constant for that reaction = ß/α
  - pure antagonist: ß/α = 0
  - agonist will have values different for differend drugs:
    - partial agonist: ß/α = small
      ↳ because only small proportion of occupied Rs will be activated
    - full agonist: ß/α = large
      ↳ because most of occupied receptors will be activated
- ∴ constant ß/α is a measure of efficacy

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'Two State Hypothesis' Drug-Receptor Interaction

- = alternate explanation of 'simple drug –receptor interaction'
- receptors may show constitutive activation ie R* can exist without any ligand bound
- ∴ equilibrium between R:R* prior to any drug added
- drug added encounters an equolibirum mixture of R:R*:
  - if higher preference for R* ⇒
    - drug cause shift of equilibrium towards R*
    - ∴ promoting activation and is called an agonist
    - if preference for R* is very large = full agonist
    - smaller preference for R* = partial agonists
  - if higher preference for R ⇒
    - shift equilibrium towards R
    - = inverse agonist (negative efficacy)
    - eg some drugs at $GABA_A$, drugs acting at canniboid & dopamine receptors
  - if no preference: prevailing R:R* equilibrium will be undisturbed:
    - = competitive antagonist (zero efficacy) ie works by dilution
- ∴ efficacy = property defined by relative affinity of ligand for R & R*

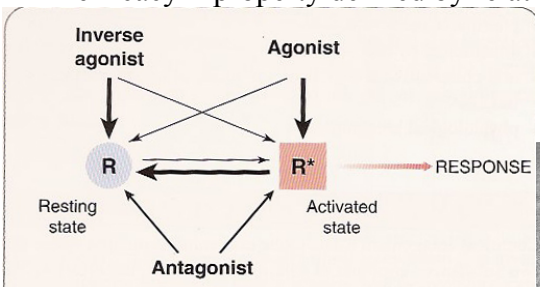


Fig. 2.10 The two-state model. The receptor is shown in two conformational states, 'resting' (R) and 'activated' R*, which exist in equilibrium. Normally, when no ligand is present, the equilibrium lies far to the left, and few receptors are found in the R* state. For constitutively active receptors, an appreciable proportion of receptors adopt the R* conformation in the absence of any ligand. Agonists have higher affinity for R* than for R, so shift the equilibrium towards R*. The greater the relative affinity for R* with respect to R, the greater the efficacy of the agonist. An inverse agonist has higher affinity for R than for R* and so shifts the equilibrium to the left. A 'neutral' antagonist has equal affinity for R and R* so does not by itself affect the conformational equilibrium but reduces by competition the binding of other ligands.

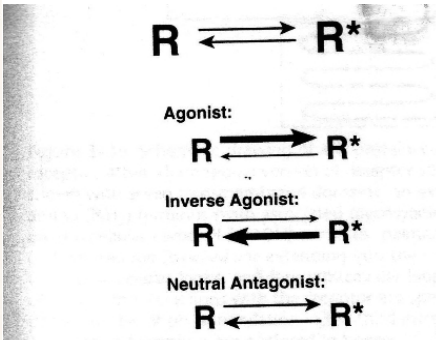


Figure 3–28 Equilibrium between inactive receptors (R) and active receptors (R*) is tissue specific and depends on the type of ligand administered. By stabilizing R*, agonists drive the equilibrium to the right. Inverse agonists stabilize R, driving the equilibrium to the left. Because neutral antagonists bind equally to R and R*, they do not affect tissue-specific equilibrium between R and R*.

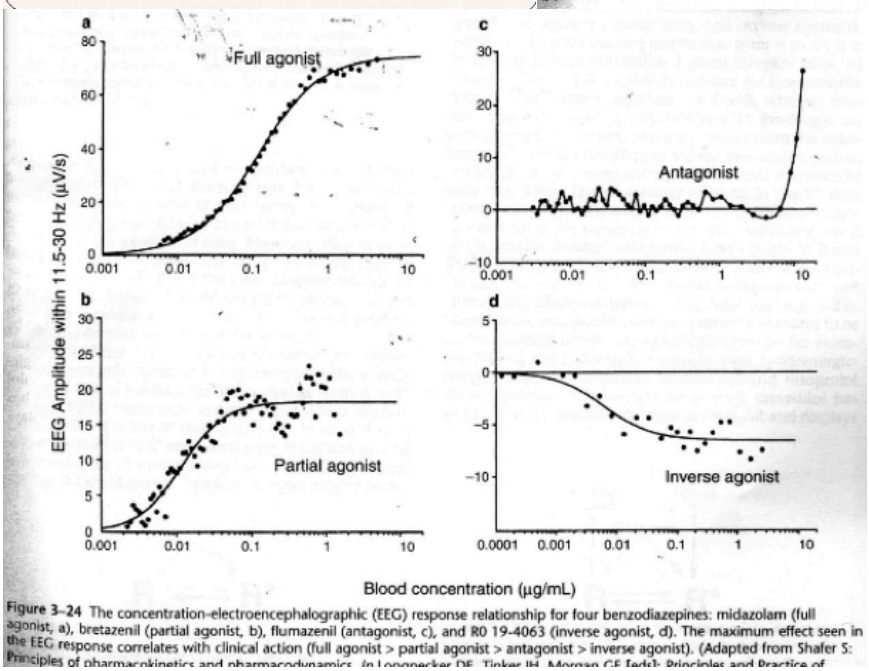


Figure 3–24 The concentration-electroencephalographic (EEG) response relationship for four benzodiazepines: midazolam (full agonist, a), bretazenil (partial agonist, b), flumazenil (antagonist, c), and R0 19-4063 (inverse agonist, d). The maximum effect seen in the EEG response correlates with clinical action (full agonist > partial agonist > antagonist > inverse agonist). (Adapted from Shafer S: Principles of pharmacokinetics and pharmacodynamics. In Longnecker DE, Tinker JH, Morgan GE [eds]: Principles and Practice of

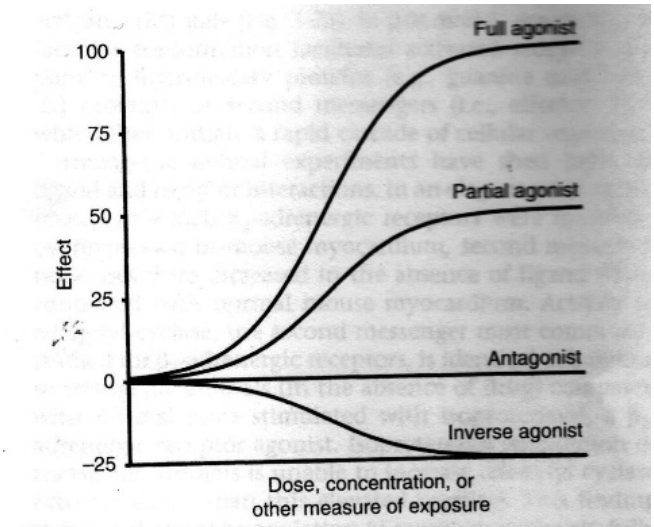


Figure 3–23 Effects of various types of ligands on receptor responses. A full agonist produces complete (100%) activation of a receptor at high concentrations, whereas partial agonist binding results in less than 100% activation, even at very high concentrations. A neutral antagonist has no activity of its own. Inverse agonists can be thought of as "superantagonists" because binding of these ligands produces a response below the baseline response measured in the absence of drug. If the physiologic effect of the baseline levels of activated receptor (R*) is small, antagonists and inverse agonists may not be clinically distinguishable.

Summary Receptor-Ligand Interactions

- full agonists =
  - can produce maximum effects
  - have high efficacy
- antagonists have zero efficacy
- 2 state model:
  - efficacy reflects relative affinity of ligand for either resting or activated states
  - agonist – selectivity for activated state
  - neutral antagonist show no selectivity – but work via dilution of concentration of ligands ∴ competing with agonists for binding
  - inverse agonists –
    - selectivity for resting state
    - only of significance in unusual situations where receptors show constitutive activity
- generally though:
  - receptor affinity = potency
  - intrinsic activity (ability to activate receptor) = efficacy

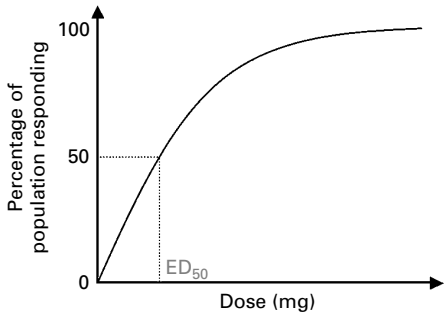
Graded vs Quantal Drug Responses

- response to drugs can be classified as either:
  - graded =
    - studied in 1 person
    - ↑ing magnitude in response with ↑ing drug dosage
  - quantal =
    - studied in population ∴ y axis must always = % response of x in a population
    - all or nothing response
- x axis can either be displayed as:
  - dose response ie parabola
  - log dose response ie sigmoid shaped
  - benefit is it creates a linear gradient between 20-80% allowing ED50 & ED95 to be calculated

Quantal responses

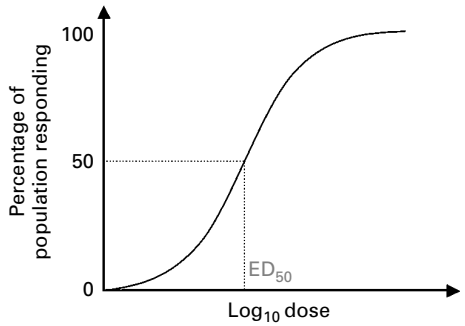
- need certain level of receptor occupancy before response triggered
- below threshold = no response
- quantal responses subject to individual variability ie different concntrations to get to threshold
- frequency of response in population is the most impt variable in describing quantal effects:
    - no. of pts who respond at given conc of drug plot ⇒ Gaussian distribution curve
    - cumulative % response @ certain dose ⇒ Sigmoid curve
- eg of quantal response:
    - IV induction agent ⇒ LOC
    - Nerve blockade
    - mortality

Quantal dose–response curves



The curve is again identical in shape but this time a population has been studied and the frequency of response recorded at various drug doses. It is, therefore, known as a quantal dose–response curve. The marker of potency is now the ED_{50} and the *y* axis should be correctly labelled as shown. This is the 'typical' dose–response curve that is tested in the examination.

Log dose–response curve Also = quantal



The curve is sigmoid as the *x* axis is now logarithmic. Ensure the middle third of the curve is linear and demonstrate the ED_{50} as shown. Make this your reference curve for a full agonist and use it to compare with other drugs as described below.

Agonists

- agonist drug ⇒ response increases ∝ to dose until the receptors are saturated
- further ↑dose does not cause any further response
- relationship:

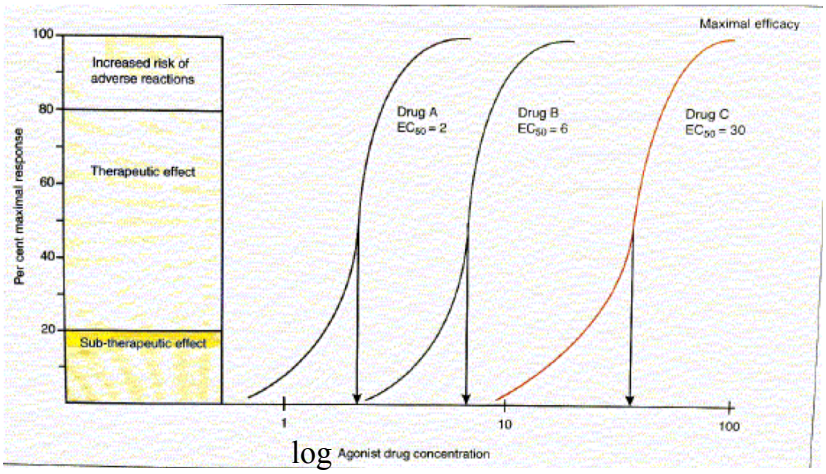
$$E = \frac{E_{max} \times C}{C + EC_{50}}$$

E = effect observed at a drug concentration of C
Emax = max response that the drug can produce
EC50 = conc at which drug produces 50% of max response

- EC_{50} = easy method for determining agonist potency & comparison of other drug

Drug Potency

- Ability of drug to produce certain effect
- Influenced by
  - pharmacokinetics (A,D,M,E) ie active drug getting to receptor
  - KD50:
    - affinity for receptor - ↑affinity moves curve parallel to L (& vice versa)
    - measured in lab
  - intrinsic activity of drug
- EC_{50}
  - reflects all 3 aspects above
  - = measure of drug potency to produce 50% of maximal response
  - E**C** = dose response
  - ↑ed EC_{50} ≈ less potent
  - Left shift (↓EC50) = more potent
  - = graded curve ie studied in 1 person
- ED_{50} =
  - E**D** = quantal
  - Effective dose needed to produce the required effect in a given percentage of **patients**
    ↳ **ie quantal curve**
- ED_{90} = produce response in 90% patients
- Potency measured on x axis
- plotting concentration – response curve shows different potencies of different drugs
- 20-80% of max response usually includes an almost linear portion
  ↳usually corresponds to therapeutic window – higher concentrations produce ↑side effects:effects

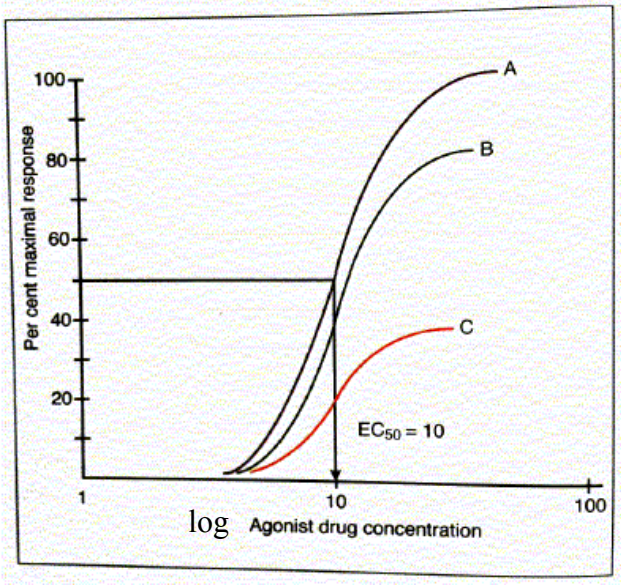


(= log dose response curves)

- Drug A x3 more potent than drug B
- Drugs differ in their potency but have same maximal efficacy

- clinically potency is not that important as long as effective dose can be given conviently

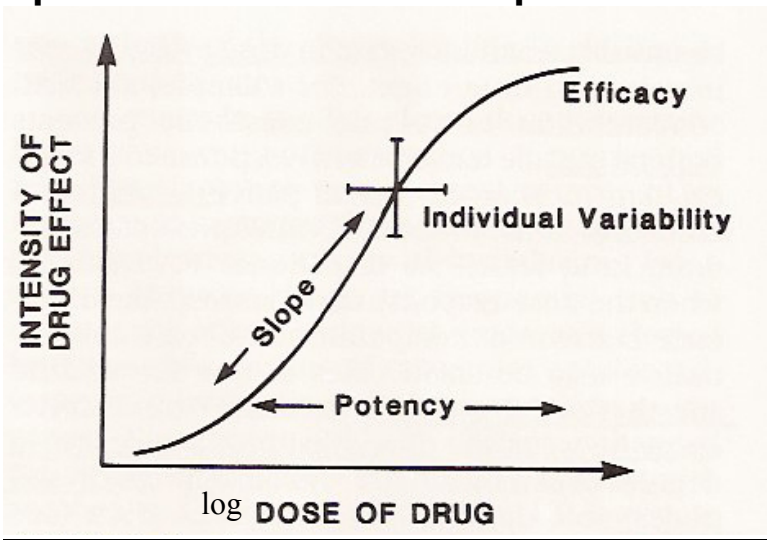
Maximal efficacy



- Drugs have same EC50 ie same potency
- Each has different maximal efficacy
  - ↳∴ Drug B & C = partial agonists

- another term for max efficacy = Emax
- measured on y axis
- very impt clinically as drug effectiveness depends on its max efficacy not potency
- antagonist has a zero efficacy; partial agonist <100% response

Slope of the Curve & Therapeutic index



- slope of the curve is influenced by number of receptors that must be occupied before an effect occurs
- threshold of occupancy = when enough receptor activation to create an effect
- steep slope = drug must occupy majority of Rs before response eg NMBs, volatiles
- drugs with steep dose-response curves imply:
  - that small ↑dose ⇒ intense ↑response
  - low therapeutic index: difference between therapeutic dose & toxic dose will be small
- therapeutic index =
  - margin of safety
  - difference between dose of drug which produces desired effect & dose that produces undesired effect
  - TI defined as ratio between median lethal dose & median effective dose (LD_{50}/ED_{50})

quantal

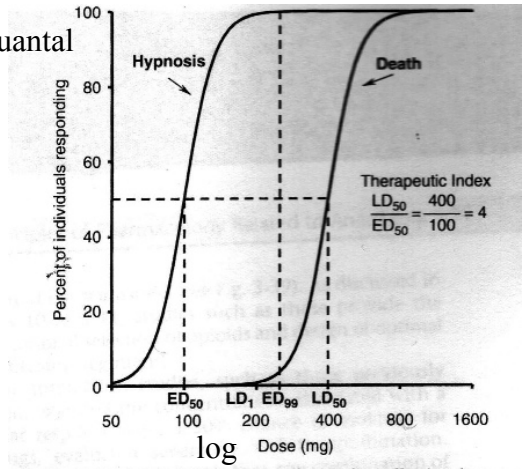


Figure 3–37 Relationships among the median effective dose (ED_{50}), median lethal dose (LD_{50}), and therapeutic index. These curves were generated from data on animals that were injected with various doses of a sedative-hypnotic and the clinical responses determined. ED_{50} is the dose of drug required to produce a specific effect (i.e., hypnosis) in 50% of animals to which it is administered *(left curve)*. LD_{50} is the dose of drug required to produce death in 50% of animals to which drug is administered *(right curve)*. The therapeutic index of the drug is the ratio between LD_{50} and ED_{50} (LD_{50}/ED_{50}). LD_1 is the lethal dose in 1% of the population, and ED_{99} is the effective dose in 99% of the population. As drawn, $LD_1 < ED_{99}$, which would not be clinically acceptable.

Antagonists

- bind with no efficacy & prevent binding of endogenous agonist
- classifications:
  - competitive antagonism (receptor blockade)
    - reversible
    - irreversible
  - non-competitive antagonism:
    - chemical
    - receptor mechanisms
    - pharmacokinetic antagonism
    - physiological antagonism

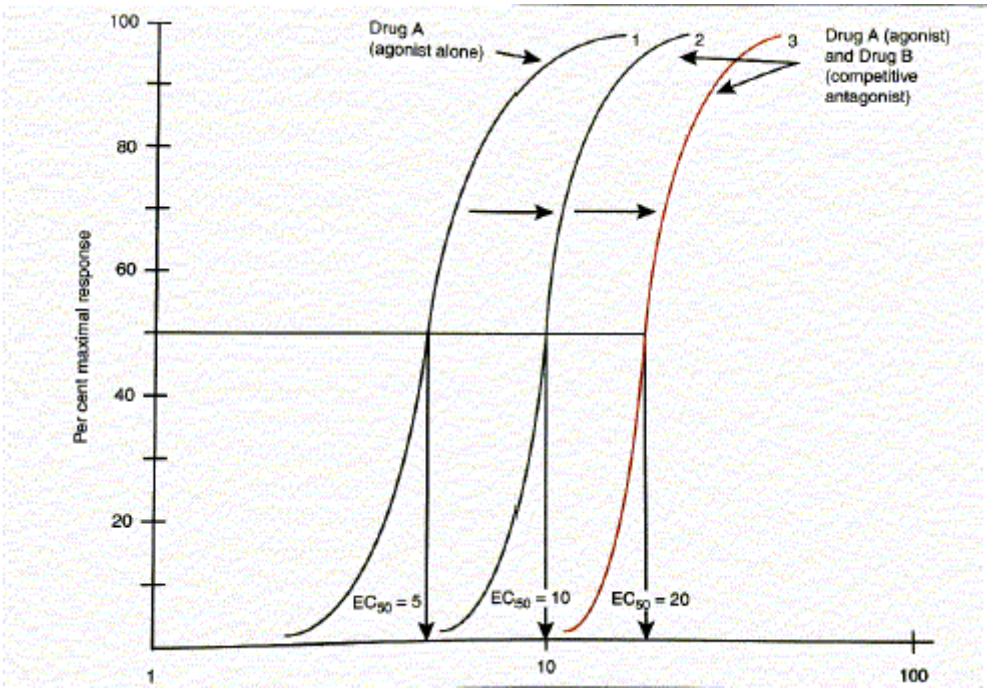
Competitive (Irreversible) Antagonists

- Target receptor permanently unavailable for binding of endogenous agonist
- Antagonist has a high affinity for receptor and dissociates so slowly = essentially irreversible
  ↳receptor death & replacement
- ∴ no change in antagonist occupancy when agoinst added
- eg
  - antagonist posses reactive groups which form covalent bonds with the receptor eg phenoxibenzamine @ α adrenoreceptors
  - irreversible enzyme inhibitors used clinically eg aspirin, omeprazole, MAOIs
- conc-response curve = slope & max achievable response of agonist will both decrease

Competitive (Reversible) Antagonists

- Action can be overcome by increasing the concentration of agonist
- Maximal response produced by agonist is NOT changed
- Conc-response shift to right ie EC_{50} is increased
  ↳amount of right shift depends on
    - Conc of competitive agonist
    - Affinity of antagonist for receptor
- Linear Schild plot:
  - Agonist able to displace antagonist from receptors (cannot evict bound antagonist)

- Displacement occurs by :
  - agonist occupying proportion of vacant receptors
  - ∴ agonist ⇒ ↓rate of association of antagonist with receptor
  - ∴ rate of dissociation temporarily > association ⇒ overall antagonist occupancy falls



- curve 1 & 2 show ↑ing concentrations of a competitive (reversible) antagonist
  ↳this causes R shift & ↓ing potency (ie ↑EC50) but no change in max efficacy

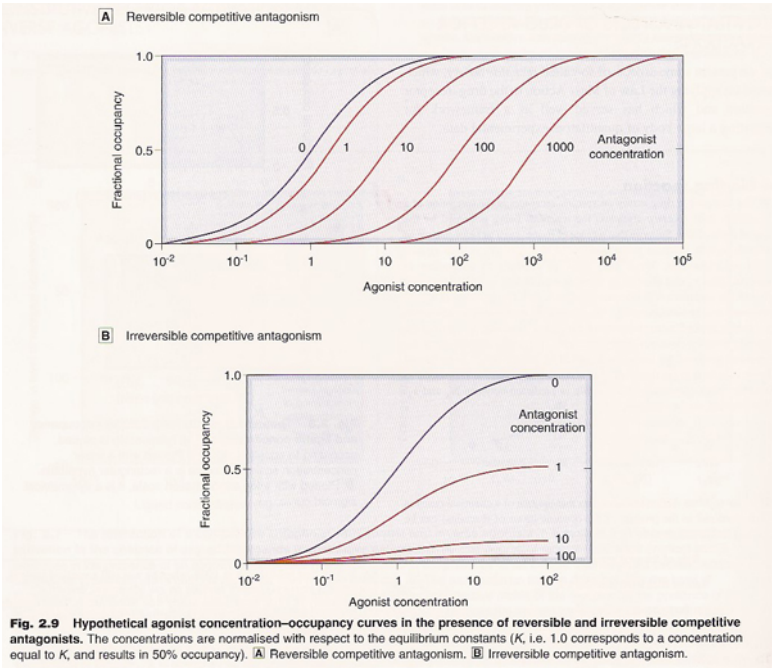


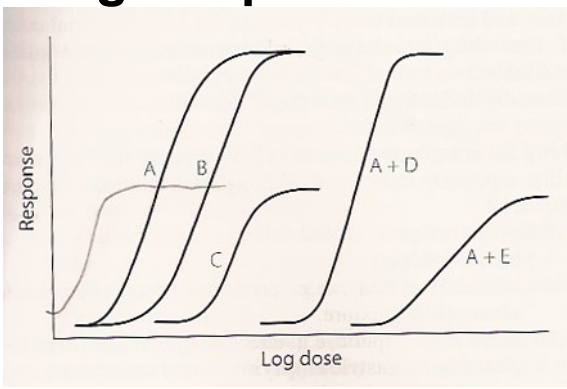
Fig. 2.9 Hypothetical agonist concentration–occupancy curves in the presence of reversible and irreversible competitive antagonists. The concentrations are normalised with respect to the equilibrium constants (*K*, i.e. 1.0 corresponds to a concentration equal to *K*, and results in 50% occupancy). A Reversible competitive antagonism. B Irreversible competitive antagonism.

Non-competitive Antagonists

- Block response to an agonist at some point in intracellular events
  ↳ie not competing for same receptor
- Same shape graph as competitive irreversible
- Effect on curve:
  - ↓ECmax
  - ↓steepness of slope

- types:
  - chemical antagonism:
    - 2 substances combine in solution ⇒ loss of drug effect
    - uncommon in practise
    - eg:
      - chelating agents that bind heavy metals eg desferrioxamine
      - digibind for digoxin
      - sugamadex binding NDMBs
  - receptor mechanisms:
    - examples of mechanisms:
      - antagonist blocks at some point the chain of events which lead to response from agonist
        - eg:CCB's prevent influx of Ca through cell membrane ∴ blocking nonspecific smooth mm contraction promoted by adrenaline on α receptors
      - antagonist causes change in affinity of receptor for agonist
        - eg Gallamine (NMB) causes tachycardia by ↓ing affinity of muscarinic Ach receptors for acetylcholine
  - pharmacokinetic antagonism:
    - antagonist ↓s concentration of agonist at site of action by affecting ADME of agonist
    - eg
      - induction of liver microsomal enzymes ⇒ ↑rate of drug metabolism
        ↳phenytoin, steroids ⇒ ↑metab of rocuronium
        - ↓rate absorption from GIT
        - ↑rate of renal excretion
  - physiological antagonism:
    - interaction of 2 drugs whose opposing actions in body tend to cancel each other out
    - eg
      - histamine & omeprazole on gastric acid secretion
      - histamine & adrenaline on CVS/resp system eg anaphylaxis

Drug Response Curve Examples



- A + B = agonists.
- A > B potency
- C =
  - partial agonist (less efficacy)
  - less potent than A &B
- D = reversible competitive antagonist ∴ shifting A curve to right (↓potency) but same max efficacy
- E = non competitive antagonist ∴ shifting to R and ↓height ie ↓potency & ↓efficacy
  (↳ or competitive irreversible)

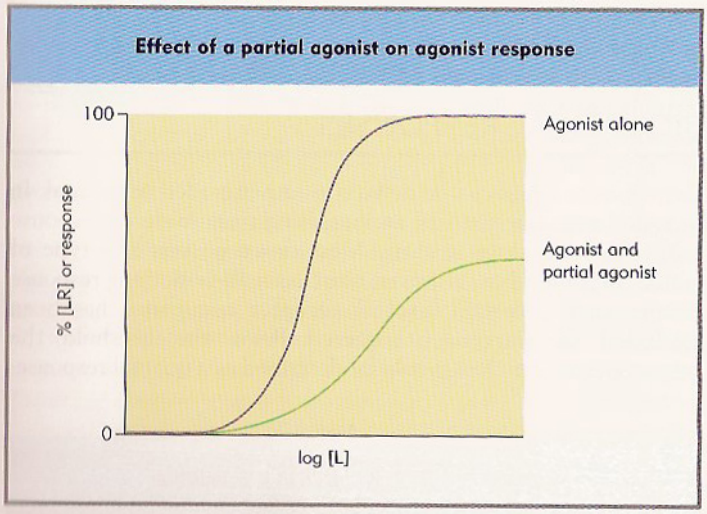


Figure 7.9 Effect of agonist in presence of a partial agonist. A full agonist alone will produce 100% response. The addition of a partial agonist reduces the maximal possible response to the agonist. The responses at lower concentrations of agonist depend on the concentration of partial agonist. In the example illustrated, the concentration of partial agonist is sufficient to produce an effect even in the absence of full agonist.

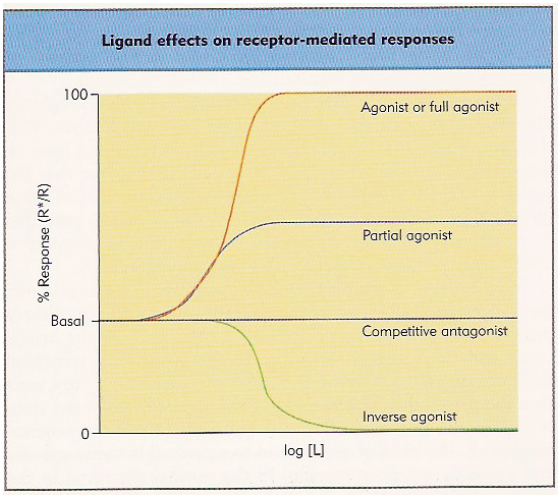


Figure 7.6 Ligand (drug) effects on receptor-mediated responses.

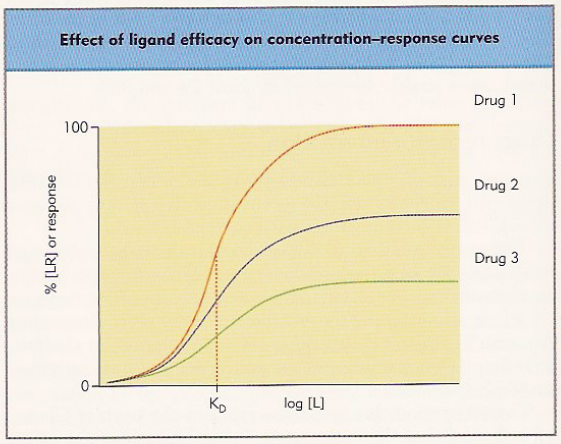


Figure 7.8 Effect of efficacy on concentration–response curves. All three drugs are equipotent, as the curves are not shifted to the left or to the right and they all have the same K_D. Drug 1 is the most efficacious and drug 3 the least.

Receptor Desensitisation & Turnover

- receptors not static
- when drugs given repeatedly or continuously, response to drug might gradually diminish
  ↳ = desensitisation

Terminology of Desensitisation

- tachyphylaxis:
  - = diminished response after repeated/continuous exposure to that same concentration of drug
  - occurs over minutes/hours
  - individuals response to 1st dose cannot be reproduced even with larger doses
  - eg transdermal GTN needs 12hours on, 12 off
- tolerance:
  - same as tachyphylaxis but over longer time course eg days/weeks
- refractoriness = used in relation to loss in therapeutic efficacy
- drug resistance = loss of effectiveness of antimicrobial or anti-tumour drugs
- desensitisation:

- = decrease in response of receptor =2nd messenger systems

- receptor super-sensitivity – caused by:
  - upregulation = ↑receptor no
    - ↳common after chronic use of receptor blocking drugs
    - ↳remove drug and may get rebound effects

Mechanisms

- pharmacodynamics or pharmacokinetic mechanisms involved:
  - change in receptors (PD)
  - loss of receptors (PD)
  - physiological adaptation (PD)
  - exhaustion of mediators (PD)
  - ↑ed metabolic degredation (PK)
  - active extrusion of drug from cells eg in chemotherapy

Change in Receptors

- Receptors coupled to ion channels:
  - Desnsitisation can be rapid & pronounced
  - Diff mechanisms:
    - Slow conformational change in receptor ⇒ tight binding of agonist molecule without opening of ion channel eg at NMJ
    - Phosphorylation of intracellular regions of receptor protein
- G-linked receptors:
  - uncoupling of receptor from 2nd messenger system:
    - phosphorylation of GPRC complex causes recruitment of arrestins
    - arrestins = cytosolic proteins which uncouple G protein from receptor
    - eg
      - ß adrenoreceptors - phosphorylation of receptor interferes with ability to activate 2nd messenger cascade
      - opioid tolerance

Loss of Receptors

- aka downregulation
- prolonged exposure ⇒ gradual ↓in number of receptors expressed on cell surface eg ß receptors
- =slower process than uncoupling (change in receptors)
  - ↳8hrs of isoprenaline ⇒ ↓10% receptors; take several days to recover
- occurs via endocytosis of patches of membrane

Exhaustion of Mediators

- depletion of essential intermediate substances in signal conduction pathway
- eg amphetamine causes release of amines (ie NA) from nerve terminals. Marked tachyphylaxis due to depletion of amine stores

↑ed Metabolic degredation

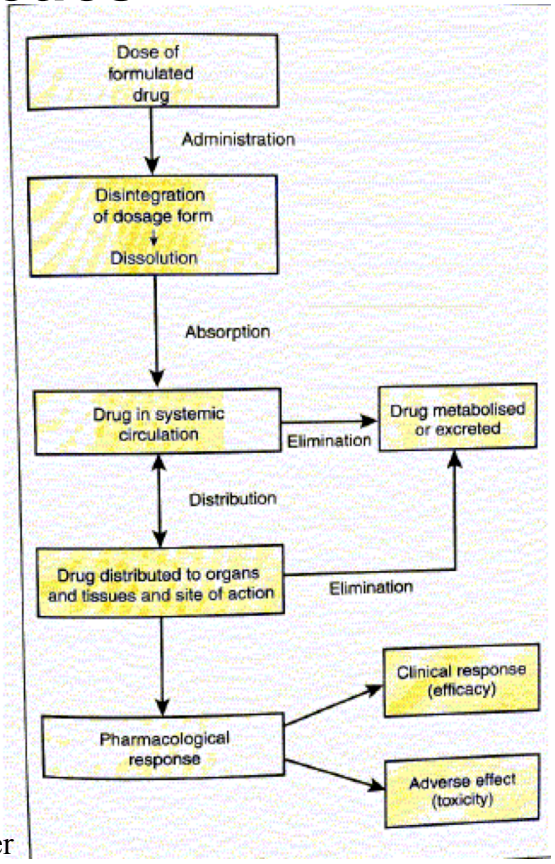
- eg tolerance to alcohol & barbituates:
  - repeated administration ⇒ enzyme induction ⇒ ↓plasma conc of agonist

Physiological Adaptation

- ↓response to drug can occur due to offset by a homeostatic response of the body
- eg
  - bp lowering of thiazide diuretic is limited by gradual activation of RAA system
  - drowsiness/nausea of drug will subside with continued use
- some mechanisms are poorly understood

By Adam Hollingworth

Pharmacokinetics



- = what the body does to the drug
- ∴ = relationship between dose & resulting plasma (or effect site) concentration
- Drug must reach its molecular target to have an effect
- Conc of drug which finally interacts with target influenced by:
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
- ADME will determine:
  - Effect site conc
  - Duration of action of drug
- NB metabolism & excretion both contribute to elimination
- Elimination = irreversible loss of drug from body

Drug Absorption

- *= process by which an unchanged drug proceeds from site of administration into blood*
- impt factor all routes except IV route
- most drugs are administered extravascularly
- process:
  - disintegration = breakdown of large solid form to smaller
  - dissolution = smaller particles into solution then ready for absorption
  - absorption – then able to occur
- drug dosage form impt:
  - faster disintegration & dissolution ⇒ ↑rapid absorption
  - hierarchy:
    - liquids, elixirs, syrups
    - suspension solutions
    - powders
    - capsules
    - tablets
    - coated tablets
    - enteric coated

Absorption

- =process of drug crossing membrane to enter blood vessels
- membrane = lipid bilayer with irregularly dispersed protein molecules along it
  ↳carriers, enzymes, receptors, antigenic sites
- lipid soluble drugs can pass across easily
- ionised or water soluble drugs difficult to cross

Passive Transport Diffusion

- the dominant process ie most drugs
- governed by Ficks Law of Diffusion
- along conc gradient across membrane
- influenced by:
  - surface area of membrane exposed to drug
  - conc gradient
  - lipid-water partition coefficient of drug = more lipid soluble the faster will diffuse across

- molecular weight of drug (less impt than solubility)
- ionisation state
- blood flow to area

Carrier Mediated Transport

- this method impt for:
  - amino acids
  - glucose
  - vitamins
  - neurotransmitters
  - metal ions
- impt in kidney, GI tract, bilary tract & bbb
- active transport –
  - energy source
  - movement against conc gradient or electrochemical gradient
  - eg Na,K ATPase pump
- drug transporters can cause uptake or efflux of drug
- 2 major families of transporters for drugs:
  - ATP binding cassette (ABC)
    - 7 subclasses
    - Rely on ATP hydrolysis
    - eg efflux transporter P-glycoprotein (P-gp)
      - first discovered in tumour cells
      - seen in multidrug resistance phenomenon in chronic anti cancer drugs eg vinc, cyclosporin:
        - chronic use ⇒ ↑P-gp ⇒ ↑effluc of anti-Ca drug from cancer cell
        - also transports other drugs eg digoxin, Ca channel blockers
    - eg uptake transporter organic anion transporting protein (OATP)
      - OATP1A2 –
        - transports wide range: bile acids, thyroid hormones, steroid sulfates, opiod peptides
        - bbb - impt in regulating barier to solutes
        - liver – uptake of bile acids, sulphate & glucuronide conjugates
  - Solute carrier transporters (SLC)
    - 43 sub-families

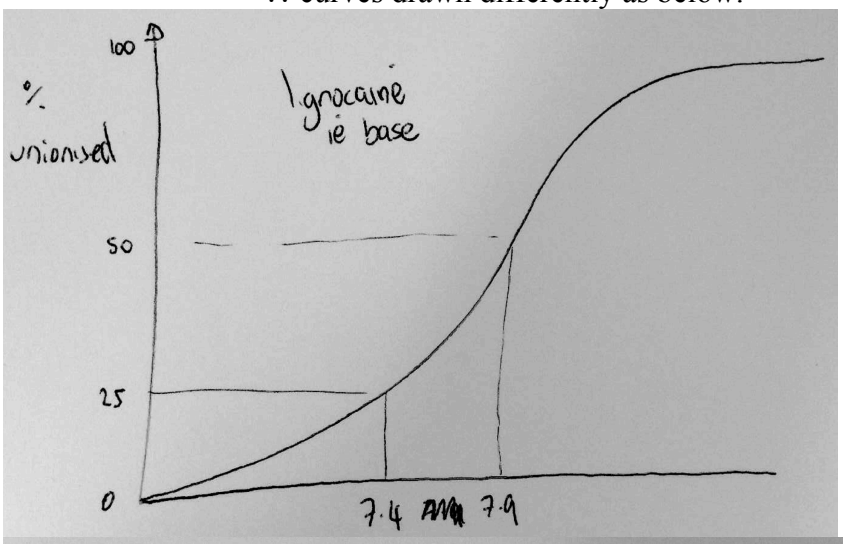
Variables the Affect Drug Absorption

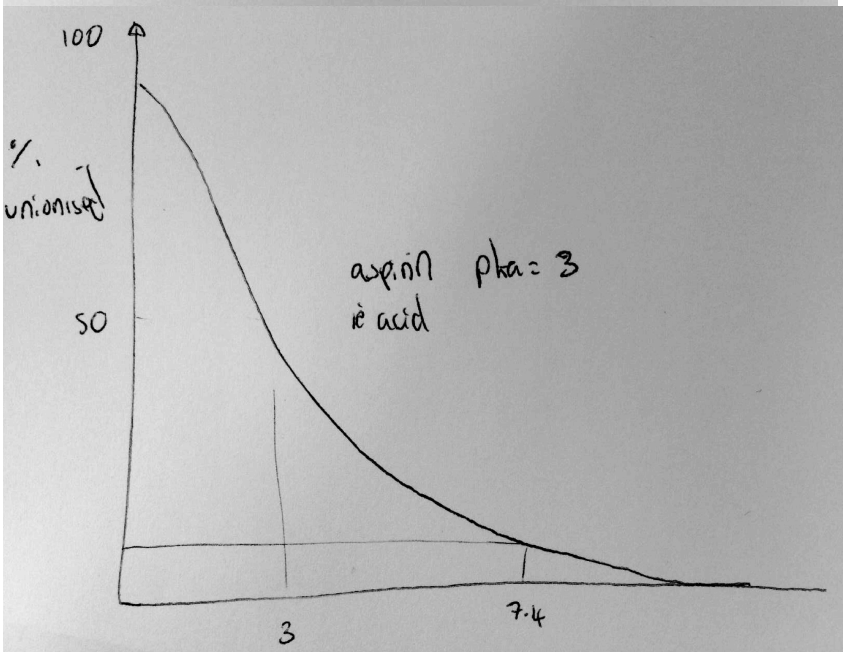
- nature of cell membrane which drug must cross:
  - depth of membrane eg intestine (single layer) vs skin (multiple cell layers)
  - size of surface area of absorbing site
    - eg anaethetics rapid absorb due to massive sa pulmon epithelium
    - small intestine > stomach sa
- blood flow:
  - rich blood supply ⇒ ↑speed absorbtion eg S/L vs S/C route
  - food ⇒ ↑splachnic blood flow ⇒ ↑speed absorption of oral drugs
  - shock/hypovolaemic state ⇒ ↓splachnic flow
  - IV drugs – immediate
- Solubility of drug:
  - To be absorbed drug must be in solution ∴ more soluble drug will be presented for absorption faster
  - Lipid solubility valuebale in GI tract/placenta
  - Insoluble particles will not be absorbed
- Ionisation:
  - Drugs exist as weak acids or bases:

- In same media tends to be unionised:
  - Weak acid in acid = unionised ; weak base in basic media = unionised
  - Weak acid in base = ionised ; weak base in acid = ionised

- In body fluids are
  - ionised (charged polar)
    - water soluble ∴ ↓↓ diffusion through cell membranes
  - unionised
    - better crossing membranes
    - eg weak acid in stomach; weak base in small intestine
      ↳NB little absorption from stomach as small sa, rapid emptying
- extent of ionisation determined by pH of environment:
  - strength of acid = tendancy to dissociate into H+ & anions
  - dissociation defined by pKa:
    - = pH at which half the chemical is in its ionised form
- degree of unionised depends on
  - whether drug is
    - acid: if pKa < physiological pH (7.4) = <50% unionised
    - base: if pKa < 7.4 = >50% unionised

    ↳ ∴ curves drawn differently as below:





- pH trapping:
  - weak acid will become ionised in compartment with high pH ∴ unable to penetrate membrane
    ↳ eg asprin (salicylate acid) trapped in alkaline urine ⇒ forced diuresis
  - weak bases will become ionised in compartment with low pH
    ↳ eg LA's trapped outside of membrane in areas of inflammation ∴ cant get to site of action

Formulation

- pharmaceutical processing can manipulate formation to achieve desirable absorption characteristics
- example:
  - active drug combine with resin from which slowly released
  - adding a vasoconstrictor – eg adrenaline with LA's
  - depot preps eg relatively insoluble salts/esters/complexs of drugs given s/c or IM eg medroxyprogesterone acetate = an ester (depot provera)
  - subcut pellets of drugs eg estradiol
  - enteric coating – vehicle which offers resistance to acid environment of stomach:
    - prevent decomposition of chem. Sensitive drugs by gastric secretions
    - prevent dilution of drug before reaches intestine
    - prevent N&V by drug effect on stomach
    - provide delayed release of drug

Routes of Drug Administration

- route of admin can effect:
  - rate of onset of action
  - magnitude of therapeutic response

Oral Route

- changes in gastro environment may make absorption unreliable
- absorbed different places along the way

From Oral Cavity

- little absorption in mouth
  ↳small surface area
- oral mucosa can absorb some drugs as long as rapidly dissolve in salivary secretions
  eg GTN – unionised, high lipid solubility ⇒ rapid through mucosa
- straight into systemic circ avoiding portal system and 1st pass metabolism
- onset of action ~2mins

From Stomach

- little absorption
  ↳thick mucus, small surface area,
- ∴ slow gastric empyting rate ⇒ ↓s absorption speed
  ↳why many drugs administered on empty stomach with water to aid dissolution
- prolonged gastric emptying time ⇒ ↑risk destruction of acid labile drugs eg erythromycin

From Small Intestine

- major site of absorptions:
  - highly vascularised
  - many villi with ↑ingly permeabile membrane
  - alkaline fluid pH 7-8 ⇒ ↑rate of absorption of unionised drugs
- ↑ed intestinal mobility eg diarrhoea ⇒ ↓exposure to intestinal membrane ⇒ ↓absorption

From Rectum

- surface area small, but vascularised ++
- veins to rectum:
  - superior ⇒ IMA ⇒ portal system
  - mid & inf – to IVC, avoiding portal system

↳approx 50% in total

Parenteral Route

- absorption from S/C & IM is faster than oral route but variable depending on blood flow to area
- types:
  - S/C – slow absorption, sustained release
  - IM -
    - In fully soluble form in aqueous solution ⇒ more rapid absorb
    - Poorly soluble form ⇒ slower absorbtion into circulation
      ↳eg testosterone, depot antipsychotics
  - IV - Immediate increase in plasma concentration as absorption bypassed
  - Intrathecal – injection into subarach space bypassing bbb
  - Epidural – injection into the spinal canal but outside of the dura matter that surround spinal column
  - Others eg I/O, intra-articular, intraperitoneal, intrapleural

Inhalational

- Must be gases or fine mists
  ↳otherwise may interrupt gas exchange

Topical

- Skin: Only lipid soluble compounds are absorbed across skin
- Eyes:
  - local effect on conjunctiva or ant chamber
  - systemic absorption via drainage through nasolacrimal canal which bypasses 1st pass metab

Bioavailability

- bioavailability:
  - = proportion of administered dose that reaches the systemic circulation intact
  - usually expressed as %
  - AUC is used to compare orally administered medicines bioavailability to IV dosing (see later)
  - symbol = F
  - $F = f_g \, x \, f_h$
- 2 factors determine amount drug reaching circulation:
  - f_g = fraction of dose absorbed
    - aka amount of drug **absorbed** from GI tract
    - varies a lot with oral route –
    - f_g = 1: drug completely absorbed
    - f_g = 0: no drug absorbed
  - f_h = difference amount of drug entering liver and that exiting liver
    - measure of amount of drug **escaping** 1st pass metabolism
    - fraction of drug not extracted by liver also = 1- E_H (hepatic extraction ratio)

  ↳eg alendronate 0.5%; warfarin 90%

Hepatic First Pass Effect

- dosage of oral drugs is compensated for first pass effect
- eg morphine 30mg oral = 10mg IV
  ↳significant hepatic first pass effect

Drug Bioequivalence

- = 2 drug formulations which contain identical concentration or active ingredient in the same dosage form and administered by same route
- referes to generic drugs used once patent ran out
- generic drug tested against old drug:
  - bioequivalent if no significant difference in:
    - bioavailability

    - therapeutic or adverse effects
- ∴ bio-inequivalence = formulations of same drug which may yield different bioavailabilities with **statistically** significant difference
- therapeutic inequivalence = **clinically** significant difference between bioavailabilities of different formulations of same drug

Biosimilars

- pharmaceutical drugs are small low molecular weight chemicals which are easy to copy and easy to make bioequivalent generic drug
- new biopharmaceutical drugs have been introduced:
    - large proteins using biotech methods eg recombinant technology
    - drug often made using microbial cells
    - any small change in manufacturing process may have major impact on activity of protein
- biosimilar drug = biological product referring but not identical to exisiting product
- many issues unresolved between biosimilars and original patented drug
- evidence shows some biosimilars not interchangeable with original durg

Drug Distribution

- = process of reversible transfer of a drug between one location & another (one of which usually blood)
- some remain exclusively in blood eg warfairn & heparin
- others distributed to organs
    - high blood supply eg kidney/liver – initially high local drug concentration
    - low blood supply eg skeletal mm/fat – initially low local drug conc

    ↳eg widely distributed drugs ethanol, digoxin, morphine
- rate of entry to department varies on factors :
    - plasma protein binding
    - lipid solubility:
    - pKa of drug ie movement across cap membranes: lipid solubility (unionised) > lipid insoluble (ionised).
    - pH of body fluid
    - regional blood flow
    - specific drug properties

Plasma Protein Binding

- proportion of drug binds to
    - proteins
    - lipo-proteins

  } ⇒ drug protein complexs
- protein binding is a reversible & dynamic process in equilibrium
- it is the free fraction of drug (generally in the interstitial space) which is pharmacologically active
- plasma protein binding expressed as
    - % of drug bound (75%)
    - fraction unbound (0.25)
- binding depends on 3 factors:
    - affinity of drug for binding sites
    - relative concentrations of drug
    - relative concentration of plasma protein (and no of binding sites on protein)
- conc of drugs following therapeutic dose generally lower than binding proteins
- majority of drugs in therapeutic range % bound & unbound constant

    ↳except eg high dose salicylates in RA: non linear binding to albumin
- nonlinear binding occurs when
    - conc of drug saturates protein binding sites
    - adding more drug ↑s disproportionally unbound conc of drug in plasma
- equilibrium between bound & unbound drug:

- as free drug removed from circ ⇒ drug protein complex unbinds replacing lost free drug
  ↳eg distribution, excretion, metabolised

- plasma proteins for binding include:
  - albumin – generally acid drugs
  - beta globulin
  - alpha acid glycoprotein – mostly basic drugs eg opioids

Albumin

- plasma albumin = most impt of plasma proteins
- binds:
  - mostly acidic drugs eg NSAIDs, warf
  - small no. of basic drugs eg TADs, chlorpromazine
- 2 binding sites/albumin molecule:
  - warfarin site
  - benzo site

  ↳ competition between diff drugs for binding at that site eg amiodarone & warfarin for warfarin binding site ⇒ displacement
  ↳ although in practise this rarely a problem as most drugs at therapeutic concentrations occupy only small fraction of binding sites
  ↳ (except sulphonamides which occupy ~50% sites at therapeutic levels)
- Competition for binding on albumin (other plasma proteins) does occur
  ↳but if clearance of drug is normal very rare to see saturation ∴ ↑drug effect as result

Hypoalbuminaemia

- Hypoalbuinaemia ⇒ ↑free drugs
  ↳need to effect dosage to avoid possible toxicity
- Eg phenytoin:
  - Unbound fraction of 0.1
  - Can ↑to 0.2 in renal failure because of
    - hypoalbuminaemia &
    - accumulation of competing endogenous compounds for albumin binding
  - ∴ ↓dose & monitor levels

High protein binding	Low protein binding	Unbound
Sulphonylureas (99%) & glitazones (99%)	Paracetamol 10%	metformin
Warfarin 99% heparin	Morphine 35%	gabapentin
NSAIDs >95%	Atropine 50%	
Candesartan 99.8%	Codeine 7%	
Phenytoin 90%	Cephalexin 14%	
Furosemide 95%	Metronidazole 10-20%	
Steroids 90%	Digoxin 20-40%	

Lipid Solubility & Adipose Tissue

- lipid soluble drugs = high affinity for adipose tissue
- adipose tissue is:
  - large non polar compartment
  - very poor blood supply
- non-polar compartment:

  - impt only for drugs with a very high fat:water partition coefficient
  - eg thiopentone fat:water coefficient ~10 (ie very lipid soluble):
    - rapid distribution to brain ⇒ anaesthesia
    - then rapid redistribution to body fat x6-12 level in plasma
    - despite long half life this means can only be useful as induction agent
  - eg morphine (as comparison):
    - fat:water coefficient ~0.4 ⇒ little redistribution into fat
- low bloody supply to fat:
  - <2% CO
  - acute drug administration means only a few very highly lipid soluble drugs will redistribute to fat
  - chronic dosing of lipid soluble drugs ⇒ significant adipose accumulation eg benzo's

Other Areas of Accumulation

Retina

- rich in melanin
- eg chloroquine has high affinity for melanin

Bone & Teeth

- due to high affinity for calcium
- eg tetracycline:
  - accumulates in bone
  - depress growth in infants
  - brown pigment to teeth – tetracycline-calcium-orthophosphate complex in tooth

Liver & Lung

- amiodarone has high affinity

Barriers to Drug Distribution

BBB

- allows distributions of only lipid soluble drugs
- ionised & poorly lipid soluble not allowed through
  ↳unless special circumstances eg meningitis
    - bbb becomes leaky
    - allows access to brain of drugs not normally be able eg penicillin

Placental Barrier

- make up of barrier:
  - physical membrane layers
  - enzymes in placenta – can inactivate some agents eg catecholamines
- more permeable than bbb
- non selective passage of drugs across placenta possible:
  - lipid soluble move faster
  - great no of water soluble drugs move across
  ↳eg steroids, narcotics, anaesthetics, some Abx

Compartmental Distribution of Drugs

- ∴ given above drugs can be said to distribute into body compartments
- these compartments are theoretical eg ICF = ICF volume of all cells in body
- major compartments in this regard are split by weight:
  - 60% body water
  - 17% protein
  - 15% fat
  - 7% mineral
- body water can be further subdivided via simple or complex models:
  - complex (60% broken down into)
    - ICF = 55%
    - ECF = 45% which broken down into

        - 20% interstitial
        - 7.5% intravascular
        - 7.5% bone
        - 7.5% dense CT
        - 2.5% transcellular fluid eg CSF, urine in bladder etc
    - simple (60% broken down into)
        - 40% ICF
        - 20% ECF
            - 5% plasma
            - 15% interstitial

Volume of Distribution

- **Apparent** volume of distribution = volume of fluid required to contain the total amount of drug (A) in the body, at the same concentration as that present in the plasma (C)
    ↳∴ a drug which distributes outside the plasma compartment would have a larger V_D than one confined to the plasma only.
    ↳ drugs which bind to proteins outside of plasma can have very very high VD eg amiodarone/fluoxetine

- calculated by

$$V = A/C$$

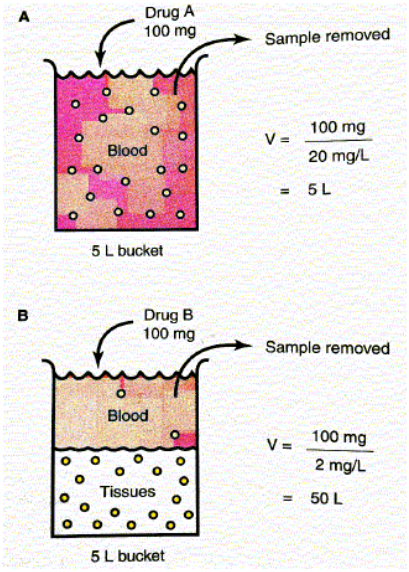
$$\frac{\text{Total amount of drug in body (A) mg}}{\text{volume of distribution } (V_D)(\text{ml}) \mid \text{Plasma Drug Conc (C) mg/ml}}$$

- abstract term, not a real volume
- if drug tightly bound to plasma proteins & remains in blood:
  volume of distribution will be close to plasma volume
- if drug diffuses into tissues ⇒ ↑volume of distribution
    ↳opposite: ↑V_D ⇒ ↑tissue bound widespread drug

Factors Effecting Vd

- Drug:
    - PPB
    - pKa/pH ∴ degree of unionisation
    - lipid solubility
- Patient:
    - sepsis
    - liver failure/kidney disease ⇒ ↓serum protein
    - dehydration
- Special groups:
    - old
    - young
    - fat
    - pregnant

Drug Examples



- In A:
  - drug tightly bound to blood plasma proteins only.
  - Concentration in blood ∴ higher ⇒ V_D 5L
- In B:
  - drug moved from plasma into tissues
  - ∴ ↓blood conc (where we measure levels) **but same** total drug
  - here ↑V_D to 50L

Volume of Distribution in Different Compartments

- NB for drug to be active
- drugs confined to plasma:
  - plasma volume ~0.05l/kg body weight
  - ∴ drugs should have V_D fairly close to plasms volume
  - these drugs are either:
    - too large to cross capillary wall eg heparin
    - strongly bound to plasma proteins
      ↳ although impt that drug to be active must be free & (generally) in interstitial space
  - Evans blue = dye which used to experimentally measure plasma volume
    ↳ as binds so strongly to plasma albumin
- Drugs distributed in ECF compartment:
  - ECF volume ~0.2l/kg (plasma = 0.05, interstitial fluid = 0.15)
  - This is ~ V_D for many polar drugs ie drugs which don't cross cell membranes, BBB, placenta:
    - NMBs
    - Gentamycin
    - Carbenicillin
- Drugs distributed throughout body water:
  - Total body water ~0.6l/kg
  - Approximates V_D of relatively lipid soluble drugs which easily cross cell membranes eg phenytoin
  - BUT if drug:
    - Binds to tissue outside of plasma compartment
    - Binds to and/or partions into fat

    ↳ then V_D ↑s greater than total body water eg morphine, TAD's, haloperidol

- Total V_D of drug = sum total of different compartmental V_D for that drug

Summary Volume of Distribution

- Volume of distribution changes with
  - Age:
    - largely due to diff %TBW:
      - <1yr V = 75-80% of weight
      - adult = 60% of weight
      - elderly <60%

      ↳∴ with age ↓total body water, ↑relative body fat
  - Body composition
  - Gender:
    - Male 60% weight
    - Female 55% weight
    -
- Examples:
  - Warf = 8L
  - Furosemide 12L
  - Digoxin 420L
  - Fluoxetine 2450L
- use clinically:
  - provides indication of accumulation of drugs in extravascular compartments
  - major determinant of half life
  - need to know V to calculate loading dose needed to achieve quick high plasma concentration

Drug Metabolism

- aka biotransformation
- = process of chemical modification of drug almost invariably carried out by enzymes
- is one of the methods of elimination (the other = excretion removes drug with no modification):
  - most drugs leave body in urine
  - drugs eliminated via urine usually unchanged or water soluble metabolites
  - lipophilic drugs are poorly eliminated by kidney cos they diffuse back into blood
  - ∴ liver metabolises them to be more water soluble to help elimination
- liver primary site of metabolism:
  - also kidney, lungs, intestine mucosa
  - cytochrome P450 is predominant
  - P450 enzymes can be extrahepatic eg adrenals for steroid synthesis
- around 70% drugs undergo some metabolism:
  - usually product is less active than parent drug
    ↳except prodrugs: eg losartan, clopidogrel, codeine
  - majority of drugs become more water soluble (polar) which can be excreted

  ↳metab ∴ clears parent drug and promotes elimination
- drugs will contain a mixture of different stereoisomers:
  - diff stereoisomers may undergo diff metabolic pathways
  - sig drug interactions can occur via inhibition of these diff metabolic pathways

Types of Reaction

- in liver either:
  - functionalization (phase 1)
  - conjugation (phase 2)

  ↳but can occur extra-hepatically:
    - plasma – hydrolysis of sux
    - lung – prostanoids
    - gut – tyramine, salbutamol
- outcomes of drugs:
  - excreted unchanged as parent drug eg gentamicin
  - undergo single/multiple functionalisation reactions eg oxidation prior to excretion eg caffeine
  - undergo immediate conjugation and then excretion eg paracet
  - undergo functionalisation & then conjugation, then excretion eg phenytoin

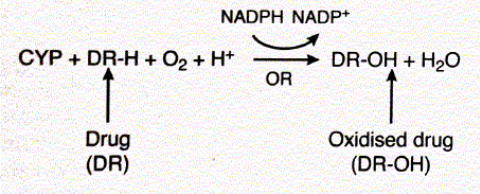
  ↳reactions can occur sequentially or at same time

Functionalisation Reactions (phase 1)

- involve introduction of a functional group into molecule
- achieved by **catabolic** reactions:
  - oxidation – most
    - = loss of electrons/hydrogen or addition of oxygen
    - CP450 involvement
  - reduction
  - hydrolysis
- product of reaction:
  - often more chemically reactive ie product may be more toxic than parent compound
  - usually a reactive group added
    - eg hydroxyl gp added to compound
    - serves as point of attach for phase 2 reactions
- produce more water soluble drugs
- major family of enzymes involved in oxidative reactions is cytochrome P450

Cytochrome P450 Enzymes (CYP)

- CYP are family of related but distinct haem containing enzymes found in Smooth ER of cells
  ↳especially in hepatocytes (zone 3 acinii)
- Known as microsomal enzymes
- Drug needs to be relatively lipophilic (non polar) to reach enzymes
- Catalyse transfer of one atom of oxygen to a substrate producing an oxidised metabolite & a molecule of water



OR = NADPH cytochrome P450 oxidoreductase
↳essential for CYP activity as provides electrons (from NADPH/H+) necessary for CYP oxidation/reduction cycle

- ~74 gene families isolated
- 3 main ones in human liver = CYP1, 2, 3
- Diff P450 enzymes have distinct but overlapping substrate specificities
- Examples:
  - CYP1A1 ⇒ theophylline
  - CYP1A2 ⇒ paracetamol, theophyline
  - CYP2 (8 families) ⇒ enflurane, isoflurane, sevoflurane
  - CYP2C9 ⇒ ibuprofen, phenytoin, warf
  - CYP2C19 ⇒ omeprazole
  - **CYP2D6 ⇒ codeine, metoprolol, tramadol**
  - CYP2E1 ⇒ enflurance, halothane, alcohol
  - CYP3A4 ⇒ fentanyl, alfentanil, methadone, midaz, diazepam, droperidol lignocaine, bupivocain, ondansetron
- CYPs involved in metabolism multiple substances:
  - Drug
  - Environmental pollutants
  - Dietary chemicals
  - Bile acids
  - Sterols
  - Hormones
  - Fatty acids
- >50 human CYPs

Induction & Inhibition of CYPs

- inhibition of P450:
  - inhibitors differ in their selectivity for isoenzymes
  - non competitive inhibitors eg ketoconazole
- inhibition occurs because of competition – 2 drugs compete for metabolism by same enzyme
- ⇒ ↓elimination eg:
  - amiodarone ⇒ ↓metab of warfarin ⇒ ↑risk bleeding
  - allopurinol ⇒ ↓metab of azathioprine ⇒ ↑risk bone marrow tox

- basis for many drug interactions = induction of metabolism enzymes
- extent of impact depends on how much induced enzyme reduces plasma conc of other drug
- may induce enzyme against self or others
- induction of P450:
  - chronic use of drugs can induce CYP
  - eg carbamazepine, phenytoin, ethanol, rifampicin, steroids
  - can result in:

- ↑metabolism of drugs which metabolised by that CYP eg ↓duration of action of rocuronium in pts on steroids
- ↑↓ drug toxicity eg paracetamol toxicity is due to phase 1 metabolites ∴ CYP induction will ↑risk of toxicity
- others:
  - smoking ⇒ ↑CYP1A2 ⇒ ↑metabolsim of caffeine, theophylline
  - rifampicin ⇒ ↑metab COCP

Other Phase 1 Reactions

- alcohol dehydrogenase: ethanol is metabolised by this enzyme as well as CYP2E1
- xanthine oxidase: metabolises mercaptopurine
- monoamine oxidase: metabolises many amines eg NA, tyramine, serotonin
- hydrolytic reactions: occur in plasma + many tissues eg ester & amide bond hydrolysis
- reductive reactions: warfarin as well as CYP2C9

Conjugation Reactions (phase 2)

- reactions generally anabolic
- mostly occur in liver but also lung & kidney
- can work on parent drug or phase 1 metabolite
- drug/metabolite needs 'weak point to attack' =
  - hydroxyl gp
  - thiol gp
  - amino gp
- = joining (conjugation) of suitable functional gp onto weak point eg:
  - glucuronyl gp – most often
  - sulphate gp
  - Acetyl gp
  - Glycyl gp
  - glutathione
- conjugated molecule is generally
  - more polar ∴ more water soluble ⇒ ↑urinary excretion
  - pharmacologically inactive – almost always
- several endogenous substances also conjugated by this system eg bilirubin & adrenal corticosteroids
- conjugation reactions are catalysed by variety of diff transferase enzymes:

Enzyme	Endogenous Cofactor	Reaction	Drug Substrate ⇒ Drug Metabolit
UDP-Glucuronosyltransferases	UDP gluuronic acid	Glucuronidation	Morphine ⇒ morphine 3 glucuronide Naloxone ⇒ naloxone 3 glucuronide Codeine ⇒ codeine 6 glucuronide
Sulfotransferases	Sulfate	Sulfation	Salbutamol ⇒ salbutamol sulphate Paracetamol ⇒ paracetamol sulphate
N-Acetyltransferases	Acetyl-CoA	Acetylation	Clonazepam ⇒ 7-acetamidoclonazepam
Glutathione transferases	Glutathione	Glutathione conjugation	Paracetamol ⇒ paracetamol-glutathione conjugate

Drug Metabolism & Excretion

- Non polar drug (lipid soluble) ⇒ limited renal excretion due to extensive tubular reabsorption of lipid soluble drug

  ↓

  Functionalisation (phase I)
- Non polar drug with acceptor group (↓ed lipid solubility) ⇒ ↑excretion due to decreased tubular reabsorption

  ↓

Conjugation (phase II)

- Conjugated drug (water soluble) ⇒ ↑↑ excretion due to active tubular secretion & low reabsorption

Individual Variability in Drug Metabolism

- Due to range factors:
  - Genetics
  - Environmental factors eg coadministered drugs, diet, alcohol
  - Age, gender
  - Disease states eg hepatic, renal , CVS
  - Hormonal changes –
    - Little male:female variability
    - Pregnancy:
      - Especially 3rd trimester
      - metabolism can be unpredictable:
        - ↑activity of CYP & UGT enzymes eg need ↑ed dose of carbamazepine & phenytoin to maintain therapeutic levels in preg
        - ↓metab of caffeine

First Pass Metabolism

- relevant to drugs which exposed to hepatic metabolism prior to reaching systemic circulation:
  - oral drugs – mostly
  - rectal – proportion of drug will get administered into hepatic circ
    ↳∴extremely unpredictable bioavailability
- ∴ causes low bioavailability
- liver (& sometimes gut) extracts & metabolises drugs so efficiently that only small amount of absorbed drug reaches circulation
- important in certain drugs:
  - aspirin
  - GTN
  - Levodopa
  - Lignocaine
  - Metoprolol, propranolol, verapamil
  - Morphine – OBA ~30%
  - Salbutamol
- BUT ways of manipulating this:
  - Prodrugs (inactive) ⇒ active metabolites eg enalapril ⇒ enalaprilat
  - Active parent drug ⇒ active metabolites (or toxic metabolites)

Elimination

- elimination = irreversible loss of drug from site of measurement & occurs by processes of metabolism & excretion
- expressed in mg/min
- ∴ **impt** difference between:
  - metabolism
  - excretion
  - elimination –will always need to be excreted but can be +/- metabolised
- ∴ a drug can be metabolised ⇒ non active state, but will not be eliminated until it has been excreted

Excretion

Renal Excretion

- variability of ways drugs handled in kidney:
  - degree of premetabolism:
    - drugs excreted unchanged in urine
    - only tiny amount of parent (unchanged) drug left

  - degree of clearing in 1 transit:
    - almost completely cleared in 1 transit eg penicillin
    - required multiple transits eg diazepam
    - most inbetween
- process achieved by 3 processes:
  - glomerular filtration
  - active tubular secretion
  - passive diffusion across tubular epithelium (reabsorption)

Filtration

- variables which affect filtration:
  - size of drug:
    - MV <20K = freely filtered
    - Large molecules eg heparin are not
    - Albumin (mw 68K) ∴ not filtered contributing to next point below
  - degree of protein binding
    - only free unbound drugs/metabolites filtered by glom
    - eg warf 98% PPB ∴ only 2% filtrate concentration ⇒ ↓ed clearance

Tubular Secretion

- 20% of renal plasma flow = filtered thru glomerulus
- ∴ ~80% drug passed into peritubular capillaries of prox tubule
  ↳∴ more impt than filtration ie most effective mechanism of renal elimination
- prox tubule = main site of secretion:
  - 2 non selective active transporters exist:
    - 1 for acidic drugs (& various endogenous acids eg uric acid)
      ↳ (organic anion, OAT) transporter incl paracet, furosemide, probenecid
    - 1 for basic drugs
      ↳ base (organic cation) transporter incl quinidine, procainamide
- transporters can move drugs against conc gradient ∴ ↓plasma conc of drug to nearly zero
- secretion not affected by PPB eg penicillin ~80% PPB but almost completely removed by prox tubular secretion
- May inhibit tubular secretion of specific drug:
  - Competitive inhibition eg by using probenecid to compete with penicillin for active secretion
    ↳⇒ prolonged ↑serum level of penicillin

Diffusion (reabsorption)

- most of water reabsorbed as filtrate moves along tubules
  - means conc gradient setup of ↑free drug in tubule:blood
  - eventual urine volume only 1% of original filtrate
- if tubule was freely permeable to drug ⇒ 99% drug passively reasorbed with water
- ↑ed lipid soluble drugs are more permeable to tubule which means:
  - slow excretion because of passive back diffusion tubule ⇒ blood
  - if urine flow rate high ⇒ ↓reabsorption of lipid soluble drug ⇒ ↑ed excretion
- water soluble drugs unable to cross membrane & are very effectively excreted
  ↳eg digoxin, aminoglycosides, some NDNMBs
- urinary pH (4.6-8.2) affects amount of drug reabsorbed in tubule as effects degree of ionisation:
  - see earlier notes on ion trapping
  - weak acid in alkaline urine = ionised ∴ water soluble ∴ unable to reabsorp ∴ ↑excretion
    ↳differences = ionised, same = unionised
    ↳eg aspirin
  - alter pH of urine can ∴ change amount of excretion of drug (function of pKa)
    ↳eg aspirin overdose (weak acid) ⇒ Rx to alkalinise urine ⇒ ↑excretion of drug
    ↳eg morphine (weak base) ⇒ Rx acidify urine ⇒ ↑excretion of drug

        - acidify urine: high dose vit C or ammonium chloride
        - alkalise urine: Sodium bicarbonate
- Renal failure:
    - ↓blood flow in ARF/CRF ⇒ ↓overall excretion
    - ↓active secretion to nearly none

Bilary Excretion

- after liver metabolism, drug metabolite may be transported to bile using transport system involving P-glycoprotein (similar to renal tubule)
- various hydrophilic drug conjugates) metabolites especially glucuronides are concentrated in bile
- bile delivered to intestine, mixes with intestinal fluid ⇒ glucuronide hydrolysed ⇒release of free fluid
- then free drug can:
    - excrete in faeces
    - reabsorbed & cycled as part of enterohepatic circulation :
        - returned to liver
        - produces a supply of recirculating drug that contributes (up to 20%) overall drug pool in body eg morphine
- several drugs undergo significant bilary excretion
    - rocuronium = excreted mainly unchanged in bile

Pulmonary Excretion

- gases & volatile drugs (eg anaesthetics) are inhaled & excreted by lungs
- absorbed across alveolar membrane
- excretion from lungs depends on:
    - RR
    - Vt
    - Exercise ∴ ↑CO ⇒ ↑pulmon blood flow ⇒ ↑lung excretion
- Ethyl alcohol pulmon excretion is basis of alcohol breath test

Excretion in Sweat & Saliva

- Relatively unimportant as process is slow & minor process

Excretion in Breast Milk

- Many drugs or metabolites cross the epithelium of mammary glands
- Risk to infant of exposure depends on:
    - Maternal plasma level
    - Amount of milk ingested
- Milk is acidic (pH 6.5) ∴ basic drugs, with low plasma protein binding & high lipid solubility achieve high level in milk
    ↳eg narcotics codeine & morphine

Clearance

- = volume of plasma cleared irreversibly from a drug / unit time
  ↳expressed volume/time: L/hour or mL/min
- ∴ describes ability of organ or whole body to eliminate a drug
- each organ clearance values are additive ∴ total clearance from circulation (CL_s) reflects all body clearance processes for that drug

$$CL_s = CL_{hepatic} + CL_{renal} + CL_{other}$$

- in general CL_{other} generally ignored eg lungs
- CL is constant for an individual
  ↳provided no physiological changes occur eg upreg of hepatic metabolism
- CL in a population will be varied according to individual characteristics

Elimination rate (mg/hr) = CL (L/hr) x plasma drug conc (mg/L)

Elimination rate (mg/hr)	
CL (L/hr)	plasma drug conc (mg/L)

- NB don't confuse clearance with elimination:
  - Clearance = vol/time
  - Elimination = mg/min

Hepatic Clearance

- Hepatic clearance depends on
  - Blood flow to liver (Q_H)
  - Hepatic extraction ratio (E_H):
    - = fraction of drug entering liver in blood which is irreversibly removed by metabolism on each pass through liver
    - E_H = 0 when no drug is extracted
    - E_H = 1 when all drug is extracted
    - eg liver clears 30L/H and has blood flow of 90L/H = 30/90 = 0.33

Maths

- Based on **Fick's Principle**:

$$Vx = Q_H(Cax - Cvx)$$

where Vx = elimination of drug x by liver (in mg/min),
Q_H = liver flow
Cax and Cvx are the arterial and hepatic venous concentrations of drug x.

- Now, $Vx = Cl_H \times Ca_x$
- Thus: $Cl_H \times Ca_x = Q_H(Ca_x - Cv_x)$

And: $Cl_H = Q_H \times (Ca_x - Cv_x)/Ca_x$
And $(Ca_x - Cv_x)/Ca_x$ = also known as the **hepatic extraction ratio** (EH)

- Thus: $\mathbf{Cl_H = EH \times Q_H}$

- inter-relation equation:

$CL_H = E_H \times Q_H$

CL_H	
E_H	Q_H

- E_H ∴ = how much drug extracted by liver on each pass
- If we know absorption value then can calculate bioavailability post 1st pass metabolism:
  - Absorption complete (fg = 1)
  - E_H = 0.88 = 88% of drug extracted on each pass in liver
  - Bioavailability of same drug = 12%

- Drugs metabolised by liver classified according to relationship of CLH & QH s having
  - High hepatic clearance = CL_H >60 or E_H >0.67
    - $Cl_H \sim Q_H \Rightarrow$
      ↳ ie intrinsic clearance (enzyme capacity) is so high that determining factor for Cl_H is liver blood flow
    - ∴ elimination is flow or perfusion limited
    - eg lignocaine, morphine, propofol
  - Intermediate = CL_H 20-60 or E_H 0.2-0.67
    ↳eg omeprazole, paracet
  - Low clearance = CL_H <20 or E_H <0.2
    - Intrinsic clearance is low
    - ∴ changes in enzymatic activity eg induction/inhibition AND PPB will have large effect on Cl_H
      ↳Changes in Q_H affects Cl_H very little
    - elimination is now = capacity-limited or restrictive
    - eg warf, brufen, most barbituates (eg thiopentone), phenytoin

- NB a low hepatic clearance only means capacity of hepatic enzymes involved in metabolism is low

Effect of Enzyme Induction/Inhibition on Hepatic Clearance

- For drugs with high hepatic clearance eg E_H 0.8:
  - Small ↑ (induction) in metabolism by other drug ⇒
    - Substantial ↓↓ bioavailability
    - Small ↑in clearance
  - Small ↓ (inhibition) in metabolism by other drug ⇒
    - Substantial ↑↑bioavailiability
    - Lesser ↑clearance

$CL_H = E_H \times Q_h = 0.8 \times 90 = 72$ L/H
F= 1 – EH = 1 - 0.8 = 0.2 or 20% bioavailability

Drug ⇒ ↑EH to 0.9
Clearance now 0.9 x 90 = 81L/H (12.5% change)
Bioavailability now (1-0.9) ie 10%

- For drugs with low hepatic clearance eg E_H 0.01:
  - Small ↑ (induction) in metabolism by other drug ⇒
    - Large ↑↑clearance
    - Insignificant ↓bioavailability
  - Small ↓ (inhibition) in metabolism by other drug ⇒
    - Large ↑↑clearance
    - Insignificant ↓bioavailability

$CL_H = E_H \times Q_h = 0.01 \times 90 = 0.9$ L/H
F= 1 – EH = 1 - 0.01 = 0.99 or 99% bioavailability

Drug ⇒ ↑EH to 0.02
Clearance now 0.02 x 90 = 1.8L/H (50% change)
Bioavailability now (1-0.02) ie 98%

- ∴ in high hepatic clearance drugs inhibition or induction of metab will change bioavailability greatly AND in low hepatic clearance drugs inhibition/induction will change clearance greatly with little effect on bioavailability

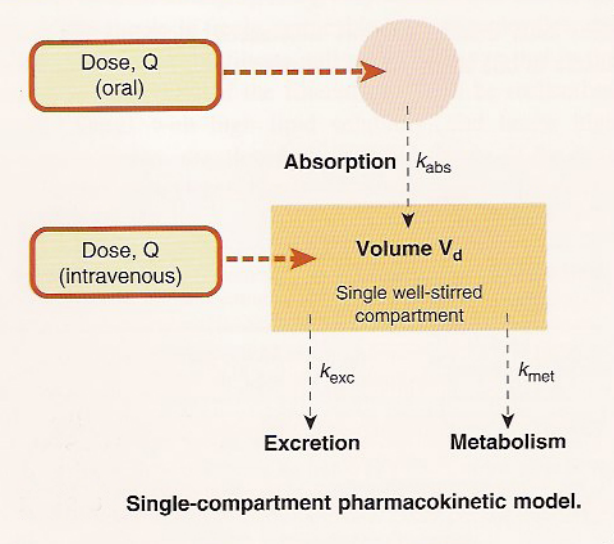
By Adam Hollingworth

Pharmacokinetic Modelling

- relationship between time course of drug & concentrations in diff regions of body during and after dose can graphically represented
- in form of concentration – time plots
- all ADME processes taken into account
- different models exist to predict conc-time plots:
  - single compartment model
  - complex multi-compartment kinetic models
- use these models to:
  - predict time course of drug action
  - recovery from action
  - basic principles of infusion pumps

Single Compartment Model

- very simplified model of human
- assumes
  - whole body = one well mixed compartment with a volume of distribution
  - A known quantity of drug (Q) introduced into well mixed compartment
  - Only way for drug to escape (eliminated) by means of metab +/- excretion



Single-compartment pharmacokinetic model.

Importance of Clearance

- continued administration of drug eventually ⇒ rate of drug in = rate of drug out ⇒ ∴ plasma conc constant
- repeated doses or IV infusion could be considered extreme of repeated dosing
- steady state achieved when rate of drug administration = rate of drug elimination
  ↳at steady state elimination rate = maintenance dose rate (MDR)
- clearance (CL) determines MDR required to achieve target plasma conc at steady state (C_{SS})

$$\frac{\text{MDR (mg/h)}}{\text{CL (L/h)} \mid C_{SS}\text{ (mg/L)}} \qquad \text{MDR (mg/h)} = \text{CL (L/H)} \times C_{ss}\text{ (mg/L)}$$

- maintenance oral can be calculated from MDR:

$$\text{Maintenance dose} = \frac{\text{MDR} \times \text{dosing interval}}{\text{Bioavailability (F)}}$$

- half lifes:
  - after 1 half life: 50% is C_{SS} reached
  - 2 ⇒ 75% C_{SS}
  - 3 ⇒ 88%
  - 4 ⇒ 94%
  - 5 ⇒ 97%
- ∴ drug concentration reaches C_{SS} exponentially
- practically steady state reached after 4-5 half lives
- this remains true for infusions or repeated dosing schedules
  ↳ie even with IV infusion still takes time to reach steady state

Example: Calculate MDR

Target plasma conc in steady state is 12.5mg/L
Given IV clearance of drug is 8L/h
IV dose ∴ bioavailability = 1 (100%)

$$\begin{aligned} MDR &= CL \times C_{SS} \\ &= 8L/h \times 12.5mg/L \\ &= 100mg/h \end{aligned}$$

Example: Calculate IV to Oral Switch

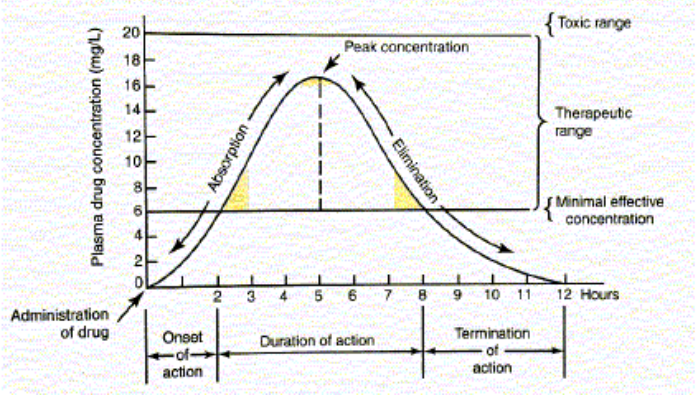
need to maintain same plasma concentration
oral formula has a bioavailability (F) of 0.8 (80%)
recommended dosing interval is 8hrly

$$\begin{aligned} \text{oral maintenance dose} &= \frac{MDR \times \text{dosing interval}}{F} \\ &= \frac{100mg/h \times 8h}{0.8} \\ &= 1000mg \end{aligned}$$

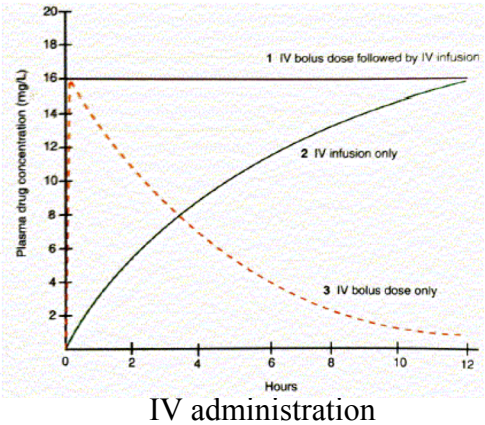
Dosing Regimes

- Each drug will have its own pharmacokinetic profile influenced by:
  - Route of administration
  - Disease state of individual
  - Genetic make up of person
  - Environmental factors
- Aim is achieve a steady state of plasma drug concentration
  - Continuous IV infusion
  - Repeated oral adminstrations

Time Profile of Drug & Plasma Concentration



oral administration



IV administration

- Graph above shows time to:
  - onset of action
  - Peak plasma conc
  - Duration of action (length of time plasma conc remains in therapeutic range)
- Plasma concentration-time profile of drug influenced by:
  - Absorption (only if not IV)
  - Distribution

- Elimination (metab & excretion)

- Within profile above are parameters of:
  - Clearance
  - Volume of distribution
  } Determined by characterisitics of patient & drug
  - Half life = composite parameter which is:
    - Related to volume of distribution of drug
    - Inversely related to clearance of drug

Area Under the Plasma Concentration vs Time Curve

- Used to calculate both the clearance of a drug and its bioavailability
- Bioavailability of a drug calculated by
  - **Oral** area under concentration-time curve (AUC) divided by AUC for IV administration of same dose/type of drug:
  - Bioavailability of IV dose = 100% by definition
  - If AUC of oral dose is half of AUC of IV dose: bioavailability of oral formulation = 50%
- AUC = total area under the curve that describes the conc of drug in the systemic circ as a function of time post dose
- AUC calculated by dividing area under curve into equal strips, then adding results
  ↳= trapezoidal rule
- Larger the AUC ≈ ↓ clearance
  ↳because of $Cl = \frac{dose}{AUC}$

Loading Doses

(refer back to volume of distribution under Distribution section)

- calculation:

$$\frac{\text{loading dose (mg)}}{V_{D\,(L)} \mid \text{desired plasma conc (C) (mg/L)}}$$

Loading dose = volume of distribution (V_D) x desired plasma conc (C)

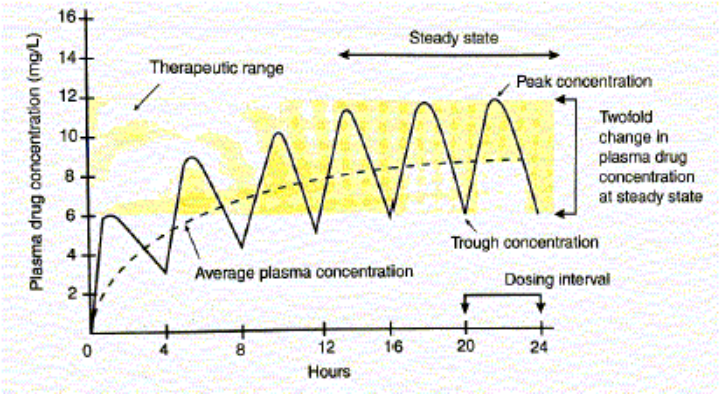
- IV infusion still takes number of hours to achieve target concentration
- IV bolus dose then infusion overcomes lag time

Half Lifes

- = time taken for blood or plasma drug concentration to fall by one half (50%)
  ↳determined by clearance (CL) & volume of distribution (V_D):

$$t_{½} = \frac{0.693 \times V_{D\,(L)}}{CL\ (L/hr)}$$

- half life is major determinant of:
  - duration of action of a drug after single dose
    ↳longer half life ≈ longer plasma conc will remain therapeutic
  - time take to reach steady state with chronic dosing – 3-5 half lives to reach desired steady state
  - dosing frequency required to avoid massive fluctuations in plasma drug conc during dosing interval:
    - once steady state achieved, half life & dosing interval ≈ fluctuation in plasma drug conc
    - drug given orally every half life: plasma conc will fall by one half between doses



- ∴2 factors influence half life:
  - CL:
    - ↓ed CL ⇒ ↑half life
    - ↑ed CL ⇒ ↓half life
  - VD:
    - ↓ed VD ⇒ ↓half life
    - ↑ed VD ⇒ ↑half life
- pt examples:
  - with heart failure has ↑ed VD & ↓ed liver blood flow (↓CL) ⇒ ↑T1/2
  - liver or kidney disease will ↓CL ⇒ ↑half life
- half life may be very poor indicator of efficacy of drug elimination
  ↳eg ↓ed VD & ↓CL ⇒ ↑↑plasma conc with no change in stated half life ⇒ ↑risk of toxicity
  ↳need to change dosing regime!!

Saturable Metabolism

First Order Kinetics

- elimination of most drugs exhibit 1st order kinetics
- = rate of elimination is directly proportional to the amount (or concentration) of drug at any point in time
- ∴ :
  - as dose & blood conc increase; elimination rate with also increase proportionally
  - drug concentration will ↓exponentially on a concentration vs time plot
  - rate of change for 1st order kinetics =

$$\frac{dx}{dt} = kx$$

dx = plasma conc of drug x
dt = time
k = constant

- drugs with 1st order kinetics will have a constant half life irrespective of dose given
  ↳ as rate of elim directly proportional to concentration

Zero Order Kinetics

- = enzyme metabolising drug reaches max capacity & cannot ↑metabolism:↑dose
- ∴ rate of elimination does not ↑ ∝ to the dose or plasma conc
- at saturation, with ↑ing dose:
  - ↓ing CL
  - ↑$t_{½}$

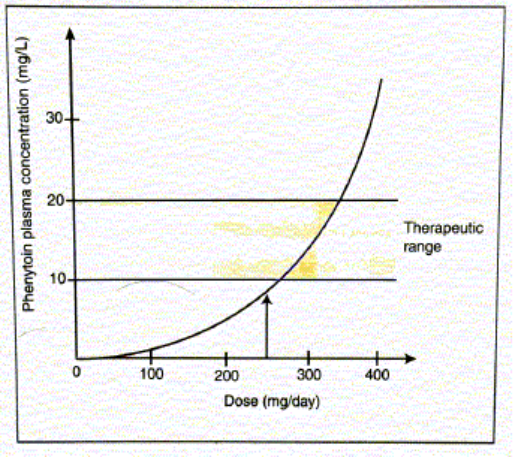
  ↳∴ small change in dose can ⇒ big ↑↑plasma conc

$$\frac{dx}{dt} = k$$

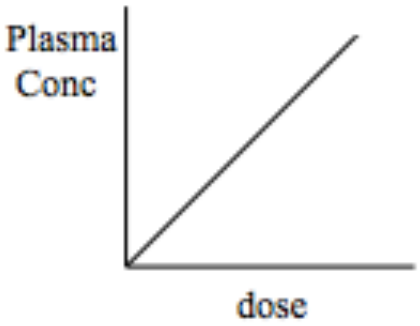
- Eg
  - phenytoin = >250mg disproportionate rise in plasma conc
  - STP
  - alcohol

Graphs to Demonstrate 1st & Zero order

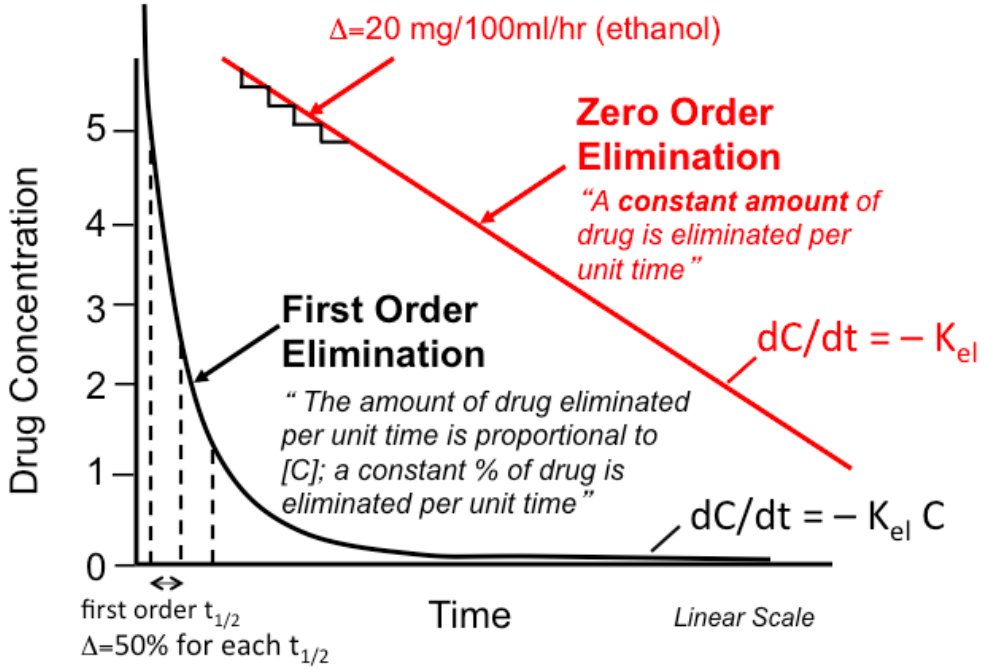
- zero order drug with ↑ing doses eg phenytoin:



- 1st order drug with ↑ing doses:

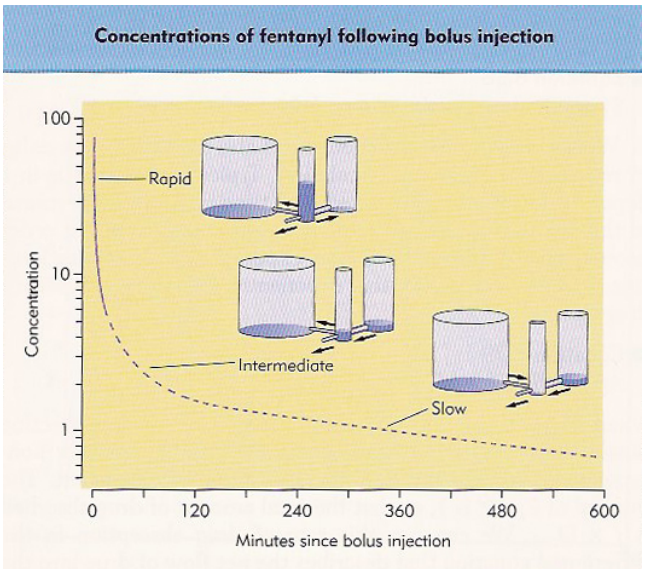


- Different kinetics After a single bolus dose:



Multicompartment Pharmacokinetics

- none of the anaesthetic drugs can really be described correctly using single compartment model
- distribution of drugs in/out of peripheral tissues plays crucial role in time course of drug effect
- IV bolus dose (eg fentanyl) plotted log concentration over time = not a straight line:



(note log-y axis)

- Conc continuously declines:
  - Initial = steep
  - Then = less steep ⇒ log linear
- Compartments:
  - Plasma
  - Rapidly equilibrating tissues
  - Slowly equilibrating tissues

  ↳ smallest ⇒ largest
- Many drugs exhibit 3 distinct phases:
  - **Rapid 'distribution phase'** (α):
    - Immed post bolus injection
    - Rapid movement of drug out of plasma ⇒
      - Either of periph compartments AND

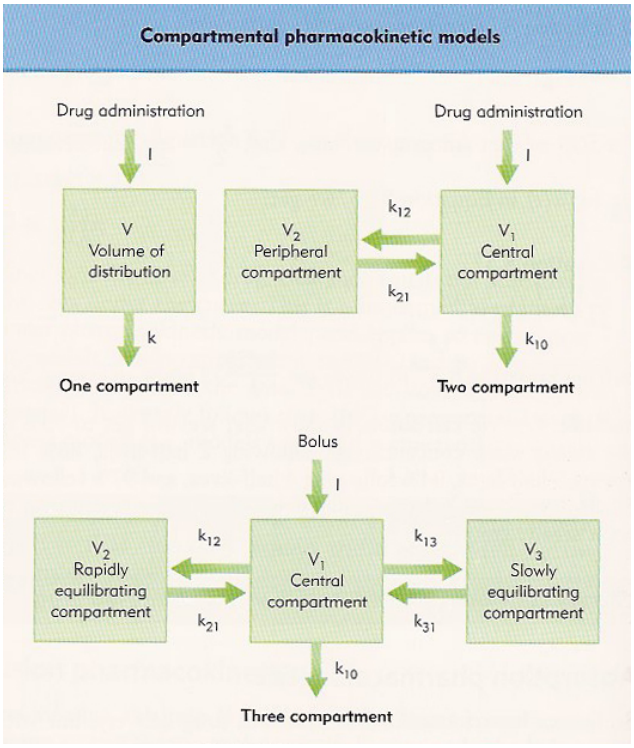
        ↳ rapid as large conc gradient away from plasma
      - Elimination (metab/excretion)

        ↳ rate of elimination (dx/dt) is highest in this phase
  - **Second 'intermediate phase'** (ß):
    - Plasma levels drop below those in rapidly equilibrating
    - ∴ net flow out of rapidly equlibriating tank ⇒ slowed rate of decline in plasma conc
    - drug leaving plasma by 2 routes:
      - slowly equilibrating tissues
      - elimination
  - **terminal phase (γ):**
    - =straight line (when plotted on semi-log graph)
    - aka elimination phase cos only mechanism for ↓ing plasma drug conc = elimination

      ↳ note elimination in this phase is much slower than phase 1&2

↳ cos plasma drug conc is less ie 1st order kinetics

- relative proportion of drug in plasma & periph volumes remains constant:
  - has reached equilibrium:
    - periph compartments draining into plasma ⇒ elimination
    - all distributions being drained by equally via plasma to elim
  - liver fighting against entire body load of drug ∴ rate of ↓ is slow



- The plasma concentrations/time after a bolus injection are the sum of 3 separate functions (A,B,C):
  - Separate functions represent 3 phases as above
  - After ~120 mins curve is usually a straight line (terminal phase)
  - Initial contribution to ↓plasma conc is mostly from A
    - ↳ then ↓in size by an order of magnitude
- Each function is assoc with a half life
- ∴ a drug with 3 functions has 3 half lives:
  - 2 rapid:
    - A = 0.693/α = distribution half life
    - B = 0.693/ß = intermediate half life
    - C = 0.693/γ = terminal half life
- Half lifes quoted in books are hard to interpret – usually = the slowest function (C or γ or terminal half life) unless otherwise stated
  - ↳may overpredict massively the time for drug conc ↓by 50%
  - ↳ie = upper limit on time needed for ↓50%
  - ↳ie actual ↓ may be much quicker

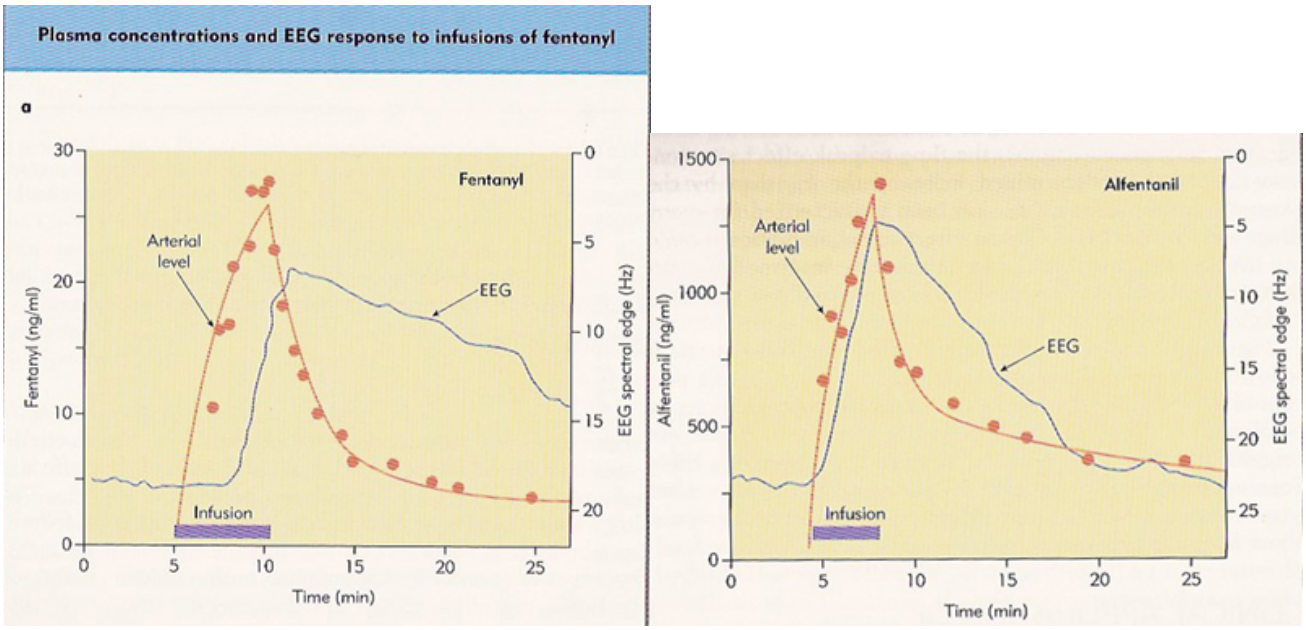
Applying Compartments to the Body

- Central compartment (V1) =
  - Rapidly mixing portion of the blood
  - 1st pass pulmonary uptake
  - eg LA's, fentanyl
- peripheral compartments:
  - rapidly equilibrating (V2) =
    - vessel rich compartments
    - eg splanchnic tissue, muscle tissue

- huge slowing equilibrating cmpt (V3)=
  - vessel poor compartments
  - eg fat, bone, connective tissue
- Vd & clearance processes remain important:
  - If drug has large Vd then = hugh amount of drug in body
    ↳eg highly lipid soluble drug = Iv induction agent

Plasma – Effect Site Equilibration

- Diagrams show time course fentanyl & alfentanil:
  - concentrations during and after a brief infusion
  - delay in onset relative to plasms conc
  - offset in drug relative to plasma conc



- delay to onset = represents time needed for drug to reach 'effect site' or 'biophase'
- the effect site is added to pharmacokinetic models via the addition of an additional compartment

- effect site compartment =
  - v small & receives almost no drug from central cmpt
  - ∴ no influence on plasma pharmacokinetics
  - is a theoretical compartment, not anatomical:

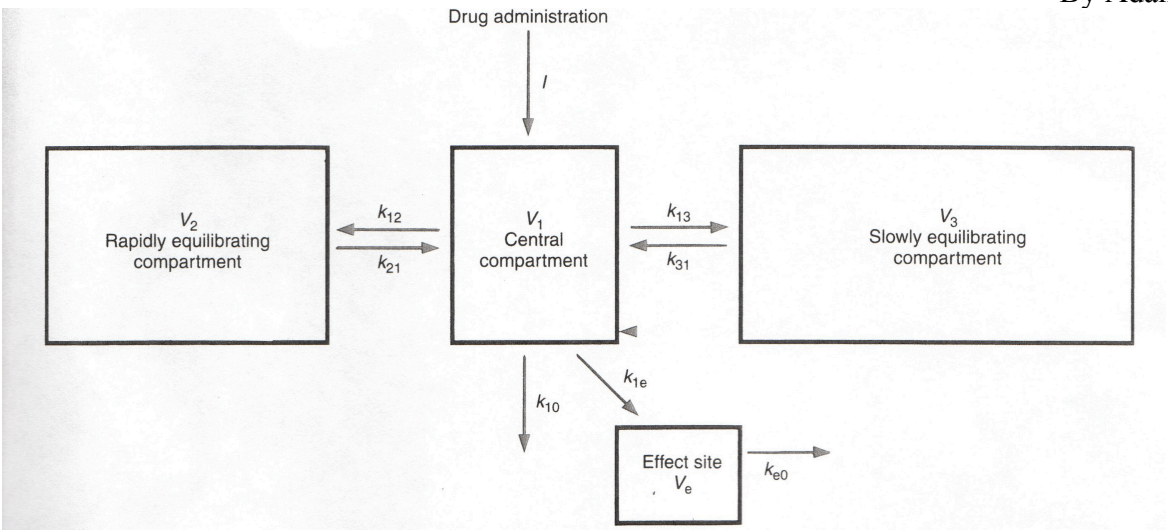


Figure 3–22 A three-compartment model with an added effect site to account for the equilibration delay between the rise and fall of arterial drug concentrations and the onset and offset of drug effect. The effect site is assumed to have a negligible volume.

- following bolus dose: onset of drug effect is function of:
  - plasma kinetics
  - $\boldsymbol{k_{e0}}$
    - = exchange constant
    - defines elimination from effect site ⇒ ∴ speed into effect site (by effecting conc gradients) ⇒ ∴ determines time course of equilibration to effect site
- drugs with very rapid ↓plasma conc after bolus:
  - effect site conc
    - peak within several secs of bolus
    - then rapid decline
    - occurs regarless of $\boldsymbol{k_{e0}}$
  - eg adenosine (half life secs)
  - occurs because plasma conc drops v quickly ⇒ lost driving pressure into effect site
- drugs with rapid $\boldsymbol{k_{e0}}$ & slow ↓plasma conc eg pancuronium:
  - time to peak effect site conc will be determined more by $\boldsymbol{k_{e0}}$ than plasma pharmacokinetics
- $\boldsymbol{k_{e0}}$ has a half life = t1/2 $\boldsymbol{k_{e0}}$
  - defines how quickly drug diffuses into/out of effect compartment
  - = half life of speed of equilibration of drug conc between plasma & effect compts
  - shorter t1/2 $\boldsymbol{k_{e0}}$ =
    - more rapid drug diffusion in/out effect site
    - ∴ quicker clinical effect
    - +/- larger clinical effect as ↑driving pressure from plasma compartment
      ↳ shown in graph below

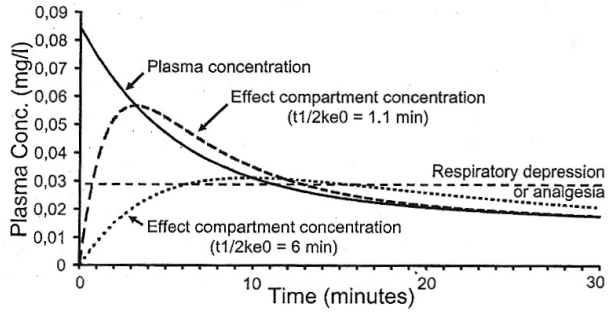


Figure 8.4
Plasma concentration-time curve of a single intravenous bolus dose of an opiate in relation to the effect compartment concentration associated with respiratory depression or analgesia for that opiate. Note the differences in effect compartment concentration curves, and hence differences in clinical effect resulting from a short versus a long $t_{1/2}k_{e0}$. Such differences in $t_{1/2}k_{e0}$ determine the clinical usage of drugs administered as intravenous boluses during anaesthesia.

- ∴ plasma overshoot is accepted in order to create driving pressure into effect site
- = concept of bolus dose ⇒ ↓time to reach peak clinical effect

- ***t1/2 k_{e0}*** has been determined for many drugs in anaesthetics:
  - rapid drugs (***quick t1/2 k_{e0}***):
    - alfentanil = 1.1min
    - thio = 1.2min
    - remi = 1.3min
    - propofol = 2.3min
  - intermediate:
    - midaz
    - fentanyl = 6.4min
    - sufentanil
    - vecuronium + panc
  - slow (***long t1/2 k_{e0}***):
    - morphine = 10-40mins

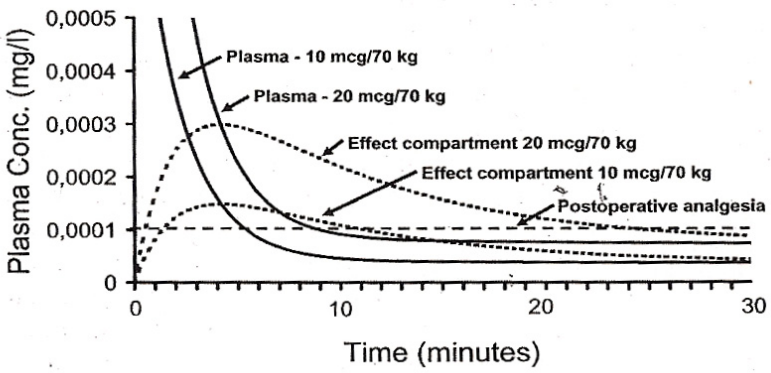


Figure 8.3

Plasma, and effect compartment concentrations of Sufentanil resulting from two different intravenous bolus doses administered to average adults. These are shown in relation to the plasma concentration of Sufentanil at which most adults experience postoperative analgesia.

Onset of Drug Effect

- most anaesthetics begin with bolus dose of IV drug
- definitions:
  - concentration (C) = amount/volume
  - desired target plasma = C_T
- Can rearrange concentration equation to find bolus required (amount) to produce C_T:

$$\text{Bolus} = C_T \times V \quad \text{ie} \quad \frac{\text{loading dose (mg)}}{\text{VD (L)} \mid \text{desired plasma conc (mg/L)}}$$

- This works for single compartment model only ie if there is only 1 volume
- Multicompartmental model = several volumes:
  - V1 = central compt
  - V2 +V3 = peripheral compts
  - V_d = sum of individual volumes
- Textbook recommendation = chose volume somewhere between V1 & V_d but range can be massive:
  - Eg fentanyl :
    - conc to dampen intubation response ~3ng/ml
    - V1 = 13litres ⇒ 3ng/ml x 13L = 39mcg
    - Vd = 360litres ⇒ 3ng/ml x 360L = 1080 mcg

- Furthermore using plasma conc to calculate bolus dose is silly cos plasma conc does not = effect site
- Better to consider time course of drug effect:
  - Need to know k_{e0}
  - Then can design dosing regime that yields desired conc at effect site
  - Eg fentanyl: plasma conc of fentanyl ↓s continuously, which effect site peaks 3-4mins after bolus
  - ∴ need to select bolus which produces desired peak conc in effct site
  - calculated based on Vd at the time of peak effect
    ↳ aka $Vd_{peak\ effect}$

$$Vd_{peak\ effect} = \frac{\text{Bolus dose}}{C_{peak\ effect}(\text{plasma})}$$

$C_{peak\ effect}$(plasma) = plasma conc at time of peak effect
= effectively C_T with a time factor

- can rearrange equation if you know $Vd_{peak\ effect}$ to find out bolus dose required

$$\text{Bolus} = C_T \times Vd_{peak\ effect}$$

- ∴ fentanyl:
  - C_T = 3ng/ml
  - $Vd_{peak\ effect}$ = 75 litres
    ↳ this factors in the known time of peak effect ie 3.6mins
  - = bolus 225mcg

Table 12–4 Volume of distribution at the time of peak effect

Drug	V_1 (L)	Vd_{pe} (L)
Fentanyl	12.7	75
Alfentanil	2.19	5.9
Sufentanil	17.8	89
Remifentanil	5.0	17
Propofol	6.7	37
Thiopental	5.6	14.6
Midazolam	3.4	31

V_1, volume of the central compartment; Vd_{pe}, apparent volume of distribution at the time of peak effect.

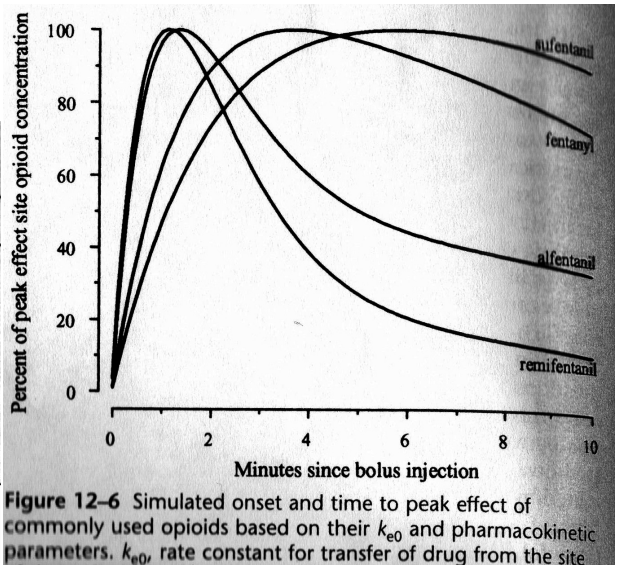


Figure 12–6 Simulated onset and time to peak effect of commonly used opioids based on their k_{e0} and pharmacokinetic parameters. k_{e0}, rate constant for transfer of drug from the site

Table 12–1 Time to peak effect and $t^1/_2\ k_{e0}$ after a bolus dose

Drug	Time to Peak Drug Effect (min)	$t^1/_2\ k_{e0}$ (min)
Fentanyl	3.6	4.7
Alfentanil	1.4	0.9
Sufentanil	5.6	3.0
Remifentanil	1.6	1.3
Propofol	2.2	2.4
Thiopental	1.6	1.5
Midazolam	2.8	4.0
Etomidate	2.0	1.5

$t^1/_2\ k_{e0}$, rate constant for transfer of drug from the site of drug effect to the environment.

Maintenance of Drug Effect

Single Compartment Model

(as discussed prev)

- steady state achieved when rate of drug administration = rate of drug elimination
  - ↳at steady state elimination rate = maintenance dose rate (MDR)
    - ↳∴ as below elimination rate = CL x Css
- clearance (CL) determines MDR required to achieve target plasma conc at steady state (C_{SS})

MDR (mg/h)	
CL (L/h)	C_{SS} (mg/L)

MDR (mg/h) = CL (L/H) x C_{ss} (mg/L)

Multi-Compartment Model

- MDR/elim rate calculations as above fail in multi-compartment models
- Drugs will distribute to periph tissues for hours during an infusion until plasma steady state reached
- ∴ single compartment equation will work BUT only when all periph tissues equilibrated with plasma
  - ↳at all other times MDR will be too slow
- strategies to overcome this :
  - starting at high infusion rate and continuously titrating downwards to avoid OD
  - use computer to solve complex equations ie TCI
- TCI mathematical modelling is limited by individual pharmacokinetic variability but in general will achieve measured concentrations within 20-25% of what is targeted

TCI Pumps

- devices contain a microprocessor with an algorithm for infusion
- eg diprifusor, remifusor, Alaris pumps
- most commonly used = TCI for propofol
  - uses a 3 compartment pharmacokinetic model
  - algorithms eg Marsh, Schnider

Calculating Bolus Dose

initial bolus dose:

- worked out using initial central volume (Vc) and target concentration (C_T)
  - ↳ following as explained prev in onset of drug section

$$\text{Dose} = C_T \times V_C$$

- for propofol:
  - Vc ~230ml/kg
  - C_T ~4-8ug/ml for typical induction
  - ∴ 70kg adult with C_T 5ug/ml:
    - 6ug/ml x (230 x70) = 9,660ug or ~100mg
- or can calculate more accurate initial bolus necessary if known $Vd_{peak\ effect}$:

$$\text{Bolus} = C_T \times Vd_{peak\ effect}$$

- $Vd_{peak\ effect}$ = 37 litres
- C_T of 4ug/ml
- = 4 x 37 = 148mg for 70kg person

Calculating Maintenance Infusion

Maintenance infusion rate (mg/min) =

$C_T . V_C.(k_{1o} + k_{12}e^{-k_{21}t} + k_{13}e^{-k_{31}t})$

units:
C x V = mg
stuff in brackets = exponential decline equation with units of 1/min

Practical Aspects of Using TCI Pumps

- variables entered by user:
  - ↳ diff variables required depending on model used
  - age
  - height
  - weight
  - desired target plasma (or effect site depending on pump) conc (1-8u/ml)
- most pumps have a minimum age limit
- in morbid obese: corrected body weight should be used (except for remifentanyl)

  CBW = (IBW) + [0.4 x(actual BWT – IBW)]

  IBW = 22 x height^2 (metres)

- user adjusts target according to clinical situation eg
  - adjuvant drugs
  - co-morbidities
  - degree of surg stim
- computer designs a variable infusion rate
- actual plasma conc do no get measured but are predicted by algorithm:
  ↳diff to volatiles where ET concentrations of volatile are measured
  - predictions done on healthy volunteers ∴ will vary in clinical setting
  - accuracy ~25%
  - use careful monitoring and titration to effect
- changing target conc alters bolus & infusion in order to get rapid achievement of new target:
  - ↑ed target ⇒ bolus & ↑infusion rate
  - ↓ed target ⇒ cease infusion until predicted plasma conc correct level then infusion restarted

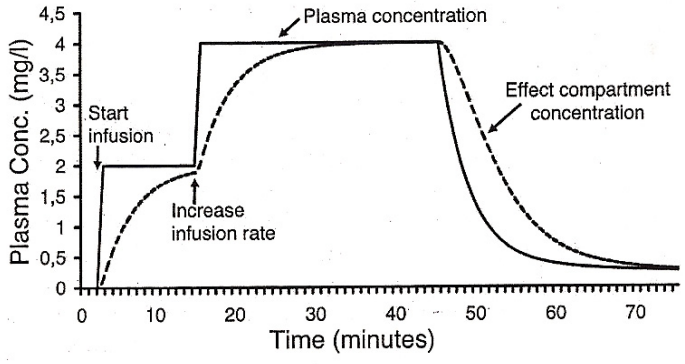


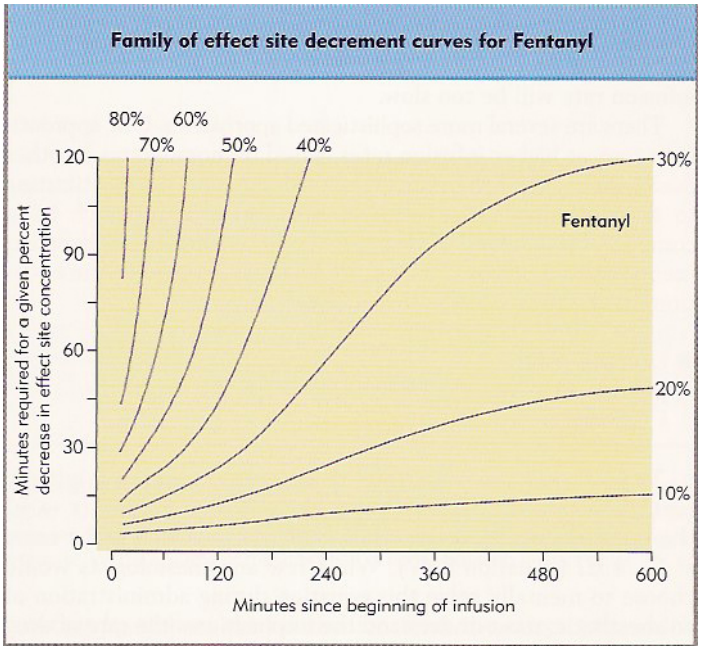
Figure 9.4

Theoretical possible plasma concentration-time curve for Propofol administered by a modern computer controlled TIVA pump with effect compartment steering. As can be seen, such modern TIVA pumps can administer step-wise increments in plasma drug concentrations, which are followed by changes in effect compartment concentrations. These are active processes controlled by the perfusor pump. However, reduction of plasma and effect compartment drug concentrations is a passive process set in action by reducing the infusion rate, or by stopping drug administration. Drug concentrations then decline due to plasma elimination, as well as exchange of drug between other compartments and the central compartment.

- some pumps allow target of effect site concentration (rather than plasma) :
  - done by accounting for effect site plasma equilibrium rate constant (k_{e0})
  - means can maintain this at a constant rate preventing effect site overshoot
    ↳NB if want rapid plasma conc target then some overshoot of plasma target conc required

Offset of Drug Effect

- As mentioned prev: offset of drug will be somewhere between:
  - t1/2α (distribution)
  - t1/2γ (terminal)
- t1/2γ = sets upper (or slowest possible) limit for how long it will take plasma conc to ↓by 50%
- anaesthetic drugs will always be faster because of multicompartment pharmacokinetic profile
- Need to use effect site decrement curves:
  - shows relationship between a
    - TCI infusion (designed to maintain constant effect site conc) AND
    - time required for decrease in effect site conc
      ↳use various lines to define how much % decrease you want and how long it will take



- diagram shows:
  - if only looking for a 10% drop (after stopping infusion) then the length of infusion isn't that impt
    ↳ie infusion length of 600mins = ~15mins to see 10% ↓ in effect site
  - BUT if looking for a 50% (or above) drop then time of infusion is v impt:
    ↳ie infusion length of 60mins = ~45mins;
    infusion length of 240mins = off the chart high >120mins
- impt concept is that these decrement curves are **not** influenced by TCI dose:
  - lines show % drops from whatever dose
  - dose can be very high or very low % change will still occur:
    - but if you run a v high TCI: you will obviously need it to fall by a bigger % to allow someone to eg start breathing at end of op AND that will take more time!

  ↳ what does effect decrement curves =
    - duration of infusion
    - distribution to & from periph compts
    - clearance
- other decrement curves:

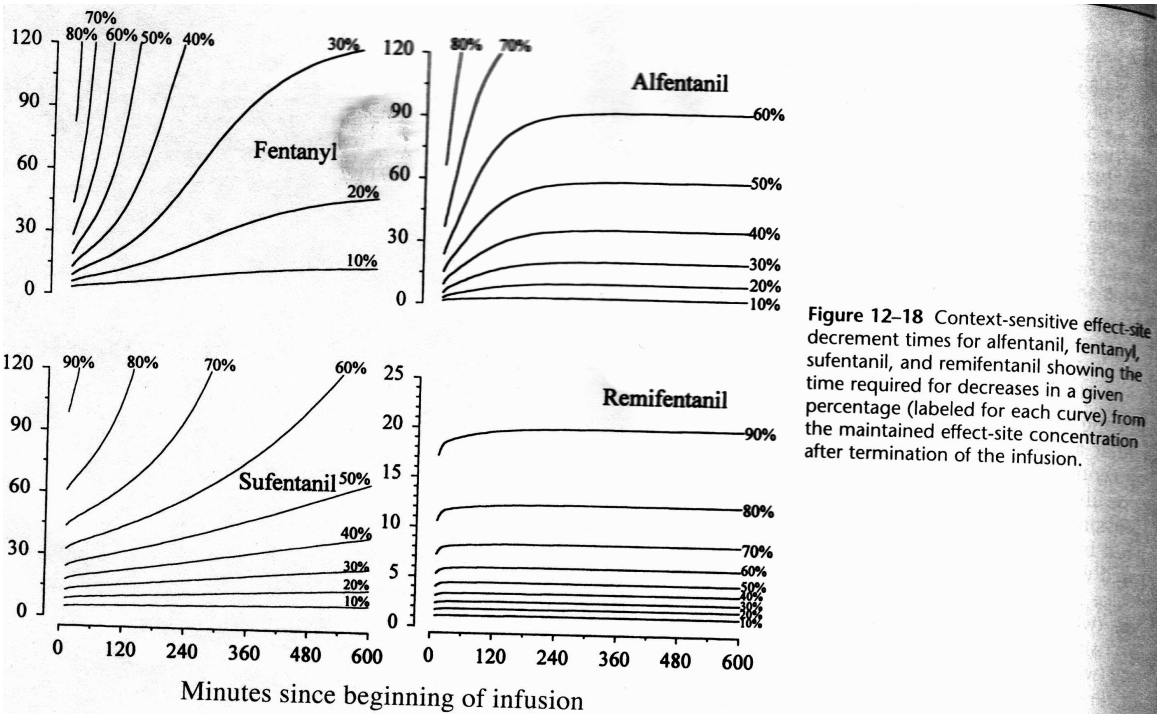


Figure 12–18 Context-sensitive effect-site decrement times for alfentanil, fentanyl, sufentanil, and remifentanil showing the time required for decreases in a given percentage (labeled for each curve) from the maintained effect-site concentration after termination of the infusion.

- points of interest:
  - remifentanyl : no accumulation occurs even though t/12γ (terminal) = 90mins
  - fentanyl, alfentanil, sufentanil have pretty similar derements if infusion <30mins
  - >30mins sufentanil shows quicker decrement – even though has the longest t1/2γ of all of them!!
    (↳ except 60% at v long infusions)

Summary of Using IV Drug Infusions

- BET scheme:
  - B = bolus dose. based on calculations either for single or multicompartment models
  - T = transfer & maintenance
    - movement of drug from V1 to V2 & V3
    - need to account for this in maintenance dosing
    - early in infusion this will be dependant on Vd>clearance
  - E = elimination
    - late in infusion plasma conc will depend on clearance>VD
      ↳ as VD will be closer to it's steady state
    - here elimination = clearance x plasma conc (Css)
- Bristol Infusion for manual propofol TCI:
  - 2mg/kg bolus
  - 10mg/kg/hr infusion for 10mins
  - 8mg/kg/hr for 10mins
  - 6mg/kg/hr thereafter

Context Sensitive Half Time ($CST_{1/2}$)

NB = not half-life!!

- modelling performed in animals only
- $CST_{1/2}$ = relationship between duration of an infusion & 50% offset or decrement in **plasma** conc
  (↳ie not effect site decrement)
- context refers to **duration** of an infusion that maintains a **steady drug conc** in plasma
- factors effecting $CST_{1/2}$:
  - clearance
  - distribution – into & out of perpiph compts
  - duration of infusion

  ↳ ie same as effect site decrement curves

remember: single compartment models, elimination half life is different:

$$t_{½} = \frac{0.693 \times V_D}{CL}$$

- anaesthetic drugs have relatively rapid plasma-effect site equilibration ∴ indistinguishable:
  - context sensitive plasma half time
  - 50% effect site decrement times
- computer simulations needed to predict time course of recovery following drugs into multicompartments:
  - computer plots CST1/2 for continuous infusions & then validates them against testing

Drug Examples

Propofol

- high clearance = 30ml/kg/min
- large Vd
- ↳ both these ∴ CST1/2 reasonably stable over wide period of infusion times:
  - ~20mins after 2hrs
  - ~30mins after 6hrs
  - ~40mins after 8hrs
- (k_{e0} = 0.29*1*/min and $t_{1/2ke0}$ = 2,4 min)

Thiopentone

- clearance undefined due to zero order kinetics
  - offset of action post bolus is due to redistribution to periphery
- if given as infusion: soon saturates periph compartments ⇒ dramatic ↑CST1/2
- ∴ unsuitable for TIVA
- as duration of infusion continues, CST1/2 approachs the elimination half life (11.6hrs)
  - CST1/2 after 3hrs = 85mins

Remifentanyl

- high clearance = 70ml/kg/min
  ↳due to breakdown by non-specific plasma esterases
- low Vd = 0.3L/kg
- ∴ considered context insensitive
- CST1/2 = same regardless of infusion 3mins
- ∴ ideal for infusions

Fentanyl

- moderate clearance = 20ml/kg/min
- very large Vd (highly lipid soluble)
- ∴ CST1/2 ↑s dramatically with ↑ing infusion time:
  - 260mins after 4hrs
- dramatic ↑ing CST1/2 explained by:
  - fentanyl extreme lipid solubility into adipose (∴ large VD)
  - moderate clearance
  - ∴ big store of drug needing to return to plasma when infusion stopped ⇒ maintenance of plasma conc

  ↳means CST1/2 can exceed elimination half life (190mins) of fentanyl if given as single big bolus
- CST1/2 examples:
  - 40mins after 2hrs
  - 70mins after 3hrs
  - 4hrs after 6hrs
  - 5hrs after 9hrs

Alfentanil

- lower clearance than fentanyl **but** has very small Vd
- ↳ explains relative stability of its CST1/2 in contrast to fentanyl
- CST1/2 example:
  - 40mins after 2hrs
  - 70mins after 6hrs
  - 80mins after 9hrs

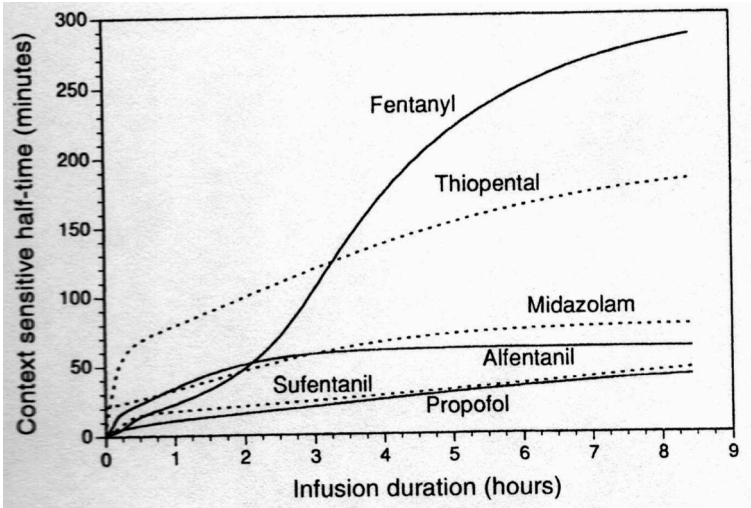


Figure 12–17 Context-sensitive half-times as a function of infusion duration (the "context") derived from pharmacokinetic models of fentanyl, sufentanil, alfentanil, propofol, midazolam, and thiopental. (From Hughes MA, Glass PSA, Jacobs JR: Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. Anesthesiology 76:334-341, 1992.)

By Adam Hollingworth

Pharmacokinetic Figures For Drug Classes

INDUCTION AGENTS

DRUG	MW	pKa	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	V_c (l/kg)	V_d (l/kg)	Cl (l/kg/h)	EC_{50} (hypnosis) (mg/l)	$t_{1/2}k_{e0}$ (min)
Thiopentone	264.33	7.6a	3.3[2]	781	0.128	3.5	0.19	10	1.2
Methohexitone	284.3	7.9a	5.6[3]	234	0.35	3.7	0.65	3.4	
Hexobarbitone	236.26		23.4[4]	299	0.54	1.4	0.2	10	
Ketamine	237.74	7.5b	11[5]	151	0.86	4	1.1	1	
Etomidate	244.28	4.24b	2.6[6]	67	0.3	2.2	1.39	0.21	1.6
Propofol	178.3	11.1b	2.5[7]	55	0.63	4.7	3.55	2	2.9

ANTICHOLINERGICS

DRUG	MW	pKa	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	V_c (l/kg)	V_d (l/kg)	Cl (l/kg/h)	EC_{50} (tachycardia) (mg/l)	$t_{1/2}k_{e0}$ (min)
Atropine	289.38	9.8b	1.7[8]	180	0.09	1.6	0.41	0.03	
Scopolamine	303.35		5.4[8]	114	0.2	1.1	0.86	0.03	

ANTAGONISTS & ANALEPTICS

DRUG	MW	pKa	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	V_c (l/kg)	V_d (l/kg)	Cl (l/kg/h)	EC_{50} (mg/l)
Naloxone	327.37	7.82b	1.8[30]	19	0.81	2.4	5.3	?
Doxapram	378.5		5.3[31]	54	0.44	3.2	0.36	2-3
Physostigmine	275.34		2.3[32]	22	?	0.6	1.2	0.004
Flumazanil	303.3		?[33]	58	?	0.82	0.6	0.02

INOTROPIC DRUGS

DRUG	MW	pKa	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	V_c (l/kg)	V_d (l/kg)	Cl (l/kg/h)	EC_{50} (mg/l)
Adrenaline	183.2		3.1[34,35]	10.9	?	1.89	7.2	0.0001
Nor-adrenaline	205.2		2[36]	34	?	1.96	2.4	0.0018
Isoprenaline	247.72		3[37]	240	?	?	?	?
Ephedrine	165.24		?[38]	405	?	3.18	0.36	?
Dopamine	153		0.9[39]	9.2	?	0.89	4.32	0.07
Dobutamine	337.84		?[40]	2.37	?	0.2	3.6	0.042
Digoxin	781		?[41]	41.2 hr	?	14.5	0.258	>0.0008

OPIATES

DRUG	MW	pKa	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	V_c (l/kg)	V_d (l/kg)	Cl (l/kg/h)	EC_{50} (postop. analgesia) (mg/l)	$t_{1/2}k_{e0}$ (min)
Morphine	285.33	7.93b	4.4[19]	111	1.01	5.4	2.01	0.015	
Methadone	345.9	9.26b	6.1[20]	2100	1.1	8.2	0.016	0.03	
Pethidine	247.34	8.5b	4.1[21]	192	0.63	3.3	0.72	0.46	
Pentazocine	285.44	9.16b	?[22]	204	?	5.6	1.2	0.1	
Buprenorphine	504.1	8.51b	2.1[23]	140	0.132	2.69	0.8	0.001	
Piritramide	416.5		4[24]	480	0.7	4.7	0.47	0.012	16.8
Phenoperidine	403.9	8.01b	2.2[25]	193	0.9	6.13	1.32	0.005	
Fentanyl	528.61	8.4b	9[26]	263	0.77	3.81	0.65	0.001	6.4
Alfentanil	471	6.5b	3.8[27]	67	0.17	0.54	0.33	0.1	1.1
Sufentanil	578.69	8.01b	1.4[28]	164	0.16	2.9	0.76	0.0001	5.8
Remifentanil	412.92	7.07b	?[29]	9.52	?	0.35	2.5	0.005	1.3

ANTICHOLINESTERASES

DRUG	MW	pKa	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	V_c (l/kg)	V_d (l/kg)	Cl (l/kg/h)	EC_{50} (mg/l)	$t_{1/2}k_{e0}$ (min)
Neostigmine	334.39		3.4[9]	77	0.22	1.02	0.55	?	
Edrophonium	246.15		7.2[9]	110	0.32	1.53	0.58	?	
Pyridostigmine	261.14		6.8[10]	112	0.3	1.4	0.52	?	

MUSCLE RELAXANTS

DRUG	MW	pKa	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	V_c (l/kg)	V_d (l/kg)	Cl (l/kg/h)	EC_{50} (mg/l)	$t_{1/2}k_{e0}$ (min)
Gallamine	891.56	>13b	6.7[11]	144	0.1	0.23	0.065	7.2	
Tubocurarine	771.84	8.6b	6.2[12]	119	0.1	0.39	0.135	0.63	4.7
Alcuronium	737.8		13.8[13]	199	0.13	0.4	0.083	0.66	
Pancuronium	732.7	>13b	10.7[14]	114	0.12	0.3	0.11	0.27	3.3
Vecuronium	637.75		7.5[15]	53	0.09	0.4	0.32	0.15	3.7
Rocuronium	609.7		14.8[16]	97.2	0.038	0.21	0.22	2	4.3
Atracurium	1243.51		2[17]	21	0.07	0.2	0.32	1.13	5.9
Mivacurium	1100.18		?[18]	2	?	0.2	4.2	0.1	6.9

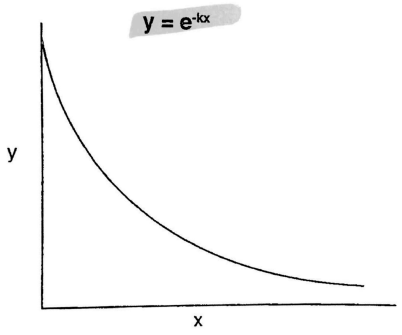
By Adam Hollingworth

Exponential Functions

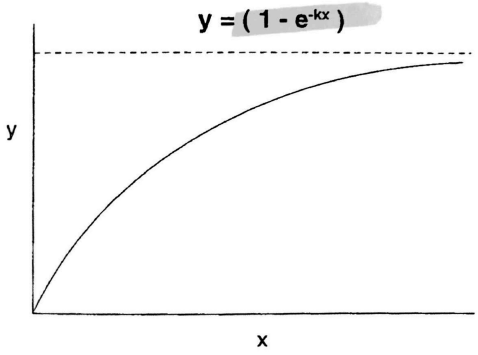
- = rate of change of a quantity at any time is proportional to quantity at that time.
- Time taken to complete is inherently infinite
- demonstrated in zero order & first order kinetics
- clinically use time constants
    - = time for an exponential function to complete if the initial rate of change had been allowed to continue
    - see resp section for examples of time constants in fast & slow alveoli

Graphs

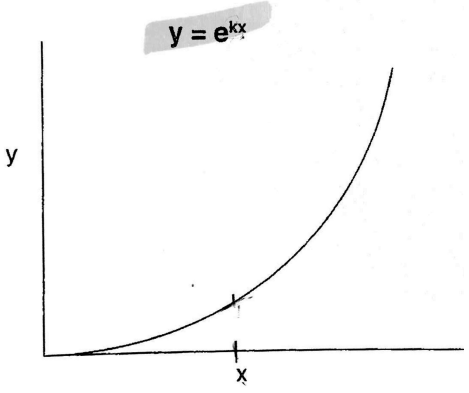
- e = a constant. is a base natural logarithm
- k =
    - rate constant
    - proportional to gradient at x
    - in multicompartment model k = 0.693/t
- y = conc of substance
- x = time
- Washout curve: (eg washout of volatile)



- buildup or wash in curve: (eg washin of O2 into FRC during preoxygenation)



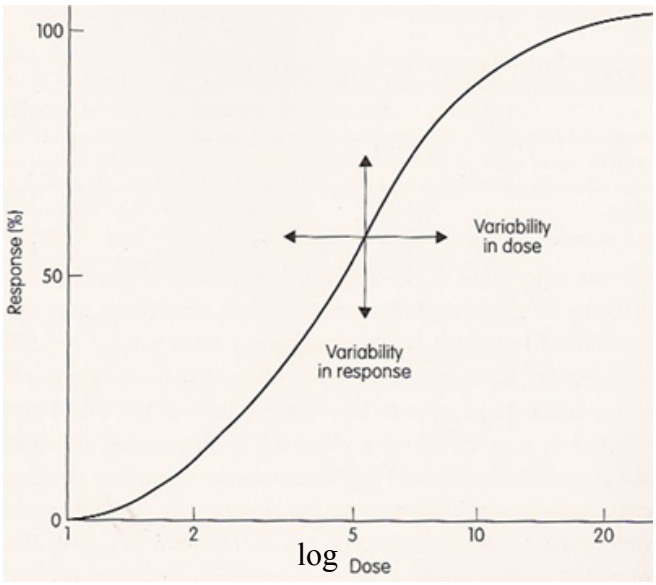
- runaway curve: (initial growth of bacterial colony from a single cell)



By Adam Hollingworth

Variability in Drug Response

- = wide variability in response of
  - diff people to identical doses of same drug
    ↳variability in response
  - same person to identical dose of drug but on different occasion
    ↳variability in dose
- dose-response curves:
  - used to reflect results from homogenous population of subjects
  - sigmoid log dose-response curve represent average results in population
  - vertical/horizontal arrows represent inter-individual variability



- vertical arrow = range of effects observed in population adter same dose of drug
- horizontal arrows = range of drug dosage needed to produce specified pharmacological effect in individual subjects

Causes of Variability in Drug Response

- classification:
  - physiological factors
  - pharmacological factors
  - pathological factors

Physiological Factors

- physiological and social factors causing variability:
- sub categories:
  - age
  - pregnancy
  - tobacco
  - alcohol

Age

- easy rule of 30 for calculating drug doses in kids:
- correlates well ith BSA
  - if weight <30kg ⇒ x body weight by 2 = % of adult dosage
  - if weight >30kg ⇒ add 30 to weight = % adult dose
- differences in pharmacokinetic & pharmacodynamics due to:
  - body composition
  - protein binding
  - distribution CO
  - maintainenance of BBB
  - functional maturity of liver/kidney/lungs
  - receptor sensitivity

Childhood

- variation mostly due to pharmacokinetic differences (ADME)
- may be pharmacodynamics differences but difficult to assess

Absorption

- in neonates:
  - stomach alkaline ⇒ ↑absorb acid labile drugs eg penicillin; ↓phenytoin
- Prolonged gastric emptying time⇒ ↑pencillin in; ↓phenytoin
- Skin thin & permeable

Distribution:

- ↓adipose content
  - ↳∴ water soluble drugs have larger volume of distribution compared to fat soluble
- ↑permeability of BBB

↳ both may contribute to lipid soluble drug accumulating in CNS

- ↓pH of neonate ⇒ affect ionisation of drug
- ↑ed total body water:
  - prem TBW= 87%
  - 3 months TBW = 73%
  - adult TBW = 55%

  ↳∴ if drug water soluble & simply scale down adult dose/kg then will ⇒ underdosing in kid
- ↓PPB – highly protein bound drugs need ↓dose to avoid toxicity

metabolism:

- Delayed maturation of hepatic enzymes:
  - Some enzymes rapid surge in acitivity eg CYP2E1
  - Others take months eg CYP1A2
  - UGTs similar profile eg paracetamol:
    - Glucuronidation ↓ed in newborn/infants (UGT1A6 & UGT1A9)
- age spread:

- neonates = immature enzyme activity
- adult levels after months
- older kids = may metabolise drug faster due to relatively large liver
- hepatic metabolism = adult at ~ puberty/10yrs

Excretion:

- ↓GFR:
  - neonate RBF = 5% of CO at term
    ↳eg drugs eliminated by renal route v slowly cleared eg digoxin, gentamicin
  - = ~adult level (25% of CO) @ 1yr
- ↓tubular secretion
  ↳ = adult @ 12 months

Others Factors

- Lungs lack mucus barrier
- Poor regulation of body temp
- Easily dehydrated

Practical Aspects Per Age Group

- neonates:
  - weight related doses of water soluble drugs ⇒ underdosing compared to adults
    ↳overcome by using doses based on bsa rather than weight
  - longer dosing intervals more appropriate
    ↳cos of ↑Vd & ↓Cl (esp renal) ⇒ ↑t1/2 elimination
  - NDNMB's = dosing requirements unexpectedly unchanged – reasons complex
  - Opiods = Some neonates show abnormal responses:
    - ↓sensitive to analgesic properties
    - ↑sensitivity to resp depression effects

    ↳due to different distribution mu1 & mu2 receptors
- @1yr old – absorb/distribution & excretion = adult
  ↳hepatic metab remains altered until >10yrs (puberty)
- older kids:
  - ie PPB, liver enzyme activity, renal func et = adults
  - still best to calculate dosage based on BSA due to ↑ed proportional body water
  - more frequent dosing may be needed (esp lipid soluble drugs)
    ↳due to ↑ed metabolism 2nd to ↑ed liver blood flow

Topical Meds in Children

- Children have
  - a larger BSA
  - ↑cutaneous perfusion
  - ↑ed hydration of skin layers
  - Neonates have a thinner stratum corneum which is v permeable

  ↳∴ ↑ed risk of toxicity for cutaneous absorption in children

Examples by Drug class

- volatiles:
  - PK differences:
    - ↑ed uptake due to ↑V_A & ↑CO
      ↳ MV = doubled to 220ml/kg
      ↳ CO is proportionally less ↑ed ∴ see ↑ed onset of volatiles
    - age related diffs in blood:gas partition coefficients may explain rapid rise in P_{Alv} in neonates
  - PD Diffs:
    - biphasic MAC responses:
      - prem & early neonates = lower MAC

- infants between 28days to 1 yr = MAC > adults
  ↳not well understood
  ↳ >1yr old MAC ↓ 6% /decade

- water soluble drugs ie neuromuscular blockers = use same dose:
  - PK:
    - high TBW% (even more in prem babies) ⇒ higher V_D & longer t1/2 elimination
    - immature renal & hepatic clearance mechanisms ⇒ longer t1/2 elimination
  - PD:
    - ↑receptor sensitivity - ?due to epsilon subunits instead of gamma in nicotinic receptors
    - BUT dose/kg same due to larger V_D
      ↳ note duration of action is longer though as per PK
- lipid soluble drugs ie Opioids (↓↓dose):
  - PK:
    - small fat compartments ⇒ ↓ed V_D
    - ↓hepatic metabolism ⇒ longer action
    - ↓renal clearance of active metabolite M6G ⇒ longer action
  - PD:
    - ↑sensitivity – esp to resp depressant effects
    - possible mechanisms:
      - immature BBB
      - changes to opioid receptor
      - PK changes ⇒ ↓clearance ⇒ ↑serum concentrations

Elderly

- Again predominant effect is pharmacokinetics
  ↳Some pharmacodynamics factors do exist
- Polypharmacy big issue

Absorption

- **Not that impt. Issues as children:**
  - slower gastric emptying time
  - alkalisation of gastric juices
    ↳↑risk of stomach irritation from eg aspirin

Distribution

- ↑proportion of body fat ⇒
  - ↓Vd water soluble drug distribution ⇒ ↑plasma & effect site concentraions ie overdosing
  - ↑Vd of distribution of lipid soluble ⇒ under-dosing
    ↳should shift from age to weight based dosing
- ↓total body water ⇒ ↑risk of toxicity with water soluble drugs
  ↳eg digoxin, lithium, gent
- ↓PPB 2nd to ↓albumin ⇒ ↑free fraction some drugs which highly PPB eg phenytoin
- Bbb more permeable – esp by lipid soluble drugs eg B Blockers ⇒ dizzy & confusion

Metabolism

- @65yr:
  - ↓45% liver blood flow – impt for drugs with high extraction ratio
  - ↓45% enzyme activity:
    - functionalisation reactions effected by aging
      ↳ie reduction, oxidation, hydroxylation, demethylation
    - conjugative metabolism not effected
      ↳ie glucoronidation, acetylation, sulfonation
  - ↓liver size
- ∴ bioavailability of drugs subject to high hepatic clearance is ↑ed eg propranolol/nitrates ⇒ risk of toxicity

Excretion

- renal changes
  - ↓renal blood flow & ↓total no of nephrons⇒ ↓GFR⇒ toxicity of drugs (esp water soluble drugs)
    ↳∴ for drugs highly dependant on kidneys for excretion ⇒ ↑half life & ↑plasma conc
    ↳eg aminoglycosides, cipro, dig, lithium, furosemide

- ∴ overall effect in elderly is ↓ed:
  - drug metabolism
  - distribution
  - renal excretion

  ↳eg diazepam half life 20hrs in 20yrs ⇒ 90hrs in 80yr+

Alterations in Pharmacodynamics

- ↓↑ target organ or receptor sensitivity
  - unknown cause
  - example
    - ↑sensitivity to opioids
    - ↓ed response to β-agonists & antagonists
    - Less sensitive baroreceptor response ⇒ ↑effect of antihypotensives & diuretics ⇒ post hypotension/collapse
    - altered periph venous tone – egagertes antiHTs & diuretics
    - ↑response to benzos (CNS depression)
    - ↓muscarinic receptor density in cortex ∴ very sensitive to antimuscarinic drugs
      ↳SEs antimuscarinics: confusion, dry mouth, blurred vision, constipation, urinary retention
- ∴ elderly have ↑sensitivity to drugs, especially CNS medications
- MAC of all volatiles progressively ↓s with age
  ↳ similar data for IV induction agents ∴ likely pharmacodynamics cause for ↑ed sensitivity

Drug Use in Pregnancy

See later section on Obstetrics in Pharmacology

Tobacco

- Smoking ⇒ induction of some hepatic enzymes – esp CYP1A2
- ∴ rates of drugs eliminated via this route ⇒ ↑↑
- studies also show smokers:
  - need more opiates
  - less effected by benzo's
  - get less angina pain relief from BB's & CCBs (?PG effect)

Alcohol

- chronic use of alcohol ⇒
  - ↑capacity of liver to metabolise it
  - pharmacodynamics tolerance
- cross tolerance between sedatives & alcohol occur due to PK & PD mechanisms:
  - GABA changes:
    - changes in GABA availability
    - alteration number of GABA receptors
    - change in nature of GABA receptors

  (↳although thiopentone = tolerance @ cellular level (because duration of action is terminated by redistribution rather than metabolism))
- after acute ingestion of alcohol:
  - addition of other CNS depressants ⇒ supra-additive effects
  - ↑half life barbituates ?due to competition for liver enzymes

Pharmalogical Factors

- subclassification:
  - idiosyncrasy
  - supersensitivity
  - tolerance/tachyphylaxis
  - hypersensitivity

Idiosyncrasy

- = genetically determined abnormal reaction to a drug
- term also been used to describe side effects to certain drugs in certain pts eg N&V to opioids
  ↳side effects disappear when diff drug in same class used
- underlying mechanisms unclear
- may present as:
  - extreme sensitivity to low doses
  - marked insensitivity to high doses
- impt examples of idiosyncrasy:
  - sux-apnoea
  - malignant hyperthermia
  - haemolytic drug reactions
  - slow acetylators – toxic effects of certain sulpha drugs
  - heridatory resistance to oral anticoagulants
  - acute hepatic porphyria:
    - precipitated by certain drugs in genetically susceptible pts
    - implicated drugs = inducers of enzyme delta amino-lae-vu-linic acid (ALA) synthetase
    - administration ⇒ ↑hepatic production ⇒ ↑urinary excretion of porphyrins ⇒ widespread demyelination of periph & central nerves ⇒ sensory changes & motor paralyses
    - eg drug classes:
      - barbituates
      - phenytoin
      - alcohol
      - sulpha's
      - sulphonylureas
      - OCPs
      - Certain steroids

Supersensitivity

- = hypersensitivity to a drug when receptor up regulation has previously occurred
- eg adrenoreceptors:
  - up regulation occur when period of
    - ↓ed catecholamine production eg following drug Rx or symp denervation
    - chronic Rx BB's, clonidine, minoxidil
  - ∴ acute reintroduction or withdrawal ⇒ exaggerated response
- eg hyperkaelaemia following severe burns or spinal cord inj & sux use
  ↳extrajunctional n-Ach receptors

Tolerance

- ie change in no. or action of receptors
- depeletion of transmitters

↳ see prev

Hypersensitivity

- see physiology notes:
  - type 1 – immediate type
    - more common with penicillins, sulpha's, muscle relaxants or stings, ingestion of proteins
  - type 2 – cytolytic reactions:

        - drugs combine with proteins in cell of rbc, wbc, plts ⇒ antibody creation
        - IgEs & IgMs then cross react with antigenic sites in cell membrane ⇒ various type 2 responses
        - Eg:
            - Haemolytic anaemia 2nd to sulpha's or methyldopa
            - Agranulocytosis 2nd to phenothiazines, antithyroid drugs
            - Thrombocytopaenia 2nd to thiazide diuretics
            - Halothane hepatitis may be type 2 HS reaction
    - type 3 – immune complex mediated responses
        - some drugs may act as haptens ⇒ serum sickness eg sulphas, pencillins
        - key features:
            - no prior exposure to drugs needed
            - need ongoing continuous production of antibdoes esp IgG
            - serum sickness usually self limiting requiring no Rx
    - type 4 – cell mediated or delayed type:
        - involved in:
            - +ve Mantoux
            - contact dermatitis – metals or drugs
            - drug rashes:
                - erythema multiforme/Stevens Johnson
                - morbilliform rash with amoxicillin in pts with CLL or glandular fever
- anaphylactoid reactions:
    - due to release of vasoactive substances from mast cells or circulating basophils after drug dose
        ↳eg histamine, 5-HT
    - mechanism is via direct or non-immunological mechanisms:
        ↳ie do not require Ig cross linkage
        - direct histamine release from mast cells – NMBs + morphine
        - complement activation – classical or alternative pathways
    - compared to anaphylaxis:
        - prior exposure not needed
        - IgE not involved
        - Severity of reaction usually dose dependant
        - Usually less severe than anaphylaxis
    - Many drugs can trigger eg IV induction agents, NMBs, ganglion blockers, contrast media, colloid

Pathological Variability Factors

- Mostly due to organ dysfunction:
    - Liver disease
    - Renal disease
    - Resp disease
    - Cardiac disease
    - Neurological disease
    - Endocrine disease

Liver Disease

- Can affect drug clearance via diff mechanisms:
    - Alterations in heaptic blood flow:
        - Obstruction
        - General anaesthetic:
            - ↓ed CO & redistribution of blood flow to periph (vasoD) ⇒ ↓hepatic clearance
            - ∴ elimination of drugs with high hepatic clearance will be ↓ed
                ↳ eg opioids, LA's, BB's
    - PPB changes eg cirrhosis

  - Changes in intrinsic clearance eg cirrhosis
  - May be assoc with ↓renal flow – hepatorenal syndrome
- Eg pancuronium:
  - Alteration in hep flow ⇒ ↓ed Clearnace & ↑ed duration of action
  - Cirrhosis & ↓PPB ⇒ ↑Vd ⇒ ↓plasma conc ⇒ ↓ed uptake at receptor sites
- Eg thiopentone: ↓PPB, ↑free fraction, ↑ed t1/2 ⇒ ↓ed dose requirement & ↑ed duration of action

Renal Disease

- Many drugs & their metabolites are wholly or partly eliminated by kidneys
- ∴ prolonged duration of action +/- toxic effects expected with ↓renal function
- elimination of acidic drugs further complicated by accumulated organic acids which competing for tubular secretion transporters
  ↳eg penicillin, NSAIDs
- alterations in PPB also possible:
  - acidic drugs binding to (normally) albumin ⇒ ↓ed
  - basic drugs show variable response but ↑free fraction or some drugs eg diazepam, morphine

Thiopentone

- dosing ↓ed:
  - ↑free fraction
  - ?altered permeability of BBB
  - ?abnormal cerebral metabolism

Opioids

- opioids & metabolites partly cleared by kidneys
- active metabolites may accumulate:
  - morphine = M6G:
    - M6G has 24hr half life which renally excreted
    - ∴ accumulation in renal failure
  - pethindine = nor-pethidine
- fentanyl undergoes rapid/extensive liver metabolism ∴ good in renal failure

Muscle Relaxants

- apparent resistant to onset of blockade
  ↳?due to altered distribution with changes in PPB
- renally cleared:
  - pancuronium = 40-50%
  - gallamine >90%
  - tubocurarine = 40-50% renal clearance BUT if ↓renal function then see reciprocal ↑bilary excretion
  - atracurium & mivacurium = 0%
    ↳laudanosine = breakdown product of atrac may accumulate but of no significance

  ↳minimal effect on vecuronium & rocuronium as mainly liver/bile excreted
- NB reparalysis after reversal is unlikely in renal failure as clearance & elimination of anticholinesterases ↓s in parallel with NDNMBs
- Variability to sux only occurs if there is also hyperkalaemia

Others

- Diazepam - ↓ed elim of active metabolites (nordiazepma, temazepam)

Respiratory Disease

- COPD:
  - Resp centre ⇒ ↓ed sensitivity to CO2 ⇒ hypoxic drive
  - ∴ resp depressive effects of opioids, IV induction, benzo's agents exaggerated
- acid base changes:
  - (and electrolyte imbalance)
  - may ⇒ variable responses to muscle relaxants eg resp acidosis ⇒ ↑ed duration of action

- V/Q abnormalities:
  - Rate of induction with highly soluble volatiles can be delayed eg halothane
  - less soluble agents (eg des) = less affected cos compensatory ↑s in alveolar concentrations seen

Cardiac Disease

- All GA agents can ⇒ depressant effects on diff CVS parameters:
  - Contractility
  - Coronary flow
  - SVR
  - Baroreflex activity

  ↳effects exaggerated in pts with ↓ed reserve from diseased states

  ↳Eg thiopentone induced myocardial depression in pt with constrictive pericarditis ⇒ profound hypotension / pulmon oedema

  ↳Eg volatiles in CCF may be of benefit by ↓cardiac work by ↓ing SVR

- Pharmacokinetic effects of cardiac disease mediated by ↓ed CO:
  - ↓distribution
  - ↓elimination

  ↳eg muscle relaxants & speed of onset
- drug with sig muscarine effects can sensitise heart to arrhythmias in response to circulating catecholamines eg sux & halothane
- steal effect:
  - = maldistribution of coronoary flow away from ischaemic areas
  - 2nd to potent coronary vasodilation eg by isoflurane
  - significance of isoflurane debated may just be a individual variability

    ↳although thought not to occur with sevo & des

Neurological Disease

Muscle relaxants

- neuro disease are assoc with abnormal response to MRs:
  - NMJ pathology eg Myasthenia Gravis, Lambert Eaton:
    - ↑↑sensitivity to NDNMBs
    - sux variable response:
      - MG: resistance to single dose, ↑chance of phase 2 block
      - LE: ↑sensitivity to sux
  - Mm fibre pathology eg dystrophia myotonica:
    - Sux:
      - prolonged myotonia, & hyperkalaemia ⇒ risk of arrhythmias
      - ∴ absolute contraindication
    - NDNMB's: duration of action prolonged ∴ give smaller doses
    - ↑ed resp depressant effects to most anaesthetic agents + opioids
    - halothane ⇒ cardiotoxic effects
  - Muscle wasting path eg paralysis, MND, MS
    - Sux:
      - extra junctional receptors ⇒ ↑sensitivity
      - ↑risk hyperkalaemia ⇒ malignant arrhythmias

      ↳in acute paralysis occurs as soon as 96hrs up to 6 months!!
  - Duchenne muscular dystrophy – sux absolute CI – MH like response
  - Others:
    - Muscular dystrophies other than Duchenne & Friedreich's ataxia = unpredictable responses to all MR's

Autonomic Disturbances

- Eg diabetic autonominc neuropathy, acute polyneuritis, Shy-Drager
- See abnormal baro-receptor responses ⇒ ↓↓MAP with most anaesthetic drugs

Endocrine Disease

- Myxoedema - ↑sensitivity to opiods + most anaesthetic drugs:
  - Multifactorial:
    - ↓liver enzyme function
    - changed Vd due to CCF/bradycardia
    - changes in body temp
- Thyrotoxicosis:
  - Enhancement of oxidative microsomal drug metabolism
  - ↓PPB of both acidic & basic drugs

  ↳∴ variable responses
- adrenal insufficiency:
  - adrenocorticosteroids exert permissive effect on catecholamines ⇒ ↓↓MAP post anaesthetic drugs
- phaeochromocytoma:
  - should avoid:
    - drugs which may cause histamine release eg morphine
    - drugs induce arrhythmias eg halothane, enflurane
- carcinoid tumours: avoid histamine releasing drugs ⇒ tachycardia & HTN

Drug Interaction

- mechanisms of interaction:
  - pharmaceutical incompatibility
  - pharmacokinetic reasons
  - pharmacodynamic reasons
  - combined toxicity
  - interactions due to changes in electrolytes/fluids

Pharmaceutical incompatibility

- pH:
  - drug precipitation if drugs with diff pHs are mixed together
    - eg thio with midazolam
  - drug inactivation/property changes due to pH differences:
    - sux & thio ⇒ rapid alkalie hydrolysis of sux
    - adrenaline changed from l- to d- isomer
- calcium:
  - calcium into infusion lines with NaHCO3 or blood ⇒ precipitation
- osmolarity:
  - infusing fluids with diff osmolarities can lead to interactiosn
  - eg blood infused with 5% dex or mannitol ⇒ haemolysis
- salting out = electrolytes added to supersaturated solutions (eg mannitol) ⇒ aggregation/precipitation in mixture
- emulsion cracking = calcium added to fat emulsions ⇒ extra cations alter repelling surface charge on fat globules ⇒ coalesce
- interaction with administration sets:
  - GTN binds to plastic ⇒ ↓ed delivery but then ongoing delivery post cessation of drug
  - Insulin can absorb to glass container/plastic syringers
  - Drugs in stomach with activated charcoal

Pharmacokinetic Causes

Absorption

- If a drug has large s.a. can bind or chelat other drug
- Drug alter gastric pH or motility
- Eg
  - propranolol –
    - Weak base
    - Small, very lipid soluble unionised fraction
    - This interferes with high lung uptake (75%) of fentanyl
  - adrenaline ⇒ ↓s absorption of LA's
  - hylaluronidase ⇒ ↑s absorption of LA's

Distribution

- Competition for PPB eg amiodarone & warfarin
- Displacement from tissue binding sites
  - ↳eg quinidine ⇒ ↑serum digoxin
  - ↳eg volatiles ⇒ ↑ed NDNMBs blood distribution

Metabolism

- Liver enzyme induction
  - Steoroids
  - barbituates
- Liver enzyme inhibition:
  - Allopurinol
  - Cimetidine

  - Omeprazole
  - Haloperiodol
  - erythromycin
- Competition for plasma esterases:
  - Remifentanyl
  - Atracurium
  - Etomidate
- Competition for plasma cholinesterases:
  - Sux
  - Mivacurium
  - Ester LA's (excluding cocaine)

Pharmacodynamic Causes

- Additive effect (1+1=2)
- Synergistic effect (1+1=4)
- Competitive or non competitive antagonism of concurrent given drugs

Combined Toxicity

- Combined use of 2 or more drugs with toxic effects on same organ ⇒ ↑↑likelihood of organ damage
- Eg ACEI + gentamicin + NSAIDs ⇒ renal impairement

Alteration in Fluids/Electrolytes

- Eg potentiation of digoxin by ↓k, ↓Mg, ↑Ca, ↑Na
- Eg dig induced arrhythmias due to sux induced hyperkalaemia

Adverse Drug Reactions

- Classification:
  - Predictable (type A)
    - =extention of expected pharmacological effect
    - ∴ usually dose dependant
  - Unpredictable (type B)
    - Idiosyncratic
    - Uncommon
    - Unrelated to known pharmacological properties of drug
    - Usually involve immune system in some way

Predictable

- Abnormally high drug conc at receptor site
  - Eg most commonly caused by pharmacokinetic variability
- Alteration in dose-response curve
  - Eg warfarin in elderly - ↑ed receptor sensitivity ⇒ ↑drug effect at same effect site conc
- Alteration in shape of dose response curve:
  - Eg propofol: drug with steep curve (low therapeutic index) = more likely assoc with dose related toxicity by small ↑in dose
- Concomitant drug therapy:
  - See drug interactions

Unpredictable

- Idiosyncratic reactions – see prev
- Cytotoxic reactions:
  - Irreversible covalent binding of drug/metabolites to tissue molecules ⇒ tissue damage
  - More common after metabolic activation to reactive metabolites (than with parent drug)
  - Activation usually occurs in microsomal oxidase system of liver (but in other organs too)
  - Binding and damage then occurs nearby eg paracetamol & liver

By Adam Hollingworth

Drug Additives

Preserving Drugs

Shelf Life

- = indicates period during which a min of 90% of drug remains intact & available for delivery
- eg sux 15months @ 4-8 degs
- factors ⇒ ↓ing shelf life:
  - drug instability
    - irreversible chemical reactions ⇒degredation of drug eg oxidation + hydrolytic reactions
    - factors incl pH, temp, addition of water, exposure to light
  - incompatibility eg conc dependant precipitation and acid-base reactions
  - maintenance of sterility ie prevent contamination
    ↳why preservatives added
- methods to prolong drugs shelf life:
  - temp – keep cool in fridge. 10% ↑temp ⇒ ↑degredation rate x2-5
  - intact packaging – prevent exposure to contaimants & light
  - light – UV light ⇒ ↑degredation eg adrenaline & amber vials
  - water – keeping water out may ↓hydrolysis reactions
  - formulation – decomposition occurs slower in powder or solid form
  - oxidation –
    - exclude O2
    - add antioxidants eg sodium bisulfate & sodium metabisulfate to adrenalin
  - pH –
    - reaction rates ↓ed at intermediate pH values (4-8)
    - buffers added to maintain neutral pH
  - usage – use drugs nearing expiry first
  - no absorption phenomena from within container – glass ampules

Utility Time

- time determined within which a drug should be administered once reconstituted/drawn up/diluted
- usually much shorter than shelf life
- eg
  - propofol = < 6hrs
  - thiopentone = 5-7days at room temp
    ↳ very alkaline resisting bacterial growth

Drug Additives

- common reasons for adding additives:
  - prevention of contamination
  - prevent degradation ie maintain potency
  - solubility eg solvents, emulsifiers
  - other – to modify tonicity, pH to prevent side effects of administration eg phlebitis

Buffers

- usually added to maintain intermediate pH ⇒ ↓degradation
- can be use to maintain pH in acidic range where other additives are maximally active eg preservatives
- pH manipulation to promote solubility/absorption
  ↳using pKa & ambient pH to determine degree of ionisation
- examples of buffers:
  - NaHCO3
    - added to LA's (weak bases) prior to administration
    - promotes unionised form ⇒ ↑diffusion across neural sheath/membrane
  - Na Carbonate:

        - Added to thiopentone to maintain pH 11 ∴ the enol form
        - Prevents precipitation as free acid
        - But may cause precipitation if thio mixed with alkaline drugs
    - NaOH – added to propofol to obtain pH 7
    - NaOH & HCL – added to midazolam to maintain pH <4 ∴ water solubility prior to injection
      ↳ eg dynamic isomerism or tautomerism
    - Besylate (iodide salt) added to atracurium to provide
        - water solubility
        - pH 3.5
        - minimise risk spont in vitro degredation
    - citric acid, sodium phosphate, NaOH – added to vecuronium to adjust pH

Anti-Oxidants

- most drugs will be degraded by oxidation or hydrolysis
  ↳esp in presence of O2, UV light, ions of heavy metals
- can ∴ prevent this by 3 strategies:
    - amber ampoules
    - excluding O2/Co2 eg thiopentone stored at 0.8 atm nitrogen
    - adding antioxidants
- antioxidants prevent oxidation by combining with free radicals
- examples:
    - alpha tocopherol – reducing agent which diverts oxidation due to low redox potential
    - ascorbic acid, Na & K salts of sulphurous acid = antioxidant synergists which act as chelating agents & combine with heavy metal ion catalysts

Antimicrobials (Preservatives)

- used in addition to sterile prep, sstorage & heat sterilisation
- selection of antimicrobial depends on:
    - nature of active drug
    - other constituents of drug
    - container
- examples include:
    - benzyl alcohol
    - chlorocresol
    - phenol
    - parahydroxybenzoic acid
- use in anaesthetic drugs:
    - propofol – none or EDTA, benzyl alcohol
    - ketamine – none or benzthonium chloride
    - lorazepam – 2% benzyl alcohol

Solubilising Agents (solvents)

- aqueous (water):
    - advantages: tasteless, non irritant, inert
    - problems:
        - any drugs lipophilic & poorly soluble in H2O
        - many drugs unstable in H20 – hydrolysis
        - easily contaminated by micro-organisms
- non-aqueous solvents:
    - used for 2 reasons:
        - solubilise lipophilic drugs
        - render stable solutions

Examples of Non-Aqueous Solvents

- propylene glycol
    - used in diazepam, GTN, etomidate, propofol

- SEs = pain on injection
- Benzyl alcohol:
  - Low conc is a preservative eg in diazepam, midazolam
  - >5% used as a solvent
    ↳limited by SEs ie vasoD, myocardial depression, LA properties
- mannitol:
  - added to dantrolene & vecuronium
  - SEs related to osmotic diuretic effect (may be useful in MH)
- Emulsions:
  - = 2 phase system
  - pair of immiscible liquids: 1 of these is dispersed in the other in form of small droplets
  - defined as wither:
    - oil in water (o/w) ie oil is droplet
    - water in oil (w/o) ie water is the droplet
  - emulsifying agents added to ↑stability of system:
    - maintain droplet in dispersed phase & prevent coalescence
    - eg surfactant, hydrocolloids
  - effects achieved by :
    - physical or chemical barrier around dispersed droplet
    - impart elec charge to ext surface of droplets ⇒ repeling
  - commercial fat emulsions
    - soya bean oil most commonly used in propofol & diazepam
    - intralipid – total solution used in propofol:
      - soybean oil 10%
      - glycerol 2.25%
      - egg phosphatide 1.2%
        ↳does not contain egg protein (from egg white) which most egg allergy people react to
      - side effects:
        - pain on injection
        - ↑calorific load – esp in prolonged infusions in kids
        - supports bacterial growth
        - cost
        - may contribute to propofol syndrome
          ↳ acidosis, bradycardia +- death
          ↳mostly in kids & ?functional palmoyl carnitine deficiency
    - cyclodextrans:
      - newer formulations of propofol
      - cyclic oligosaccharides derived from starch
      - 3-d hollow cone with hydrophilic exterior surface & lipophilic core
      - drug encapsulated into core allowing soluble in aqueous solution

Problems with Additives

- must be very careful when administering neuraxial drugs
  - preservatives:
    - esp antioxidants/antimicrobials
    - implicated in neurotoxicty/arachnoditis
    - ∴ all neuraxial drugs should be additive free
    - proven neurotoxic eg: alcohol, phenol, formaldehyde, sodium metabisulfite
  - glycine:
    - as is also a inhibitory neurotransmitter added glycine may ⇒
      - agitation

        - incoordination
        - pain
    - is used as a solvent + antimicrobial in some drugs eg remifentanyl
- majority of additives also used in food industry ∴ more likely to get bigger exposure from food
- adverse reactions can be:
    - dose related:
        - uncommon
        - highest risk = neonates, TPN, long term IV Rx, indwelling pumps
    - allergic/hypersensitivity eg sodium metabisulfate sometimes added to adrenaline – allergies against it common

By Adam Hollingworth

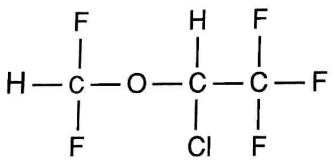
Isomerism

- isomers = 2 or more compounds that have same atomic composition (ie chemical formula) but different structural arrangements, often causing different properties
- classified into:
  - structural isomers = same atomic composition, but different chemical structure
  - stereoisomers =
    - same atomic composition & chemical structure
    - different spatial arrangements of atoms
    - subclassified:
      - enantiomers = mirror images of each other due to presence of chiral centre
      - diastereomers = multiple chiral centres mean not mirror images of each other
      - geometric isomers = arrangement of atoms around double bond or ring structure

Structural isomers

- same chemical formula but diff chemical structures
  ↳ie atoms are arranged differently
- examples:
  - isoflurane & enflurane - similar type actions
    ↳ NB most volatiles have chiral atomes ∴ have stereoisomers as well
  - promazine & promethazine – diff actions
- tautomerism = dynamic isomerism:
  - = where 2 structural isomers exist in equilibrium
  - shift of equilibrium = pH dependant
  - eg thiopentone:
    - enol form:
      - in syringe (post reconstitution)
      - ionised & water soluble
      - pH 11
    - keto form:
      - in blood
      - pH 7.4
      - highly lipophilic
  - eg midazolam:
    - open ring:
      - in ampuole
      - pH <4 = hydrophilic
    - closed ring:
      - in blood
      - pH 7.4 = highly lipophilic

Isoflurane



Enflurane

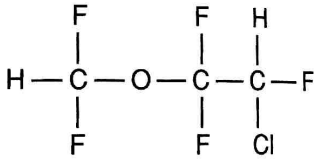


Figure 5.1. Structural isomers: (a) $C_{18}H_{23}NO_3$; (b) $C_3H_2ClF_5O$.

Stereoisomers

- same chemical formula & chemical structure BUT diff spatial orientation

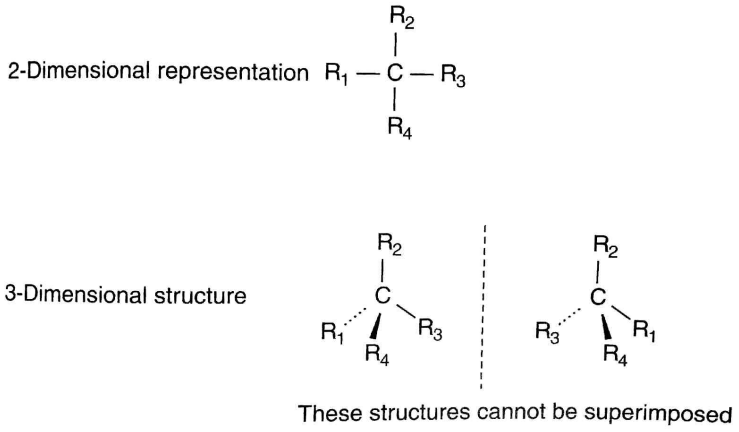


Figure 5.2. Chiral centres.

Enantiomers (aka optical isomers)

- = mirror images of each other
- substance needs to have a special atom = chiral atom
- chiral atom
  - = centre of 3D structure with atoms arranged around it in an asymmetrical fashion
  - chiral atoms often = carbon
  - attached atoms differ in their special orientation between enantiomers so that they form mirror image of each other
- enantiomer has old & new classification:
  - direction which they rotate the plane of polarised light:
    - old system been replaced
    - to right = +, dectro or d
    - to left = -, laevo or l
  - R/S system:
    - R = rectus or right
    - S = sinister or left
    - R/S system describes configuration around chiral atom:
      - R enantiomer has atoms arranged in clockwise manner according to periph atoms molecular weight declining
      - ∴ L mw periph atoms must decline anti-clockwise
- each enantiomer may have very different effects to it's mirror image
  ↳supports receptor theory
- a racemic mixture
  - = mixture containing equal amounts of enantiomers
  - eg volatiles (except sevo), atropine, racemic bupivacaine
  - although mixture has equal proportion, drug effect may come completely from one enantiomer
- enantiopure preparations:
  - = selecting the more desirable enantiomer & producing it as a single isomer
  - eg ropivocaine & bupivacaine: R form has more toxic profile ⇒ ∴ S form selected

Diastereomers

- same chemical formula & structure but differ in spatial orientation & are NOT mirror images of each other
- arise due to:
  - more than 1 chiral atom present
- eg atracurium –
  - 4 chiral centres with 16 potential combinations (but as some overlap see 10 possible variations)

- cis-atracurium is one of these 10

Geometric Isomers

- aka cis-trans isomerism
- = special form of stereoisomer where arrangements of paired atoms or groups around
  - a double C bond or
  - rigid C single bond in a ring structure
- -cis = both substituents being on same side of double bond
- -trans = one substituent on each side of bond
- geometric isomers are not usually optically active
- have different physical & chemical properties eg atracurium & mivacurium

Stereoisomers in Clinical Practise

- S-ketamine (vs R-ketamine) ⇒
  - ↑ed anaesthesia & amnesia
  - ↓ed emergence phenomena
  - faster recovery
- thiopentone:
  - given as racemic mixture
  - S-thio is more potent but has shorter t1/2
- Levo-bupivacaine: fewer side effects (esp cardiac) than traditional racemic preparations
- Morphine:
  - Has 5 chiral centres ⇒ ∴32 possible isomers
  - l-morphine – stereoselecitvely synthesied for use
    ↳d-morphine has no opioid effects ie opioid receptors are highly stereoselective
- l-nalxone = 10,000x antagonistic than d-naloxone
- tramadol:
  - chemical structure = 2 pairs of isomers:
    - (1R,2R), (1S,2S), (1R,2S), (1S, 2R) ie all combinations seen
      ↳1st 2 = enantiomer, last 2 = diastereomers
    - only enantiomers are used:
      - (1R,2R)tramadol =
        - greater affinity for u & delta receptors
        - potent inhibitor of 5-HT uptake (and enhances its release)
      - (1S,2S)tramadol = potent inhibitor of NA uptake

      ↳both produce antinociception & may display synergism
- adrenaline & NA:
  - S or L isomer = x50-500 more potent than d-isomer
  - racemic mix (dl) adrenaline sometimes used in croup
    ↳50% potency but longer duration of action
- isoflurane: still presented as racemic mixture but S form has higher potency & +/- less CVS depressive effects

Examples of Diff Dimers by Classification

- Examples of drugs available as single stereoisomer include:
  - l-hyoscine,
  - cisatracurium,
  - S ropivacaine,
  - l-adrenaline,
- Examples of racemic preparations:
  - bupivacaine,
  - adrenaline
  - ketamine, thiopentone
  - the volatiles

- Examples of mixtures of more than two stereoisomers:
  - Atracurium and mivacurium

  ↳Atracurium has 4 chiral atoms and thus potentially 16 enantiomers

  ↳but only 10 exist because of molecular symmetry (from geometric isomerism)

  ↳One of these 10 isomers = cisatracurium and is available for commercial use:
    - same kinetics as atracurium
    - but x4-5 more potent & more CVS stable with minimal histamine release

Pharmacology of Pregnancy

- Any drug administered may reach fetus or neonate by placenta or milk
- Major problem is effect of drugs on embryo when woman unaware pregnant
- Different trimesters infer different risks:
  - 1st – congen malformations (teratogenic effects)
  - 2nd & 3rd – altered function and growth
  - perinatal – affect birth & neonate
- Australasian Drug Eval Committee (ABCDX system):
  - Class A = adequate human studies. Safe
  - Class B = animal study ok, no human studies
  - Class C = Unknown human risk. Studies show harm in animals
  - Clsss D = Unsafe. Suspected human risk
  - Class X = Permanent damage in humans proven!
- Summary of issues in pregnancy:
  - pharmacokinetic & pharmacodynamic differences
  - effects on fetus eg teratogenicity/feotoxicity
  - effects on pregnancy / uterus eg tocolytics / oxtyocics

Embryo Development

- Possible effects:
  - Teratogens = any substance which interferes with normal development ⇒ abnormalities
  - Mutagens = physical or chemical agent which causes genetic mutation or ↑ed mutation rate
  - Carcinogens = agent which causes development of cancer or ↑incidence of cancer
- Critical periods for drug effects on fetus =
  - Wks 1-2 - rapid cell proliferation
  - Wks 3-12 – organogenesis
- Examples:
  - Thalidomide
  - Cocaine abuse:
    - Spont abortion
    - Fetal hypoxia
    - Premature delivery
    - Congen abnormalities eg skull, heart
    - Cerebral infarction/stroke
    - @birth – cocaine withdrawal eg ↑RR, ↑HR, ↓apetitie
    - long term behavioural abnormalities
- epilepsy & pregnancy
  - anti-epileptics shown to ↑x2-3 fold risk of fetal abnormalities
  - ↑risk with poly-pharmacy anti epileptics
  - malformations incl:
    - congen heart disease
    - cleft lip/palate
    - neural tube defects
    - urogenital defects
  - clonazepam best!

Maternal Pharmacokinetics

Absorption

- pregnancy does not directly affect absorption BUT:
  - GIT:
    - delayed gastric emptying –
      - ↑absorption of drugs absorbed from stomach eg diazepam
      - delayed absorption of drugs absorbed from upper GIT eg paracetamol

        - changes to GIT blood flow
        - ↓GI motility
        - ↓HCl production from stomach eg ⇒ ↓absorption for drugs requiring acid environ
          ↳overall ↑ or ↓ absorb
    - IMI/sc/neuraxial – ↑ed CO & ↑ed regional blood flows ⇒ more rapid uptake of drug from these sites

Distribution

- change in distribution compartments:
    - ↑plasma volume 50% (and other compartments ↑in size ?%)
    - ↓PPB esp 3rd trimester eg diazepam, theophylline, pethidine

    ↳∴ ⇒ ↑Vd of all drugs (lipophilic & hydrophilic)

    ↳but ↓PPB has compensatory effect ⇒ ↑proportion of free drugs with high protein binding
    - ↑CO 30%
    - ↑body fat 25%

    ↳↓blood conc

Metabolism

- ↑CO:
    - hepatic blood flow +/- unchanged or slight increase
- ↑LDH, transaminase, ALP (progesterone effect) ⇒ may lead to faster metab of drugs with high hepatic metab
- pseudocholinesterase:
    - ↓activity:
        - ↓25% before delivery
        - ↓33% @ 3 days post partum
        - return to normal 2-6weeks post partum
    - actual activity of sux:
        - remains mostly unchanged – large Vd offsets ↓ed metab
        - may slight prolongation of duration of action fitst few days pp due to rapid ↓ECF volume
    - clinically of little relevance to other drugs metabolised by pseucholinesterase

Excretion

- ↑CO ⇒ ↑renal blood flow & ↑GFR in 1st & 2nd trimester ⇒ ↑excretion of renally eliminated drugs
- ↑CO & ↑alveolar ventilarion (V_A) ⇒ NET enhanced uptake & elimination of volatiles

Specific Drugs Pharmacokinetics

Volatiles

- PK:
    - faster induction with:
        - insoluble volatiles- ↓ed size of FRC ⇒ faster FA/FI ratio
        - soluble volatiles - ↑ed V_A
- PD:
    - ↑ed sensitivity –
        - starts early in gestation
        - ↓in MAC 16-40%
        - likely caused by progesterone ⇒ neurosteroid anaesthetic effect

Muscle Relaxants

- PK
    - ↑40% duration of action of steroid blockers - vec & roc
      ↳preg induced changes in hepatic blood flow or competition for liver uptake by sex hormones
    - atracurium = duration unaffected
    - psuedocholinesterase – as above. ↓25% but sux action unchanged

Local Anaesthetics

- total dose of LA's needed is ↓ed by 25-30%

- PK:
  - epidural anesthetics:
    - engorgement of epidural veins ⇒ ↑ed spread of LA's in late preg
    - ↓PPB ⇒ ↑free drug & ↓Vd of amides (bupivacaine & ropivacaine) ⇒ risk of toxicity from ↑ed plasma conc
      ↳lower threshold for seizures & CVS collapse shown for bupiv in sheep
      ↳ropivocaine remains less cardiotoxic ∴ use this
- PD:
  - quicker onset of block
  - ↑sensitivity to amide's ⇒ ↑ed spread of epidural
    ↳established at 8-12/40

IV Anaesthetics

- ↑sensitivty to thiopentone – need ↓18% dose in 1st trimester
  ↳other induction agents not studied but likely same ↑ed sensitivity
  ↳likely a PD effect but PK could contribute via ↓PPB & ↑V_D

Opioids

- opioid mediated ↑ed pain threshold in preg:
  - mechanism:
    - functional up regulation of mu & kappa receptors
    - ↓substance P levels

Anaesthetic Effects on Feto-Placental Unit

- considerations:
  - direct toxic effects incl teratogenicity
  - indirect toxic effects
  - anaesthesia/surg/disease ie any intervention may ↑chance of prem labour

1. Direct Fetotoxicty/Teratogenicity

- teratogenicity = any significant change in postnatal form/function in offspring due to ante-natal Rx
- exposure to agents can be classified by stage of gestation:
  - in early pluripotential stage of development ⇒ in all or nothing effects
    ↳ie embryonic death or survival with no effects
  - during organogenesis (31-71 days after LMP) ⇒ structural malformation
  - 2nd trimester & later ⇒ interference with CNS maturation ⇒+/- behaviour/development problems
- ∴ only give drugs if benefits outweigh risks

Volatiles

- conflicting animal data
- weak evidence less teratogencity with iso/enflurane compared to halothane
  ↳no studies newer agents
- manufacturers state fetotoxic effects only occur at concentrations which would also cause maternal toxicity (rat studies)
- ∴ prob not teratogenic ⇒ avoid halothane

Nitrous Oxide

- rat study: need >24hrs of >50% ⇒ teratogenic effects
- folate supplementation had no effect ∴ is not simple inhibition of methionine synthase ⇒ ↓DNA synthesis
- N2O = sympathomimetic agent ⇒ implicated in situs invertus in rats
- implicated (not proven) ↑ in miscarriages in healthcare workers
- ∴ not CI'ed in pregnancy but easy to avoid

IV Anaesthetics

- v few studies
- Unlikely to be problem:

  - thiopentone
  - etomidate
  - ketamine
- propofol:
  - no data to suggest teratogenicity
  - reproductive studies suggest adverse effects on peri-natal survival
    ↳∴manufacture state should avoid it

Benzodiazepines

- weak evidence from animal study showing teratogenicity – in very high doses
- ∴ unlikely for isngle dose short acting BZD to be teratogenic ie can use in 1st trim if needed

Opioids

- avoid pethidine!
- peri-op use ok
- long lasting behavioural effects of babies of drug addicted mothers
- long term use ⇒ fetal dependence & withdrawal

NSAIDs

- aspirin – not considered a human teratogen
- NSAIDs considered safe in 1st trimester (except ketorolac ⇒ vascular malformation)
- NSAIDs in 3rd trimester may cause:
  - premature closure of ductus arteriosus/tricuspid incompetence
  - pulmon HTN ↳inhibits prostaglandin synthesis which keeping duct open
  - non closure of DA post natally

  ↳∴ avoid >32/40

NMBs

- serum fetal conc <10% of mothers ∴ large margin of safety
- non-depolarizers are not teratogenic at clinical concs

LA's

- no teratogenicity with amides
- cocaine = teratogenic with maternal abuse
- regional anaesthetic is best

Antiemetics

- metoclopramide – long Hx of safe use
- prochlorperazine (& phenothiazones/butyrophenones):
  - non teratogenicity
  - but prolonged Rx in late preg ⇒ ↑ed risk jaundice/extra pyriamidal distrubances
- cyclizine = nil proven probs
- ondansetron = fine in animals. no human data

Summary

- so most anaesthetic drugs are fine
- but surgery/anaesthesia in pregnancy clearly shown:
  - ↑miscarriages
  - ↑still births
  - IUGR
  - prematurity

2. Indirect Toxic Effects

- main issues are:
  - delivery of oxygen & nutrients to fetus
  - concentration of free drug reaching fetus

Delivery of O2 & Cardiovascular Effects

- remember delivery of O2 to uterus:

$$DO_{2Ux} = UBF \times CaO_2$$

- remember that uterine blood flow is directly related to pressure (ie has no inherent autoreg system):

$$UBF \sim UPP$$

- Hyperoxia:
  - in vitro causes uterine vasoconstriction
  - But clinically prob not significant
  - fetal PaO2 rarely >40mmHg (never >60mmHg) ∴ v **unlikely** even with maternal FiO2 1:
    - prem closure of ductus arteriosus
    - retrolental fibroplasia
- hypoxaemia:
  - moderate hypoxaemia:
    - does not cause compensatory ↑uteroplacental perfusion
    - ↑O2 extraction – HbF helps ↑margin of safety
  - severe prolonged maternal hypoxia ⇒ uteroplacental vasoC ⇒ redistribution of flow away from placenta
- hypercarbia:
  - CO2 diffuses freely across placenta ⇒ fetal resp acidosis
  - severe fetal acidosis assoc with myocardial depression
  - mod maternal hypercarbia may initially ↑uterine flow but >60 ⇒ vasoC
- hypocarbia:
  - maternal alkalaemia (met or resp) ⇒ linear ↓uterine blood flow due to ↓ed maternal PaCo2 or H ions
  - ∴ maternal hyperventilation & hypocapnia should be avoided ie good periop analgesia

Concentration of Free Drug @ Fetus

- concentration of free drug reaching fetus depends on:
  - fetal circulation (or absorption)
  - fetal distribution: PPB
  - fetal metabolism
  - fetal renal excretion

  ↳ie pharmacokinetics!!!

Fetal Pharmacokinetics

- transfer across placenta of drug depends on:
  - physiochemical properties of drug:
    - transfer generally passive diffusion but active methods present:
      - facilitated process for glucose, lactate
      - active processes for aa's, Ca, PO4, vitamins
      - endocytotic mechanisms for Ig transfer to fetus
    - low molecular weight drugs (250-500) freely cross placenta
    - high molecular weights >1000 eg heparin cross poorly
  - protein binding
  - lipid solubility –
    - lipophilic drugs with mw <600D highly transferable
    - eg NMBs – hydrophilic poorly cross
  - duration exposure to drug

- in late gestation:
  - ↑movement of drug across placenta due to:
    - ↑uteroplacental blood flow
    - thinner membrane to cross
  - result in ↑transfer unionised lipid soluble free drugs

Drug Metabolism in Fetus

- blood flow into fetus via umbilical vein
- only 40-60% to fetal liver; rest to IVC
- fetus has immature hepatic metab enzymes:
  - activity first noted at 5-8 wks
  - @12-14 wk 30% capacity of adult
  - full metab not until 10yr old
- if metabolite of drug is water soluble very difficult to excrete back across placenta
  ↳∴ accumulation in fetus and amniotic fluid
- fetus has ↓overall drug excretion:
  - placenta
  - kidneys ⇒ urine ⇒ amniotic fluid ⇒ reabsorbed by fetus ↑drug levels
- neonatal withdrawal symptoms:
  - seen esp in drugs given just before delivery:
  - eg alcohol, cocaine, benzo's, some antidepressants, opiates

Specific Drug Examples of Indirect Toxic Effects

- thiopentone:
  - thio induction ⇒ transient ↓uterine blood flow
  - although difficult to isolate drug cause alone as intubation & laryngoscopy ⇒
    - potent symp stim ⇒ maternal HTN & vasoC ⇒ ↓uterine blood flow
- propofol:
  - induction & laryngoscopy with prop does not seem to effect uterine flow despite maternal SNS/HTN response
  - TIVA with prop & 50% N2O for up to 2hrs causes no change in uterine flow
- ketamine:
  - 3rd trim: ↑uterine flow
  - 2nd trim: may cause uterine hypertonus similar to ergometrine
- etomidate:
  - may cause suppression of neonatal cortisol level & ↑risk of hypoglycaemia
- volatiles:
  - all = uterine relaxants with direct effects on maternal regional flow
  - <1.5 MAC:
    - Ux relaxation
    - vasodilation maintains flow despite ↓maternal CO
  - >2 MAC: ↓ing maternal CO predominates ⇒ fetal hypoxaemia/acidosis

  ↳similar for all agents
- regional anaesthesia:
  - if systemic hypotension avoided RAis tolerated well by fetus
  - no prob with neuraxial opioids (as long as aoid maternal resp depression)
- catecholamines/vasoactives:
  - indirect sympathomimetics (ephedrine) good at Rx maternal bp & restoring Ux perfusion
  - α agonists – thought ↓Ux perfusion (despite norm maternal bp)
    ↳although phenylephrine in C section may cause less fetal acidosis than ephedrine
    ↳?venoconstriction helping preload before adverse Ux vasoC
- antihypertensives:
  - labetalol – maintains Ux perfusion (good agent for PET)
  - hydralazine – good alternative to labetalol

- GTN – no adverse effect on fetal acid-base even >2hr infusions
- SNP – does not improve Ux flow in mat HTN & potential fetal cyanide toxicity
- Esmolol – can cause ↓↓Ux flow & fetal bradycardia
- CCBs:
  - L type CCBs (nifedipine, nimodopine) has been assoc with fetal hypoxaemia/acidosis
    ↳can persist after delivery
  - need to weigh risks to fetus eg nimodipine for cerebral vasospasm in SAH
- Mg: in normotensive & HTN animals ⇒ ↓maternal HTN & ↑Ux flow by ~10%

Other Drugs in pregnancy

- Safe:
  - Penicillin
  - Cephlasporins
  - Nitrofurantoin
  - Clindamycin
- NOT safe & critical time period
  - Abx:
    - metronidazole in 1st trimester
    - chloramphenicol – grey baby syndrome
    - Aminoglycosides – vestibular damage to fetus
    - Co-trimoxazole (trimethoprim) – teratogenic risk – folate antagonist
    - Tetracyclines – damage to bones & teeth
    - Antimalarial's – may cause methaemoglobinaemia & haemolysis in neonate
  - Alcohol –
    - <12 wks heart defects & CNS abnormalities
    - >24wks delay development & low birth weight
  - Anti epileptic - neural tube & craniofacial defect
    - carbamazepine - <30days
    - valproate 1st trimester
    - Phenytoin – clept lip & palate, cardiac abnormalities
  - Endocrine:
    - carbimazole – may cause neonatal hypothyroidism
    - glucocorticoids in high doses – adrenal suppression
    - Sulphonylureas – assoc with fetal hypoglycaemia
  - CVS:
    - warfarin – bone abnormalities & neonoatal haemorrhage
    - beta blocker – growth retardation
    - Amiodarone – neonatal goitre
    - Statins – congen abnormalities reported
    - ACEI – renal damage & oligohydraminos
  - Retinoic acid – hydrocephalus & CNS abonrmailites up to 2yrs after Rx
  - diruetics:
    - amiloride ⇒ elec chem. disturbances
    - spiron ⇒ feminisation male fetus
    - Thiazides – neonatal thrombocytopaenia

Immunisations in Pregnancy

- Only vaccines contraindicated are live ones eg MMR
- Thus ok to give with caution:
  - Tet & diphtheria
  - Pneumococcal
  - Hep B
  - Influenza

Drug Use in Lactation

- almost all maternal drugs may be transferred to colostrum & breast milk
- mammary glands normally limited route for maternal excretion of drug
- neonate has limited metab and excretion capcities
- mammary alveolar epithelium:
  - lipid barrier with water filled pores
  - more permeable to drugs during colostrum phase (1st week postpartum)
- factors which enhance excretion of drug by milk:
  - ↑ed ionisation
  - low molecular weight
  - greater fat solubility
  - higher conc
- transfer passively & carrier mediated
- absorptive process in infant relatively similar to adult
- drug effect on infant depends on:
  - age ∴
    - amount of drug containing milk consumed
    - immaturity of organs
  - fat solubility of drug - ↑fat soluble ⇒ ↑conc of drug at midday and end of feeding
  - infant has ↓ed plasma protein content ⇒ ↑free drug in infant
  - infant slower hepatic metabolism reactions
  - immature glom filtration & tubular function ⇒ ↓ed drug excretion
- if concern about drug in mothers milk:
  - stop breast feeding for 24-72hrs
  - pump breasts to remove drug containing milk

  ↳or stop breast feeding
- can take meds after each feed to minimise impact
- contrainidcations to breastfeeding:
  - drug so toxic minute amounts will profoundly effect infant
  - drug has high allergic potential
  - ↓mothers renal function ⇒ ↑excretion via breast milk
  - prolongd administration of high dose of drugs eg chemo
  - eg avoid altogether:
    - amiodarone
    - high dose aspirin
    - BBlockers
    - COCP
    - Diazepam
    - Iodine
    - Lithium

Respiratory Drugs

AntiMuscarinics

- ACh M3 receptors present on bronchial smooth mms & gland cells ⇒
  - bronchoconstrictin
  - ↑bronchial secretions
- ∴ any antimuscarinic drug eg atropine ⇒ ↓both of these

Ipratropium

MOA

- M3 activation ⇒ ↑phospholipase C ⇒ IP3 release ⇒ ↑Ca [in]
  ↳∴ antimuscarinic ⇒ ↓Ca [in] ⇒ relaxation

Pharmacokinetics

Uses

- inhaled ipratropium or tiotropium used as bronchodilator
- should not be used as relief for symptoms but as adjunct to steroids

Adverse Reactions

- resp SEs:
  - ↓bronchial secretion
  - ↓mucocilary transport

  } accumulation of thickened secretions ⇒ difficult to expectorate
- anticholinergic effects:
  - dry mouth & throat
  - urinary retention
  - constipation
  - exac of glaucoma & prostatism

Cautions/Contraindications

Interactions

- additive effects with all other antimuscarinics

Dose

Agonist Bronchodilators

MOA

- activation β2 in smooth mm ⇒ ↑cAMP ⇒ ↑Ca extrusion from cell & binding of Ca within the cell ⇒ ↓active intracellular Ca ⇒ relaxation smooth mm
- also used in utero to relax uterine smooth mm to delay threatened miscarriage

Administration

- inhaled
- some inevitably swalloed ⇒ systemic adverse reactions

Uses

- short acting β2 agonists:
  - salbutamol & terbutaline
  - relievers – symptom relief
- long acting β2 agonists (LABA)
  - preventers
  - eg salmeterol & eformoterol
  - half life 6-12hrs
  - some study show ↑exac of asthma with LABAs

↳esp if monotherapy without inhaled steroids

Adverse Reactions

- cross over to stim β1 & α receptors especially in high doses ⇒ SEs in
  - CVS – tachycardia
  - skeletal mm – tremor
  - CNS – anxiety
- non selective β agonists may ⇒ downregulate receptors ⇒ tolerance to bronchodilator therapy ⇒ overdose ⇒ other system SEs eg CVS arrythmias
- some people have β2 polymorphism ⇒ ↓lung function & ↑asthma exac

Salbutamol

MOA

Pharmacokinetics

- time to onset 5-15mins
- peak effect 1-2hrs, duration of action 3-6hrs
- salbutamol metab in liver; excreted kidneys
- terbutaline excreted unchanged
- amounts of drug which are swallowed are rapidly metabolised

Uses

- symp relief acute asthma
- prophylactic against exercise induced asthma
- symptom relief bronchospasm COPD & allergic reactions

Adverse Reactions

- mild:
  - tremor, restlessness
  - ↓K
  - palps, tachy
  - anxiety
  - ↑glucose
  - unusual taste in mouth
- symptoms of overdose from excessive α or β1 stim ie HTN, palps

Cautions/Contraindications

- caution in:
  - CVS disease
  - DM
  - ↑thyroid
- safe in preg, breastfeeding & elderly

Interactions

- other sympathomimetics ⇒ excessive symp stim ie tremor & tachycardia
- βblockers ⇒ antagonist effects ⇒ bronchoconstriction
- xanthine derivatives, steroids, diuretics ⇒ additive effect ↓↓K
- antidepressants ⇒ ↑CVS effects

Dose

- 1-2 puffs (100mcg salbutamol; 500mcg terbutaline
  ↳second inhalation should be >1min after 1st puff
- rpt in 4-6hrs

Methylxanthine Derivatives

- incl caffeine & theophylline
  ↳= methylxanthines
- cause:
  - relax smooth mm
  - stimulate cardiac mm & CNS
  - diuresis - ↑renal perfusion & ↑Na/Cl excretion
- theophylline
  - best in asthma
  - shown low dose may enhance steroid effects

Theophylline

Chemical

- often presented as aminophylline =
  - 80% theophylline
  - 20% ethylenediamine
    ↳ has no therapeutic effect but ↑s solubility

Presentation

- tablets – formulated as slow release
- solution for infusion

MOA

- not well understood!
  - inhibition of all 5 phosphodiesterase isoenzymes which responsible for metabolising cAMP
    ↳∴ ↑cAMP levels ⇒ smooth mm relaxation
    ↳but in vitro need higher levels of theophylline to make this occur
- other considered mechanisms:
  - inhibition cGMP phosphodiesterase
  - directly release NA from symp neurones
  - synergy with catecholamines ⇒ ↑intracellular cAMP
  - interferes with Ca translocation into smooth mm
  - competitive inhibition adenosine (which would normally ⇒ activates adenylate cyclase)
    ↳adenylate cyclase causes
    - cardiac depressor,
    - histamine release ⇒ bronchoconstriction, proinflamation
    - inhibition platelets

Effects

- resp:
  - bronchodilators
  - ↑contractility of diaphragm
  - ↑sensitivity of resp centre to CO2
  - inhibit late inflam phase of asthma
  ↳ good in combo with ß2 agonists as diff MOA to ↑cAMP
- CVS:
  - mild ↑ionotrope & ↑chronotrope
  - mild coronary & peripheral vasoD
  - arrhythmogenic esp ventricular pattern
    ↳ ↑ed concern if used with halothane
- CNS:
  - Stimulation ⇒ ↓seizure threshold
    ↳ alkyl gp at 1-position – also present in caffeine
- renal:
  - alkly gp also ⇒ inhibition of tubular Na reabsorption ⇒ weak diuretic +/- hypokalaemia

Pharmacokinetics

- very variable parameters
- oral:
  - uncoated tabs & liquids – rapidly absorbed; peak level 1-2hrs
  - enteric coated & sustained release – delayed & unreliable absorb; peak level 4-13hrs
- bioavailability generally 100%
- half life varies with age & concurrent illness:
  - newborn 30hrs
  - children 3.5hrs
  - adult non smoker 3-12hrs; smoker 3-4hrs
  - elderly 10hrs
  - hepatitis 19hrs; cirrhosis 32hrs; ↑thyroid 4.5hrs
- protein binding 50%
- distributes across placenta & into breast milk
- liver metab ⇒ various uric acid & xanthine derivatives;
- smoking ⇒ ↑ed clearance of amionphylline
- excretion via kidneys (10% unchanged)

Level Monitorring

- narrow therapeutic window
- levels 10-20mg/L

Uses

- most common sustained release tabs for maintenance Rx COPD & asthma
- acute life threatening asthma

Adverse Reactions

- dose dependant related to other actions:
  - CNS – N&V, headache, insomnia, tremor, anxiety
  - diuresis
  - GI - ↑gastric acid
- toxicity >35mcg/ml:
  - hepatic enzymes become saturated & kinetics change form 1st order to zero order
  - cardiac toxicity = arrhythmias incl VF
  - CNS toxicity = seizures, death
  - rhabdomyolysis

    ↳ NB may also occur at norm plasma levels

Cautions/Contraindications

- caution in:
  - pts with fever
  - GI disorders
  - CVS disorders
  - thyroid dysfunction
  - liver dysfunction
  - elderly

Interactions

- acyclovir, allopurinol, quinolones, macrolides ⇒ ↑theophylline conc

  ↳enzyme inhibitors
- phenobarbitone, phenytoin, rifampicin ⇒ ↓theophylline conc

  ↳enzyme inducers
- β agonists or diuretics ⇒ ↓↓K
- lithium, macrolides, pancuronium, phenytoin – theophylline ↓s conc or response to these drugs

Dose

- adjust dose to maintain 10-20mcg/ml
- eg start 10mg/kg/day for 3 days then incr by 3mg every 3days

CorticoSteroids

- glucocorticoid effects of steroids required in resp disease ie
  - anti inflam ⇒ ↓early & late phase inflam response
  - ↓bronchial hyper-reactivity
  - immunosuppressant effects

Beclomethasone

MOA

- enter cytolplasm of cells where bind to glucocorticoid receptors
- complex translocates to nucleus ⇒ bind to target genes ⇒ induction or inhibition of transcription
- action in asthma:
  - ↓activation of lymphoid cells & eosinophils
  - ↓production & activation of cytokines involved in chemotaxis & bronchospasm
  - ↓generation of VD postaglandins
  - ↓histamine release from basophils
  - ↓IgE & IgG
  - ↓long term production of mast cells
- max improvement in pulmon function at 1-4wks

Pharmacokinetics

- up to 80% of inhaled dose likely to be swallowed then absorbed from GI tract
- preak plasma conc 3-5hrs
- metab in liver; excretion in faeces & urine

Uses

- maintenance & prophylaxis in asthma
- not used in asthma attack – not a bronchodilator

Adverse Reactions

- much fewer with inhaled forms ⇒ ↓systemic absorption
- is link with inhaled steroids & bone mineral density ⇒ ↑risk osteoporosis
- rinse mouth with water post dose to ↓oral fungal infections
- if oral dosing SEs include:
  - adrenal suppression
  - growth suppression
  - altered deposition of fat/skin/bone/hair
  - eye probs
  - infections
  - psych disturbances

Cautions/Contraindications

- oral deposition can be ↓ed by spacer & rinsing of mouth
- use βagonist/antimuscarinic inhaler before inhaled steroid
- safe in preg & breast feeding

Interactions

- none significant

Dose

- step up or down 25% every 3months

Other Drugs

Mast Cell Stabilisers

- eg Cromoglycate
- inhibit release of histamine & leukotriens from mast cells & macrophages
- MOA unclear – may also :
  - block Cl channels

  - suppress sensory nerves ⇒ ↓neuronal reflexs
  - inhibit release of cytokines
- inhale before attack ⇒ ↓bronchoconstriction
- no bronchodilator effect
- no effect on inflam mediators already released

Leukotriene Receptor Antagonists

- eg montelukast
- MOA:
  - block receptors which component of slow reacting substance of anaphylaxis
    ↳∴ ↓inflam in early & late phase asthma
  - inhibit cytokines ⇒ ↓inflam, ↓mucus, ↓bronchoconstriction
- not used in acute attack
- has additive effects in β agonists in maintenance therapy

Drugs Used in Pulmonary Hypertension

Iloprost

- used in pulmonary hypertension
- nebulised in 20mcg doses (with special equip) every 2hrs up to 48hrs
- response =:
  - ↑ed CO or ↑ScvO2
  - may not actually see a drop in PA pressures
- MOA:
  - synthetic prostacyclin analog
  - causes drect vasodilation of pulmon arterial bed
  - minor effects on systemic vascular bed
- uncommon to see rebound pulmon HTN or systemic hypotension
  ↳ major adv over nitric oxide!
- can use concurrently with sildenafil as have diff MOA
- adverse reactions:
  - platelet function inhibition
  - bronchospasm
- caution in:
  - severe liver failure
  - severe asthma
  - active bleeding
  - pregnancy

Sildenafil

- used prophylactically in pulmonary hypertension
  ↳ only available in tablet form
- inhibits phosphodiesterase 5 (PDE IV) ⇒ ↑conc of NO ⇒ vasoD on smooth mm
- can react potently with other vasoDs – esp nitrates

Nitric Oxide

Chemical

- Nitric oxide (NO) = very different to nitrous oxide (N2O)
- NO = endogenous molecule but potentially a contaminant in nitrous oxde cylinders
- formerly called endothelium-derived relaxing factor (EDRF)
- synthesis:
  - from 1 of terminal guanidine nitrogen atoms of L-arginine
  - process catalysed by nitric oxide synthase (NOS)

- NOS present in 2 forms:
  - constitutive –
    - present in endothelial, neuronal, skeletal mm, cardiac tissue, platelets
    - Ca2+/calmodulin dependant
    - stimulated by cGMP
  - inducible –
    - only seen after exposure to endotoxin or certain cytokines from endothelium, smooth mm, myocytes or immune cells
    - large quantaties of NO able to be produced ⇒
      - cytotoxic
      - form free radicals ⇒ cellular damage & capillary leakage

Uses

- pulmonary hypertension

Adverse Reactions

- CVS:
  - vasodilator tone in small arteries & arterioles = dependant on continual localised supply of NO
  - shear stress ⇒ ↑NO production ∴ accounting for flow dependant vasoD
  - NO from endothelium inhibits platelets aggregation
  - septic shock ⇒ ↑↑↑NO ⇒ hypotension & capillary leakage
- resp:
  - endogenous NO = basal vasodilatory tone in pulmon & bronchial vessels
    ↳ can be reversed in hypoxia
    ↳no active broncho-dilatory properties
  - neonates: inhaled NO can cause:
    - ARDS – improved V/Q matching
    - ↓ed pulmon HTN
  - inhaled NO has no CVS effect as rapidly inactivated by rbcs
    - affinity for Hb x1500 that of carbon monoxide
- immune: NO synthetised in macrophagues & neutrophils:
  - impt in killing certain pathogens
  - impt in host defence system
- haem: NO inhibits platelet aggregation
- neuronal:
  - nerves containing NO widely distributed
  - roles (proposed):
    - modulation of state of arousal
    - pain perception
    - apoptosis
    - long term neuronal depression or excitation
- sodium nitroprusside & nitrates eg GTN – exert effect by release of NO or metabolism to NO in smooth mm cells

Calcium Channel Antagonists

- see separate section under CVS drugs

Cholinergic Drugs

Anticholinergic (Antagonists)

- all = competitive antagonists of Ach at:
  - [normal doses] - muscarininc-Ach receptors
  - [v high doses] – also nictonic receptors at autonomic ganglia & eventually NMJ

Chemistry

- categorised by structure:
  - tertiary amines
    - naturally occuring
      - eg atropine & hyoscine = alkaloid of atropa belladonna
      - eg scopolamine = alkaloid of datura stramonium
    - synthetic form of atropine is made = homatropine
    - contain:
      - ester group (of tropic acid)
      - organic base gp (tropine for atropine, scopine for hyoscine)
    - atropine & hyoscine form water soluble salts
    - ionised at pH 7.4 but still lipophilic enough to cross membranes (BBB, placenta)
  - quaternary amines
    - all synthetic
    - eg glycopyrrolate & iptratropium bromide
    - do not cross bbb as highly polar (ionised)
      ↳∴ no central effects
- categorised by selectivity:
  - non selective for muscarinic receptors
    - atropine, hyoscine, glycopyrrolate
  - selective antagonists:
    - M1 = pirenzipine
    - M2 = gallamine

Structure-Activity

- all contain ester & basic group in same relation as Ach
- drugs have acetyl replaced by bulky aromatic ring
- this ring not hydrolysed by AchE or P-chE
- drugs contain cationic (+ve) portion that fit in muscarine-Ach receptor

Pharmacokinetics

A

- oral absorption not predictable
- glyco –
  - must be given IV or IM as is highly polar with v poor oral absorption
  - much quicker absorption via IM compared to atropine
- transdermal used in lipid soluble scopolamine/hyoscine

D

- atropine & hyoscine = large Vd(incl CNS) = 2.6L/kg
- glycopyrollaye + ipratropium = small Vd (v polar) = 0.66L/kg

M

- liver/tissue ester hydrolysis

E

- atropine
  - 18-50% excreted unchanged via kidneys
  - T1/2 alpha 1min, T1/2 beta 2hrs
- hyoscine:

  - almost fully metabolised (1% renal unchanged)
  - T1/2 2.5hrs
- glycol:
- 60% renal unchanged elim
  - T1/2 aplha 2-3min; T1/2 beta 1hr

Pharmacodynamics

Table 34.2 Comparison of antimuscarinic/anticholinergic drugs

Drug	Sedation	Heart rate	GI tone	Airway secretions	Mydriasis cycloplegia	Duration IV	Duration IM
Atropine	+	+++	−−	−	+	15–30 min	2–4 h
Scopolamine	+++	−/+	−	− −−	+++	30–60 min	4–6 h
Glycopyrrolate	0	++	− −−	− −−	0	2–4 h	6–8 h

− − −, markedly depressed; − −, moderately depressed; −, mildly depressed; 0, no effect; +, mildly increased; ++ moderately increased; +++, markedly increased; IM, intramuscular; IV, intravenous; GI, gastro-intestinal.

CVS (atropine > glycol)
- initially = bradycardia:
  - ?central effect ?ganglionic ?Bezold Jarisch reflex
  - occurs in vagotimised pts as well
- tachycardia – 80-90mins
- response to exercise unaffected
- ↑CO – esp in kids whose CO is rate dependant
- ↓diastolic time ⇒ ↓coronary flow ie it is not lusitropic
- ↑risk of ventricular arrhythmias

Secretions (glycol >atropine)
- ↓salivation, lacrimation, sweating, bronchial, GIT secretions

Smooth MM
- ↓GIT motility
- ↓Lower oesophageal sphincter tone ⇒ ↑reflux
- bronchodilation:
  - esp against reflex bronchospasm
  - effect is dose dependant:
    - low dose ⇒ ↓airways size by preferential blockade of neuronal M2 receptors
    - large dose ⇒ dilation via M3
  - not effective in bronchoconstriction from local mediators eg histamine
- bladder ↓tone

Eyes
- mydriasis ⇒ ↑IOP in acute narrow angle glaucoma
- cycloplegia (cilary mm relaxation) ⇒ cannot accommodate to near focus

CNS (atropine, hyoscine only)
- atropine:
  - low dose – restlessness
  - high dose – agitation & disorientation
  - kids – pyrexia – due to loss of sweating
- hyoscine:
  - low dose – sedation & amnesia
  - high dose = excitatory
- antiemetic = more with hyoscine
- antiParkinson = atropine & benzotropine

Other
- atropine also has LA properties

Posioning

- children eating berries of atropine belladonna
- Rx:
  - ↓body temp
  - +/- controlled ventilation
  - supportive care
  - antidote = physostigmine – tertiary ie crosses BBB

Atropine

Chemical

- =racemic mixture: levo form = active

MOA

- very little action at nicotinic receptors
- produces wide range of effects via M recpetors through body
- has affinity for M2 antagonism

Pharmacokinetics

- ready absorb oral/IV/mucus membranes/IM
  ↳very variable oral absorption
- peak plasma conc post IM 30mins
- duration of actin 4-6hrs
  ↳ocular effects can last longer
- 50% drug bound to plasma proteins
- crosses bbb & placenta
- metab in liver; excreted urine (30-50% unchanged)

Pharmacodynamics

- onset of action:
  - CVS effects within 1 circulation time
  - 5-10mins for ↓secretions

Adverse Reactions

- see earlier notes on anti-muscarinic drugs

Cautions/Contraindications

- contra:
  - known hypersensitivity to other muscarinic antagonists
  - myasthenia gravis
  - obstructive GI disease
  - narrow angle glaucoma
  - prostatic hypertrophy
  - urine retention
  - UC
  - intestinal atony/paralytic ileus

Interactions

- TCAs, antihistamines, phenothiazines – anticholinergic effects of these drugs have additive effect ⇒ ?delirium
- ↓gastric motility with atropine ⇒ ↓absorb of some drugs

Dose

- bradycardia: 500mcg IV upto 3mg
- arrest: 3mg IV stat

Glycopyrrolate

- lacks central effects
- less effects than atropine in:

  - ↓vagolytic,
  - ↓cardiac
  - ↓eye
- longer duration even though t1/2 beta only 1hr
  ↳ drying effects last up to 8hrs
- kinetics mimic neostigmine much better even in renal failure

Muscarinic Agonists

- aka cholinergic agonists
- are called muscarinic agonists as most active at muscarinic receptors but are nonselective ie also active at N-Ach receptors
- exogenous drugs mimick endogenous agonist Ach
- modications of drugs leads to receptor sensitivity & reistance to hydrolysis:
  - cabachol
    - carbamyl substtitues the acetyl
    - active at M-Ach & N-Ach Receptors
    - not hydrolysed
  - pilocarpine:
    - tertiary amine
    - not hydrolysed
    - partial M agonist
    - act at eye & exocrine glands
      ↳ less effective at heart, GIT

Effects

- CVS (M2):
  - brady cardia
  - ↓CO (↓atrial ionotropy)
  - vasodilation (via NO)

  ↳ all lead to ↓↓↓MAP
- smooth mm (M3):
  - ↑GIT motility
  - bronchi constrict
  - bladder contract, spincter relax
- exocrine glands (M3)
  - ↑salivation, lacrimation, sweat, bronchial secretions, GIT secretions
- eye:
  - myosis – constrictor pupilae ⇒ ↓IOP
  - contraction of cilary mm ⇒ accommodation ie near focusing

Usage

- little in anaesthesia
- glaucaome – pilocarpine eye drops – tertiary amine ∴ absorbed well
- bladder atony - carbachol

By Adam Hollingworth

VasoActive Drugs

Adreno-receptor Effects

(see physiology – neurophysiology section)
↳ summary:

- alpha receptors = overall ↑periph vasoconstriction
  - alpha 1
    - vascular (vein & artery) smooth mm contraction to all organs
      ↳ less effect on cerebral, coronary, pulmon circulations
    - mydriasis
    - contraction of bladder sphincter
  - alpha 2
    - post synaptic:
      - brain & spinal cord
      - aggregation platelets
      - ↓insulin release from pancreatic ß cells
    - presynaptic:
      - peripheral SNS nerves - inhibition further transmitter release
- beta 1 receptors =
  - +ve myocardial effects = chronotropy, ionotrophy, lusitropy (myocardial relaxation)
  - –ve myocardial effects = ↑VO2, arrhythmogenic
  - (relaxation on-sphnicter part of gut)
  - (aggregation of platelets)
  - (amylase secretion from salivary glands)
- Beta 2 receptors = overall VD & energy creation for activity
  - vasodilation (periph vascu, renal vasc, lung smooth mm)
  - (glycogenolysis in liver (also α effect)
  - (mm tremor)
  - (inhibition of histamine release from mast cells)
- B3 receptors =
  - (lipolysis of adipose)

Catecholamine Synthesis

(see physiology – neurophysiology section)
↳ summary:

l-phenylalanine → l-tyrosine → l-DOPA → dopamine → noradrenaline → adrenaline

↑1 ↑**2** ↑3 ↑4 ↑5

- 1= hydroxylase (liver)
- 2 = tyrosine hydroxylase
- 3 = DOPA decarboxylase
- 4 = dopamine ß hydroxylase
- 5 = phenyletanolamine-N-methyltransferase (PNMT)

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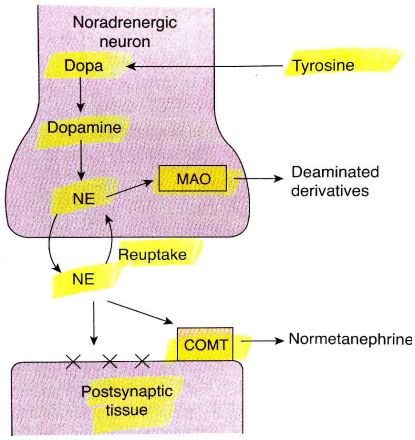
Cathecholamine Termination

(see physiology)



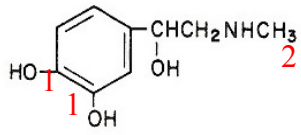
Summary of Drugs

	t1/2$_\beta$	α_1	α_2	β_1	β_2	Main uses
Direct acting Agonists						
Noradrenalin	~ 2min	+++	+++	++	+	ICU/ sepsis etc
Adrenalin	~ 2min	++	++	+++	+++	CPR/anaphylaxis
Isoprenaline	~2 hr	0	0	+++	+++	chemical pacing
Phenylephrine	~3hrs	++	0	0	0	↓BP/nasal decongest
Clonidine	12 hr	0	+++	0	0	HTN, analg/sedative
Salbutamol	4 hrs	0	0	0	+++	asthma/ prem labour
Terbutaline	4 hrs	0	0	0	+++	asthma
Dobutamine	2 min	+/-*	0	+++	+	ICU (CCF)
Indirect Agents						
Ephedrine	6 hrs	+	+	+++	++	↓BP/nasal decongest
Metaraminol*		+++	+	++	0	↓ BP
Antagonists						
Phenoxibenzamine	12 hr	+++	+++	0	0	Phaeochromocitoma
Phentolamine	2 hr	+++	+++	0	0	Phaeo / HTN crisis
Ergotamine		++(PA)	++	0	0	migraine
Prazocine	4 hr	+++	+			HTN, BPH
Doxazosine		+++	+	0	0	HTN, BPH
Yohimbine		+	+++	0	0	
Propranolol	5 hr	0	0	+++	+++	HTN,tremor,↑thyroid
Atenolol	6-9 hr	0	0	+++	+	HTN, IHD
Metoprolol	3 hr	0	0	+++	+	HTN, IHD
Alprenolol	2-3 hr	0	0	++(PA)	++	
oxprenolol	2-3 hr	0	0	++(PA)	++	
Labetolol	4 hr	+	+	++	++	HTN (PET)
Esmolol	9 **min**	0	0	+++(PA)		HTN, anti-arrhythm

Summary of CVS Effects

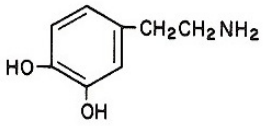
Drug, IV infusion dose (μg/kg/min)	Cardiovascular effects					
	CO	*Inotropy*	*HR*	*Preload*	*TPR*	*RBF*
Synthetic catecholamines						
Isoproterenol, 0.015	⇑–⇓	⇑⇑⇑	⇑⇑⇑	⇓	⇓⇓	–⇑
Dobutamine, 5	⇑⇑	⇑⇑	–⇑	?	–	–⇑
Synthetic noncatecholamines						
Indirect acting						
Ephedrine, 5–10 mg IV push	⇑	⇑	⇑	⇑⇑	⇑	⇑–⇓
Metaraminol, 0.5	–⇓	⇑	Reflex ⇓	⇑	⇑⇑⇑	⇓⇓⇓
Direct acting						
Phenylephrine, 0.15	–⇓	–	Reflex ⇓	⇑⇑⇑	⇑⇑	–⇓
Methoxamine, 5–10 mg IV push	–⇓	–	Reflex ⇓	–	⇑⇑	⇓⇓

Structure of Drugs

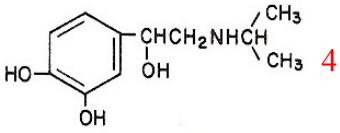


Epinephrine

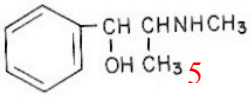
Norepinephrine



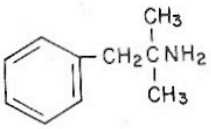
Dopamine



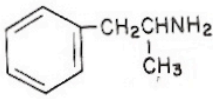
Isoproterenol



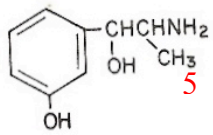
Ephedrine



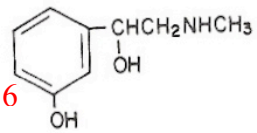
Mephentermine



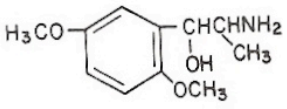
Amphetamine



Metaraminol



Phenylephrine



Methoxamine

Structure Activity Relationships

- 1 = all catecholamines have –OH groups in positions 3 & 4 of aromatic ring
- 2 = end terminal methyl group added by PNMT ⇒ ↑ß action
- 3 = ß carbon hydroxylation added by dopamine ß hydroxylase ⇒ ↑α receptor activity
- 4 = bulky amine ⇒ ↑ß receptor activity
- 5 = α carbon methylation prevents degredation by MAO ∴ longer duration of action & ↑NA release
- 6 = -OH gp on position 3 only ⇒ ↑α activity ie phenylepherine
- -OH group on 3 & 5 aromatic ring ⇒ ↑ß2 activity ie salbutamol

Adrenergic Drugs Classification

- diff types:
  - 1. direct acting agonists–
    - mimic affects of NA from nerve terminals or adrenaline from adrenals on adrenoceptors
    - eg adrenaline, NA
  - 2. Mixed/indirect acting agonists –
    - release NA indirectly and directly activate adrenoceptors
    - metaraminol & ephedrine, amphetamines
      ↳ ephedrine & amphetamines also block NA metabolism/reuptake
  - 3. other drugs with adrenergic effects:
    - phosphodiesterase inhibitors:
      - eg methylxantines, milrinone, levosimendam
    - glucagon
    - Ca2+
    - T3
  - 4. other drugs affecting noradrenergic neurons:
    - affect synthesis, storage, release or reuptake
  - 5. adrenoceptor antagonists:
    - α blockers
    - ß blockers
    - mixed blockers

1. Direct Acting

- naturally occurring catecholamines:
  - adrenaline
  - norad
  - dopamine
- synthetic catecholamines
  - dobutamine
  - isoprenaline
- synthetic agents:
  - phenylephrine
  - salbutamol
  - salmeterol
  - terbutaline

Adrenaline

MOA

- strong alpha and Beta agonist GPCRs:
  - α1 ⇒ ↑phospholipase C ⇒ hydrolyses PIP2 & release of IP3 ⇒ ↑intracellular Ca2+
  - α2 ⇒ inhibit adenylate cyclase ⇒ ↓cAMP conc
  - ß ⇒ a citvate adenylate cyclase ⇒ ↑cAMP conc
- low dose: predominate B activity on heart
  ↳B2>B1 activity (10x)
- high dose: ↑ing α ceptor action

Effects

- cardiac – vary according to dose:
  - [low dose] ⇒ ß effects predominate
  - [high doses] ⇒ α effects predominate
  - examples of action:

        - ↑iontropic – 2nd to ↑Ca [in]
        - ↑chronotropic effect – 2nd to effect on pacemaker cells in SAN
        - extrasystoles & ↑risk fibrillation – 2nd ↑excitability of purkinje fibres
        - ↑AV conduction - +ve dromotropic effect
- vasc effects:
    - [low dose]: ↓total periph resistance ⇒ ↓bp
    - [high dose]: ↑ing α action:
        - ↑periph resistance ⇒ ↑bp

      ↳however NET response norm vasodilation:
        - VC of vessels in skin & splachnic muscles
        - VD of skeletal mm
- renal:
    - renal art VC ⇒mod ↓renal blood flow
    - ↑bladder sphincter tone
    - direct ↑Na reabsorption of tubular Na transporters
    - ↑renin release via β1 receptors
- electrolytes:
    - [initially] ↑k release from liver
    - [later] ß2 effect of ↑K into cells

- CNS:
    - not a CNS stim at therapeutic doses

      ↳↑bp ⇒ ↑cerebral blood flow ⇒ 2nd improvement in CNS function
    - restlessness & tremor from skeletal mm effects
- Visceral smooth mm:
    - GI relaxation with contracted sphincters
    - urinary bladder: detrusor relaxation with contraction of sphincters
    - uterine relaxation – prevent premature labour
- Resp:
    - small ↑in minute volume
    - powerful bronchodilator (may make secretions more thick)
    - inhibits histamine from mast cells
- Metabolic:
    - overall ↑metabolic rate
    - ↑BSL by ↑glucose output from liver & ↓glucose uptake peripherally (via insulin effects)
    - insulin secretion initially ↑ed (ß2 effect) then ↓ed (α effect)
    - glucagon secretion ↑ed
    - ↑lipase activity ⇒ ↑free fatty acids in blood ⇒ ↑FFA oxidation & ketogenesis in liver
    - ↑serum lactate
    - ↑o2 consumption

Uses

- anapylaxis
- cardiac arrest
- vasoC adjuvant to LA's
- upper airway vasoC properties in upper airway oedema
- haemostatic agent
- ocular surgery –
    - induce mydriasis
    - ↓IOP
- 3rd line ionotrope/pressor for septic shock mostly

Drawbacks

- ↑oxygen consumption by heart ∴ not for IHD/failure

- tachycardia
- lactic acidosis
- hyperlactaemia
- arrhythmias

Pharmacokinetics

- not given orally – rapid metabolised by COMT & MAO of GI tract
- onset 3-5mins after inhalation
- metabolised as explained in physiology section
- short half life due to rapid metabolism ~2mins

Interactions

- α blockers ⇒ β effects predominate ⇒ ↓bp
- β blockers ⇒ α effects predominate:
  - VC ++ ⇒ ↑bp
  - severe bradycardia +/- heart block
- digoxin: additive effect ⇒ ↑risk arrhythmias
- halogenated anaesthetics: additive effect ⇒ ↑risk arrthymias
  ↳esp halothane but also enflurane, isolfurane
- TCAs, MAOIs, cocaine:
  - potentiate all effects of adrenaline ⇒ arrhtymias, ↑HR, ↑bp, hyperpyrexia

Warnings & Contraindications

- caution in people with DM, closed angle glaucoma, HTN, IHD, hyperthyroid, Parkinsons
- end artery areas ⇒ risk necrosis

Dose

- 1:1000 (IM)= 1ml = 1mg
- 1:10,000 (IV formula):
  - 1ml = 0.1mg
  - 10ml = 1mg

Noradrenaline

Presentation

- contains preservative sodium metabisulphite

MOA

- overall:
  - strong alpha 1 agonist ∴ VC in all vasc beds
  - mild B1 activity ∴ ↑ion/chrono-tropic cardiac effect
    ↳although v little NET effect on heart 2nd to vagal compensations & changes in periph resistance
  - no B2 ∴ avoids VD
- dose related effect:
  - [v low dose] (<0.02mg/min): ↑ed β1 stim
  - [high dose] (>0.04mg/min): α1 recruitment ⇒ VC

Effects

- CVS:
  - peripheral vasoC in all beds ⇒ ↑systolic & diastolic bp
  - may cause reflex bradycardia
  - CO may fall
  - ↑ed myocardial o2 consumption
    ↳but see vasoD coronary circulation & ↑coronary blood flow
  - ↑ed vasc resistance:
    - pulmonary
    - splachnic

        - uterine ⇒ ↓UBF ⇒ +/- foetal bradycardia
          ↳also may see uterine contractile effect ⇒ foetal asphyxia

Use

- =1st line for someone with refractory hypotension
  ↳shock (NB not cardiogenic ie ACS)
  - VC recruits blood from venous & splachnic system into arterial system
  - ↑systolic & diastolic pressure ⇒ ↑mean bp

Pharmacokinetics

- not for oral admin – same reason as adrenaline:
- onset of action 30 sec – 3mins
- 25% taken up as passes through lungs
  ↳not seen in adrenaline or dopamine
- metabolised by
  - reuptake:
    - 1 = neuronal ⇒ MAO or recycle
      ↳ predominant route
    - 2 = non neuronal ⇒ COMT
  - degredation (COMT & MAO)
- half life of 2mins due to rapid metabolism

Interactions

- see adrenaline

Warnings

- caution in pt with athersclerosis, PVD, HTN, cardiac ischaemia

Dopamine

- immediate precursor of NA
- endogenously exists as neurotransmitter

MOA

- acts
  - ↑release of NA
  - direct effect on receptors:
    - Dopaminergic receptors (D1 & D2)
    - β1
    - α1 & α2

Effects

- CVS = dose related:
  - [low] (0.5-2mcg/kg/min) : D1 receptors ⇒ VD of renal & mesenteric arteries
    ↳ now proven no clinical effect!!
  - [mod] (<10mcg/kg/min):
    - direct β1 stim
    - indirect β1 stim by ↑NA release from myocardial storage sites

    ↳⇒ ↑SV (less ↑HR) with no change in periph resistance
  - [high] (>10mcg/kg/min): α stim ⇒ ↑periph resistance ⇒ ↓renal blood flow
    ↳despite D1 effects
  - also ?less arrhythmogenic than adrenaline
- resp:
  - attenuation of carotid body to hypoxaemia
  - ↑pulmon vasc resistance
- splachnic: vasodilate mesenteric vessels via D1
- renal:
  - ↑UO actually thought to be due to mixed:

  - inhibition of prox tubule Na reabsorption
  - ↑ed CO & bp

  ↳rather than selective renal artery vasoD

- CNS:
  - cannot cross bbb (although L-dopa precursor can)
  - N&V via stim CTZ
- GI:
  - gastric transit time is increased

Uses

- now very limited clinical use.
- NA generally been shown to be preferential in all diseae gps

Pharmacokinetics

- IV infusion
- rapid onset 2-5mins & short duration of action 5-10mins
- dose not cross bbb ∴ doesn't activate central D receptors
- metab by MAO_B & COMT in liver, kidney & plasma
- 25% of dose is converted to NA in symp nerve terminals
- excrete via urine

Warnings

- see NA

Isoprenaline

MOA

- = β1, β2, β3 agonist (non selective β)
  - β1 – NET +ve cardiac effect
  - β2 – NET response VD in lung, skeletal mm, splachnic bed & GIT
    ↳also glycogenlysis in liver & insulin secretion
  - β3 – lipolysis & ↑insulin
- dose related:
  - [higher doses]: β2 effects > β1 effects ⇒ hypotension even though ↑CO

Effects

- CVS:
  - ß1 effects most notably ↑automaticity & AV nodal conduction in severe heart block
  - ↓myocardial O2 delivery 2nd via ↓myocardial blood flow caused by:
    - tachycardia
    - ↓diastolic bp – which drives coronary perfusion
      ↳ although is some myocardial vasoD to counteract this
- resp:
  - potent bronchodilatory & inhibitor of histamine release
  - ↑V/Q mismatch
  - ↑anatomical dead space

  ↳ ⇒ systemic hypoxaemia
- CNS: stimulant effect
- splachnic - ↑mesenteric & renal blood flow
- metabolic – as ß expected

Uses

- withdrawn in UK
- only real clinical use is in complete heart block as 'pharmacological pacing'

Pharmacokinetics

- oral administration erratic
- IV dosing – biphasic plasma conc:

  - 1st phase- 5mins – rapid uptake in smooth & cardiac mm
  - 2nd phase – several hours – widespread metabolism
- metab in by COMT in GIT, liver & lungs
- excreted in urine 60% unchanged

Interactions

- B Blockers – antagonise it
- entacapone – inhibits metab of isoprenaline ⇒ ↑plasma levels

Warnings & Contraindications

- caution in DM, elderly, ↑thyroid, IHD
- contraindicated if:
  - tachycardia
  - vent arrthymias
  - ACS

Dobutamine

Presentation

- either:
  - 20ml water containing 250mg dobutamine & sodium metabisulphite
  - 5ml water containing 250mg dobutmaine & ascorbic acid

MOA

- synthetic catecholamine derivative of isoprenaline
- ß1 effects predominate (with small ß2 effect):

Effects

- CVS:
  - ↑iontropy, contractility, myocardial O2 requirement
  - bp usually ↑ed despite small ß2 effect ⇒ ↓ed SVR
  - ↑AV conduction & risk of arrhythmia's

    ↳must avoid in cardiac outflow obstruction eg AS, tamponande, HOCM
- splachnic - no affect on periph vasculature
- renal - ↑UO only as a result of ↑pressures

Uses

- short term Rx of patients with low cardiac output states:
  - cardiogenic shock - ACS
  - heart failure

    ↳it causes progressive ↑CO & ↓PAWP ⇒ ↑vent contraction

Pharmacokinetics

- onset action 1-2 min
- half life 2mins 10mins
- plasma half life <3mins – rapid metab by COMT ⇒ excreted via kidney

Cautions & contraindications

- similar to norad & isoprenaline
- contraindications:
  - AF
  - vent arrthymias
  - phaeocytochromia

Phenylephrine

Chemical

- direct acting sympathomimetic synthetic amine

Presentation

- IV liquid

- nasal spray as decongestant
- mydriatic eye agent

Mechanism of Action

- potent α1 agonist
- no effect on ß receptors

Effects

- CVS:
  - raises SVR of all beds ⇒↑bp
  - reflex bradycardia

  ↳∴ drop in CO but is not arrhythmogenic
- no CNS effects
- renal effects as NA
- uterus – shows more favourable cord gas profile

Pharmacokinetics

- rapid onset lasting 5-10mins
- IM injection ⇒ 15min onset, then 1hr duration
- not metabolised by MAO
- products of metab & route of elimination have not been identified

Pharmacodynamics

Adverse Reactions

Dose

Comparisons

- Adrenaline > dobutamine for alpha receptors
- Noradrenaline > adrenaline for alpha
- Adrenaline > phenylephrine for beta 1
- isoprenaline all β

2. Mixed/Indirect Agents

Ephedrine

Chemical

- natural product of ephedra plant
- synthesised for medical use

Presentation

- tablet, elixir, nasal drps, injection solution
- exists as 4 isomers but only L-isomer is active

Mechanism of Action

- various mechanisms:
  - direct ß > α
  - indirect:
    - causes NA release from nerve terminals:
      - similar enough structure to be transported into nerve terminal by uptake-1
      - causes displacement of NA from vesicle into cytosol

        ↳prone to tachyphylaxis as NA stores are depleted
    - inhibits NA metabolism by inhibiting MAO
    - competes with NA for reuptake presynaptically

Effects

- generally v similar to adrenaline ie ß > α effects

  ↳but is less potent & longer acting
- CVS:

- ↑CO due to:
  - ß1 effects
  - indirect α mediated venoconstriction ⇒ ↑preload
- also ↑SBP + DBP, ↑coronary flow, ↑myocardial VO2

- renal/splachnic:
  - ↓flow ⇒ ↓GFR
- CNS:
  - stimulating effect ⇒ ↑MAC
    ↳ less than amphetamines which have marked CNS penetration & stimulation

Uses

- Anaesthetic associated hypotension
- obstetrics – less significant maternal hypertension than with pure α agonists
  ↳but does ⇒ worse cord gas pH compared to phenylepherine
- bronchospasm
- nocturnal enuresis
- narcolepsy

Pharmacokinetics

- well absorbed via all routes
- not metabolised by MAO or COMT ∴ longder duration of action & t1/2elim (4hrs)
- some metab in liver
- 65% excreted unchanged in urine

Metaraminol

Chemical

- synthetic amine

Mechanism of Action

- mixed action:
  - direct effects: α1 > ß
  - indirect: stimulates release of NA

Effects

- CVS:
  - ↑SBP & DBP 2nd to ↑SVR
  - reflex bradycardia
  - despite ß action CO often drops due to ↑ed SVR
  - coronary artery flow ↑ed by indirect mechanism
  - ↑ed PVR ⇒ ↑pulmon vasc pressures

Pharmacokinetics

- onset within minutes
- duration of effect 30-90mins depending on dose
- very comparable to phenylephrine:
  - onset <1min
  - effect lasts 15-20mins depending on dose

3. Other Drugs With Adrenergic Actions

Theophylline

- = non selective phosphodiasterase inhibitor
- see resp drugs section

Milrinone

Chemical

- = bipyridine derivative
- selective phosphodiesterase III inhibitor
  ↳ = cardiac subtype

Mechanism of Action

- prevents degredation of cAMP +/- cGMP in cardiac & vasc smooth mm
- myocardium:
  - ↑cAMP within myocardium ⇒ ↑slow Ca inward current during cardiac AP
  - ⇒ ↑Ca release from intracellular stores ⇒ ↑Ca conc in vicinity of contractile proteins ⇒ +ve ionotropy
- smooth mm: interferes with Ca flux into smooth mm ⇒ vasoD

Effects

- CVS:
  - 'ionodilator': +ve ionotropy & vasoD
  - vasodilation of all beds incl pulmon vasc bed
  - bp unchanged or ↓ed
  - ↑HR
  - only mod ↑ed chance of arrhythmias
  - ↓ed atrial & ventricular & AVN refractoriness
- special CVS populations:
  - pts with heart failure:
    - ↑CO 30%, ↓end diastolic filling pressures by 35%
    - myocardial O2 extraction ratio unchanged due to:
      - ↓ed wall tension
      - ↑coronary artery perfusion
  - pts with IHD:
    - ↓in coronary perfusion pressure & ↑HR may outweigh improved myocardial blood flow ⇒ more ischaemia
- agranulocytosis also been reported

Pharmacokinetics

- 70% PPB
- t1/2elim 1-2.5hrs
- 80% excreted unchanged in urine
  ↳ should have ↓ed dose in renal failure

Levosimendam

- v new stereoselective drug
- Ca sensitising agent:
  - troponin C activity is enhanced ⇒ removal of troponin I ⇒ ↑force of contraction for same level of intracellular Ca
- also activates mitochondrial K-ATPase which cardioprotective in ischaemia
- seems to have better inotropic effect with smaller ↑myocardial VO2 than milrinone

Glucagon

- secreted endogenously from α cells in pancreas
- glucagon receptors (GPCR) activation ⇒ stim adenylate cyclase ⇒ ↑intracellular c-AMP
- effect is +ve ionotropic
- = physiological antagonist to BBlockers
- side effects:

- hyperglycaemia
- ↑K

Calcium

- exogenous IV Ca will often improve blood pressure for a few minutes but only transient
- only really used in hyperkalaemia or CCB overdose

T_3

- T3 & T4 both have +ve inotropy & chronotropy via intracellular mechanisms
- only used in hypothyroidism

4. Other drugs affecting noradrenergic neurons

Drugs Affecting NA Synthesis

- alpha-methyl-tyrosine:
  - inhibits tyrosine hydroxylase (rate limiting enzyme)
  - sometimes used in inoperable phaeochromocytoma
- carbidopa:
  - inhibits DOPA-decarboxilase
  - used as adjunct with L dopa in parkinsonism:
    - prevents L-DOPA being metabolised to dopamine & NA peripherally ∴ ↓periph dopamine/NA side effects
    - cannot cross bbb ∴ doesn't inhibit central dopamine production
- **methyldopa**:
  - tablets or IV formulation
  - 20% PPB
  - 50% excreted unchanged in urine
  - readily crossed bbb
  - uptake into neurons where decarboxylated to α-methyl-noradrenaline
  - α-methyl-noradrenaline has various actions:
    - MAO unable to metabolise it ⇒ ↑conc in neurone ⇒ displacement of NA from vesicle ⇒ ↑ed NA MAO metabolism ⇒ depletion of NA ⇒ ↓SVR ⇒ ↓bp
    - potent α2 agonist > α1 (10:1):
      ↳ see antiHTN section (centrally acting drugs)
      ↳ ie clonidine like effect
      - periph presynaptic α2 stim ⇒ ↓NA release
      - central α2 stim in nucleus tractus solitarii ⇒ ↓central NA release ⇒ ↓centrally mediated SNS tone ⇒ ↓bp
  - used in gestational HTN
  - unique side effects:
    - haematological - +ve direct Coombs in 10-20%
    - allergic:
      - autoimmune haemolytic anaemia
      - eosinophilia with fever is possible in first few weeks
      - hypersensitivity ⇒ myocarditis
    - renal: urine darker due to breakdown products of drug
    - hepatic: long term liver function deteriorates

Drugs Affecting NA Storage

- reserpine:
  - central & peripheral action
  - non selective – also affects dopamine & 5-HT
  - blocks uptake of NA from cytosol ⇒ vesicles

- NA ∴ degraded by MAO ⇒ ↓NA (via depletion)
- effects:
  - antihypertensive use – NA depletion
  - central effect also inhibits uptake of dopamine & 5-HT in brain ⇒ depression

Drugs Affecting NA Release

- drugs preventing exocytosis of NA containing granules:
  - prevent them from fusing with membrane in norm way
  - eg guanethidine, bretilium
- causing ↑ed release of NA in absence of nerve terminal depolarisation:
  - ie indirect acting drugs – ephedrine & metaraminol
- interaction with presynaptic receptors:
  - enhancing ß2 or inhibiting α2

Inhibitors of NA Uptake

- inhibits either uptake-1 or uptake-2:
  - neuronal (1) = impt in removing NA affects (released or exogenous)
  - non-neuronal (2) = impt in clearing endogenous adrenaline
- uptake 1 inhibitors:
  - Tricyclics:
    - main effect in CNS due to high lipid solubility eg euphoria, excitement
    - periph effects eg tachycardia, HTN, arrhythmias
  - Ephedrine
  - Cocaine:
    - periph or central effects
- uptake 2 inhibitors:
  - not affected by most drugs which inhibit uptake 1
  - eg steroids ⇒ explains beneficial effect in asthma

5. Adrenoceptor Antagonists

- subclassification:
  - α antagonists
  - ß antagonists
  - mixed antangonists

α Antagonists

- classified into:
  - non-selective (α1, α2):
    - all produce:
      - vasodilation ⇒ ↓bp
      - ↑ed reflex tachycardia as α2 not blocked ∴ ⇒ ↑NA release acting on unaffected ß1
      - ↑GIT mobility with diarrhoea as side effect
    - examples:
      - phentolamine = reversible competitive
      - phenoxybenzamine = irreversible competitive
        (↳ but both have some α2 effects)
  - selective:
    - more useful as isolated vasodilation of arteries, veins & arterioles ⇒
      - ↓CVP ⇒ ↓CO ⇒ ↓↓bp
      - also beneficial ↓LDL & ↑HDL
      - usually less reflex tachycardia as no α2 blocking affects
      - useful in urinary retention
    - examples:
      - α1 = prazocin (short acting), doxasozin or terazosin (longer acting)
      - α2 = yohimbine

---

revision:

- alpha receptors = overall ↑periph vasoconstriction
  - alpha 1
    - vascular (vein & artery) smooth mm contraction to all organs
      ↳ less effect on cerebral, coronary, pulmon circulations
    - mydriasis
    - contraction of bladder sphincter
  - alpha 2
    - post synaptic (CNS & spinal cord)
      - α2a = sympatholysis & sedation
      - α2b = vasoC & anti shiver
      - α2c = behaviour & startle response
    - presynaptic (perioh SNS nerves): inhibition further transmitter release

---

Summary of Uses of α Blockers

- HTN – α1 blockers better as
  - less reflex tachy, arrhythmias or diarrhoea
  - ↓LDL, ↑HDL
- BPH – α1 blockers
- phaemchromocytoma:
  - preop – irreversible non selective α blockers & ß blocker
    ↳ must establish α blockade first otherwise ↑↑HTN due to unopposed α1 affect
  - intraop – reversible short active α blockers for tumour manipulation

Phentolamine

Chemical

- = imidazolone
- = reversible competitive non selective α blocker
- affinity for α1 receptors is x3 than α2 receptors

Presentation

- phentolamine mesylate pale yellow solution

Pharmacokinetics

- OBA 20%
- 50% PPB
- 10% excreted unchanged in urine
- t1/2elim 20mis

Uses

- hypertensive crises due to excessive sympathomimetics
- MAOI reactions with tyramine
- phaeochromocytoma esp during tumour manipulation

Effects

- CVS:
  - α1 block ⇒ VasoD incl pulmon artery pressures & nasal congestion++
  - α2 block ⇒ ↑HR & ↑CO
- resp: acute bronchospasm – sulphites in preservatives may ⇒ hypersensitivity reactions
- GIT: ↑secretions & motility
- metabolic: ↑insulin secretion ⇒ ?hypoglycaemia

Dose

- 1-5mg titrated to effect
- onset of action in 1-2mins
- duration of action is 5-20mins

Phenoxybenzamine

Chemical

- =long acting irreversible non selective α blocker
- high affinity for α1

Presentation

- straw coloured
- phe-noxy-benzamine hydrochloride with
  - ethyl alcohol
  - hydrochloric acid
  - propylene glycol
- IV or oral

Uses

- pre-op managemement of phaeochromocytoma – allows expansion of intravascular compartment
- HTN crises
- adjunct to Rx of severe shock

Mechanism of Action

- reactive intermediate forms a covalent bond on the α adrenoceptor ⇒ irreversible blockade
- in addition to receptor blockade drug also inhibits uptake of catecholamines into tissues

Effects

- CVS: - same in class
- CNS:
  - marked sedation

  - seziures after rapid IV injection
  - meiosis
- misc: impotence, contact dermatitis

Pharmacokinetics

- OBA 25% - variable absorption
- plasma ½ life = 24hrs
  ↳ but 3 days to synthesise new α receptors
- metab in liver
- excreted in urine & bile

Dose

- oral 10mg daily, titrated up to 1-2mg/kg/day
- IV: CVL injection 1mg/kg/day as slow infusion
- max effect 1hr following IV dose
- effects persist for 3 days

Prazosin

Chemical

- =quin-azo-line derivative
- highly selective α1 antagonist:
  - short acting
  - terazosin, doxazosin = longer half lives ∴ once daily dosing

Presentation

- tablets

Uses

- antihypertensive
- heart failure
- Raynauds syndrome
- BPH

Effects

- CVS:
  - vasoD or arteries, veins ⇒ ↓SVR (diastolic falls the most)
  - CO in norm will ↓ due to ↓preload
    ↳if heart failure may see ↑CO depending on Starling curve
  - minimal reflex tachycardia
- Urinary – relaxes bladder trigone & sphincter mm ⇒ improved urine flow
- CNS: fatigue, headache, vertigo, nausea
  ↳ but get better with continued use
- misc: may produce false +ve when screening for phaeo ie VMA & MHPG

Pharmacokinetics

- plasma level peaks 90mins post oral dose, plasma half life 3hrs
- variable OBA 50-80%
- high PPB to albumin
- extensive liver metab ⇒ some active metabolites
- excreted mostly in bile ∴ safe in renal failure

Dose

- tds dosing: 0.5mgtds which ↑ed to 20mg/day
- onset of action ~90mins, lasted around 3-4hrs

Yohimbine

- principle alkaloid of the bark of the yohimbe tree is formulated as the hydrochloride
- used in Rx of impotence

- causes:
  - presynaptic α2 block ⇒ NA release:
    - ↑HR & bp
    - may precipitate orthostatic hypotension
    - can block hypotension caused by clonidine
  - postsynaptic α2 block complex related to organ:
    - ADH effect
    - anxiety & mania

ß Blockers

Subtypes

- all = competitive antagonists which block actions of catecholamines
- features used to classify ß blockers:
  - β1 selective blockers =
    - cardioselective
    - eg atenolol, esmolol, metoprolol
  - effects at other receptors – eg:
    - propranolol – also has action to block Na channels
    - (carvedilol - also α blocker)
    - (labetalol – also α blocker)
  - intrinsic sympathomimetic activity ie = partial agonists
    - eg labetalol, bisoprolol, carvidelol
  - membrane stabilising qualities
    - eg metoprolol, labetalol, carvedilol, propranolol

  ↳ variation of these per drug create differences between diff drugs
- prolonged administration may ⇒ tachyphylaxis ie ↑in number of ß receptors
  ↳& thus risk with sudden withdrawal of rebound

Drug	β_1 potency ratio[a]	Relative β_1 selectivity	Intrinsic sympathomimetic activity	Membrane stabilizing activity	Lipid solubility	Elimination half-life (h)	Total body clearance (mL/min)	Metabolism
Atenolol	1.0	++	0	0	low	6–9	130	renal
Carvedilol	10.0	0	0 +	++	moderate	7–10	0.6	hepatic
Esmolol	0.02	++	0	0	low high	0.15	27 000	esterases[b]
Labetalol	0.3	0	+?	+	low	3–4	2700	hepatic
Metoprolol	1.0	++	0	+	moderate	3–4	1,100	hepatic
Nadolol	1.0	0	0	0	low	14–24	200	renal
Pindolol	6.0	0	++	+	moderate	3–4	400	renal/hepatic
Propranolol	1.0	0	0	++	high	3–4	1000	hepatic
Timolol	6.0	0	0	0	low	4–5	660	renal/hepatic

Receptor Selectivity

- highly ß1 selective =
  - atenolol
  - esmolol
  - metoprolol

  ↳ if give high dose will also see ß2 antagonism
- ß2 antagonism ⇒ unwanted effects

Intrinsic Sympathomimetic Activity (ISA)

- partial agonists = unable to elicit max response (that seen with full agonist) despite normal receptor affinity

- effects of ISA depends on endogenous levels of circulating catecholamines:
  - low catecholamine + partial agonist ⇒ +ve sympathomimetic tone
  - already high catecholamine (eg severe heart failure) + PA ⇒ -ve sympathomimetic tone ⇒ bradycardia & heart failure

  ↳ feature of the partial agonists

Membrane Stabilising Activity

- effects of little clinical significance as doses required to elicit them are too high in vivo

Effects

- cardiac effects:
  - β1 blockade ⇒
    - ↓chronotropic, ↓inotropic ⇒↓CO
    - ↓SAN automaticity, ↓conduction velocity across atria
    - AVN ↑conduction time ⇒ bradycardia

      ↳ change in myocardial oxygen supply/demand –

      ↳ with balance to the better ∴ use as anti-anginal

      ↳ need to be careful if LV failure however
      - good:
        - [↑supply] bradycardia ⇒ ↑s diastole ∴ ↑coronary perfusion time
        - [↓demand] ↓ed contractility
      - bad:
        - [↑demand] prolonged systolic ejection time
        - [↓supply] dilation of ventricles (↑ed wall tension)
        - [↓supply] ß2 block ⇒ ↑ed coronary vasoC

- circulatory effects:
  - antiHT effect not fully understood but:
    - ↓CO with no reflex change in periph resistance
    - ↓HR
    - baroreceptors reset at lower level
    - ↓SVR:
      - ↓symp outflow from central vasomotor centre
      - blockage of pre-synaptic ß2-facilitatory receptors ⇒ ↓NA release

      ↳initial compensatory α1 mediated vasoC – unmasked with time
    - inhibition renin-AT system:
      - ß1 block at juxtaglomerular apparatus ⇒ ↓renin relase from kidney
      - ⇒ ↓AT I & ATII ⇒
        - ↓vaso C
        - ↓aldosterone ⇒ ↓volume
  - ß2 blocking effects will ⇒ element of vasoconstriction:
    - appears to have little effect on bp
    - will cause poor periph circulation & cold hands
- resp:
  - all ßB's in sufficient doses will block ß2 ⇒ bronchoconstriction
- metabolic:

  (catecholamines normal role in ↓BSL = ↑glycogenlysis & glucogenesis from liver via ß2)
  - ∴ non selective ß blockers may:
    - in exercise & hypoglycaemia ⇒ prevent ↑in blood sugar

      ↳lipolysis = ß3 response
    - @rest in diabetics ⇒ ↑in blood sugar

    ↳ ∴ don't use with hypoglycaemic agents

  - ßB may mask normal symptoms of hypoglycaemia
  - altered lipid metabolism ⇒ ↑LDL & ↓HDL
- CNS effects:
  - more predominant in more lipid soluble ßBs (metoprolol, propranolol)
  - include:
    - Antidepressant/antianxiety although may see opposite effect
    - fatigue, insomnia, nightmares,
    - ↓melatonin release via block CNS β1 ⇒ sleep disturbances
- ocular: ↓IOP - ↓ed reduction of aqueous humour
- Gut: dry mouth & GI disturbance

Indications

- angina
- HTN – as above
- anti-arrhythmogenic – as above
- post ACS – acute & long term – as above
- heart failure – selective β1 blockers ↓risk of arrhythmias in low dose
- thyrotoxicosis – problems occur via catecholamine overdive
- benign essrntial tremor
- migraine prophylacis
- phaeochromocytoma
- glaucoma – topical

Perioperative ßB's

- periop use has been shown to ↓mortality
  ↳despite additive myocardial depressant affect from volatiles/IV agents
- controversy on prophylactic use & how long to continue use
- pts must continue to take BB therapy during periop period

Pharmacokinetics

- varying liver solubility confers biggest difference:
  - low lipid (atenolol) =
    - poor absorb from gut
    - little hepatic metab
    - excreted largely unchanged
  - high lipid solubility (metoprolol):
    - well absorbed
    - extensive liver metab
    - shorter half life
    - cross bbb easier ∴ more CNS side effects
- either eliminated by liver OR excreted free drugs eg
  - metoprolol – metab in liver ∴ better in pts with renal failure
  - atenolol – predom cleared by renal ∴better in pts with liver impairment

Atenolol:

- IV or oral
- 50-100% bioavailability
- 5% PPB
- t1/2elim 7hr (but actions last longer)
- elim unchanged renally 85-100%
- dose 25-100mg/day

Esmolol

- highly lipophilic, cardioselective
- rapid onset & offset
- 10mg boluses to effect

- useful in short term Rx of tachycardia & HTN & acute SVT
- no ISA or membrane stabilising
- irritant to veins & extravasation may ⇒ necrosis

PK

- IV only
- 60% PPB
- rapid metabolism by red blood cell esterases to
  - inactive metabolite (has a long half life)
  - methyl alcohol

  ↳esterases not P-ChE ∴ no change in action of sux
- t1/2elim 10mins

Metoprolol:

- cardioselective, no ISA
- early use in MI:
  - ↓infarct size
  - ↓incidence of VF

PK

- 40% bioavailability (rapid complete absorption but high 1st pass metab)
  ↳↑ed with food
- 20% PPB
- 90% hepatic metabolism exhibits genetic polymorphism with 2 half life profiles or 3 or 7 hours
  ↳fast or slow metabolisers
- crosses bbb & placenta well

Sotalol

- 100% OBA

otherwise see arrhythmia section

Propanolol

- =non selective with no ISA
- has Na channel blocking effect ie membrane stabilising
- racemic mixture:
  - S-isomer confers most of effects
  - R-isomer only responsible for stopping periph conversion T4 ⇒ T3
    ↳ ∴ ßB of choice in thyrotoxicosis

PK

- OBA 30% (well absorbed but high 1st pass metab)
- high lipid soluble
- high PPB – may be displaced by heparin
- hepatic metabolism:
  - R-isomer is more rapid than S-isomer
  - one of metabolites remains active (4=hydroxyl=propranolol)
- elimination is impaired in renal failure (unknown mechanism)
- t1/2elim 4hrs but duration of action longer

ßB Withdrawal

- must withdraw drugs slowly to avoid rebound syndrome:
  - ↑bp
  - angina
  - vent arrythmias
  - ACS

  ↳∴ half dose ev 2/7 over 14/7

Interactions

- adrenaline ⇒ severe ↑bp & bradycardia

- antidiabetic agents – oral hypoglycaemics, insulin ⇒ mask symptos of hypo
- digoxin – additive effect ⇒ ↑AV conduction time
- Ca channel blockers ⇒ ↑cardiac depression effects ⇒ ↓HR ↓SV ↓conduction
- Clonidine – severe adverse reactions. Each assoc with withdrawal symptoms eg reboung HTN
- NSAIDs – additive effect: ↓bp

Cautions, Contraindications

- contraindications:
  - asthma/COPD – inhibition of β2 bronnchodilation
  - heart block/bradycardia
  - severe ↓bp/cardiogenic shock

Beta Blocker OD

- life threatening and severe toxidrome!
- Treatment options:
  - high dose insulin/dextrose infusion
  - IV calcium
  - glucagon – limited effect. Need extreme high dosing
  - intralipid
  - pacing
  - dialysis (atenolol & sotalol only)
  - CPB
- Features:
  - CNS toxicity - ↓GCS, confusion, seizures
  - Oesophageal spacitiy – rare
- Symptoms of toxicity take 2-4hrs start
- emetics should not be used as cog decline can lead to aspiration
  ↳eg ipecacuanha derivatives
- glucagon
  - takes ~ 1min to reach max serum conc
  - half life ~6mins
  - SE:
    - N&V – as relaxes lower oesophageal tone

Mixed Acting α & ß Blockers

Labetalol

- = α & ß blocker:
  - α1 selective
  - ß non selective

Mechanism of Action

- contains 2 asymetric centres
- exists as mixture of 4 stereoisomers present in equal proportions:
  - SR-stereoisomer = α1 effects
  - RR-stereoisomer = ß effects
- ratio of α1:ß block depends on route of admin:
  - oral = α 1:3 ß
  - IV = α 1:7 ß

Effects

- summary effect is to ↓myocardial afterload & ↑myocardial oxygen demand:
  - α1 block ⇒ vasoD ↳ ∴ ideal for angina
  - ß block ⇒ prevents reflex tachycardia

Uses

- IV:
  - HTN crises
  - facilitate hypotension during surgery
- oral:
  - HTN & angina
  - HTN of pregnancy

Pharmacokinetics

- OBA 25% (well absorbed but high 1st pass metab
  ↳↑s with age & administration with food
- PPB 50%
- liver metab ⇒ inactive metabolites

AntiAnginals

A Comparison

Effect	Nitrates	BBlockers	Ca Channel Blockers
systolic bp	↓	↓	↓
vent volume	↓	↑	↓ or -
HR	↑	↓	↓↑ or -
myocardial contractility	-	↓	↓
coronary blood flow	↑	↑ or -	↑
coronary vessel resistance	↓	↑ or -	↓
coronary spasm	↓	↑ or -	↓
collat coronary blood flow	↑	-	↓

Classification of Anti-Hypertensives

- many ways to classify them
- considerable overlap between groups
- by mechanism of action:
    - centrally acting:
        - clonidine
        - dexmedetomidine
        - methyldopa
    - ganglion blockers
        - not used anymore
        - eg trimetaphan -
    - noradrenergic neurone blockers
        - eg reserpine,
        - α-methyl-tyrosine
    - adrenoreceptor blockers :
        - α blockers
        - ß bockers
        - mixed blockers

        ↳ see prev adrenoceptor section
    - vasodilators:
        - ACEIs
        - nitrovasodilators
        - K channel activators
        - misc - hydralazine
    - Calcium channel blockers
    - diuretics
    - others:
        - ketanserin
        - adenosine

Central Acting Anti-Hypertensives

- sub classification:
  - α2 agonists:
    - clonidine
    - dexmedetomidine
    - methyldopa

Alpha-2 Receptor

- GPCR (Gi): agony ⇒ ↓c-AMP
- 3 subtypes:
  - α2-a
  - α2-b
  - α2-c
- types found throughout the body and large overlap & misunderstanding between specific effects but:
  - type α2-a:
    - sedation & hypnosis – via locus ceruleus (LC)
    - analgesia – mostly spinal (but also periph & supraspinal)
    - sympatholysis ie ↓bp
    - inhibition of seizures
  - type α2-b:
    - vasoC ⇒ ↑bp (coupled to L-type Ca channel)
      ↳ mechanism of HTN in etomidate
    - antishivering – hypothalamus effect
    - endogenous analgesia mechanism
    - analgesic effect of H20
  - type α2-c:
    - learning/behaviour
    - startle response
    - feedback inhibition of adrenal catecholamine release

Summary of Alpha-2 receptor effects

(remember from vaso-active section
↳ primary explaining periph receptor effects)

- alpha 2
  - post synaptic: CNS & Spinal cord
  - presynaptic: periph SNS inhibition further transmitter release

- following in regards to central & periph effects

1. Haemodynamic Effects

- hypotension & bradycardia
  - = most notable affect @ therapeutic doses
  - mainly central mechanism:
    - ↓SNS outflow via inhibition of vasomotor centre in brain stem:
      - stim of α2 neurons of NTS ⇒ enhances its inhibitory action on symp neurons of medulla
    - inhibit presynaptic symp neuronal activity in lat horn of Tx spinal cord
    - ↓ed ganglionic transmission
- periph vasoC:
  - action on post synaptic mostly α2-b receptors
  - effect depends on speed of injection:
    - rapid IV bolus ⇒ transient HTN

- slow increments ⇒ initial ↓bp, then as conc ↑s start to see ↑bp
  ↳ ie overcoming central sympatholytic effect
  ↳with therapeutic doses sympatholysis predominates

2. Cerebral Circulation

- mechanisms which may ⇒ cerebral ischaemia:
  - vasoC of cerebral vessels ⇒ ↓cerebral flow (without influencing cerebral metabolic O2 demand)
  - reactivity of vessels to CO2 is preserved/modestly attenuated

↳ despite this α2 agonists are neuroprotective following ischaemia (in animals)
↳ unkown mechanism

3. Hypnosis/Sedation

- α2-a ⇒ inactivation of locus ceruleus (LC) giving effects:
  - ↑sedation & MAC lowering effect
    ↳ this effect can be antagonised by α1 agonists
    ↳explains why clonidine can't produce complete anaesthesia (α2 200:1 α1 ratio)
  - Rx of drug withdrawal syndromes eg alcohol, opioids, cocaine

4. Analgesia

- sites & mechanisms not fully understood but spinal level likely most impt site

Spinal Analgesia

- activation of post-synaptic α2-a receptors on WDR neurons in dorsal horn
  - eg clonidine mimicks NA's role here ie potentiates descending inhibitory noradrenergic pathway:
    - from PAG, LC, dorsal raphe nucleus
    - descending pathway ⇒ NA release ⇒ -ve modulation of afferent signals from A-delta & C fibres from periphery ↳occurs in superficial dorsal horn
  - chronic pain ⇒ ↑number of α2-a receptors in dorsal horn
- synergistic action with opioid & cholinergic agonists
- neuraxial α2 agonist ⇒ release of NO
  - NO can help
    - ↓ perception of visceral pain
    - prevent allodynia, hyperalgesia, chronic pain
    - act directly on Na & K channels & block AP transimission ie LA effect

Supraspinal

- controversial what the mechanisms are
- ?effect at PAG, LC

Peripheral

- intrarticular injections ⇒ LA effect by ?release of enkephalins at nerve endings
- periph nerve blocks ⇒ prolonged duration of action

5. Endocrine

- blunt neuroendocrine surgical stress response in particular:
  - ↓cortisol
  - ↓vasopressin
  - ↓b-endorphins
  - ↓adrenaline & NA
- α2 agonists ⇒ ↑GH release

6. GIT

- ↓GIT motility via central & periph mechanisms
- total GIT transit time is delayed – worsened by concurrent opiates
  ↳ but gastric emptying **not** delayed

Clonidine

- originally developed in 1970 as nasal decongestant
- then used as anti-HTN drug

- due to sedative effects now 2nd line

Chemical

- =imidazole compound

Mechanism of action & Effects

- see above
- α2 agonist 200:1 α1 agonist

Pharmacokinetics

A

- OBA 100%
- onset 30mins: peak effect 60-90mins
- duration 8hrs

D

- PPB 30-40%
- Vd ~2L/kg

M

- main metabolite = inactive

E

- excretion:
  - 50% renally unchanged
  - 20% faeces
- t1/2 10-20hrs

Uses

- anti – HTN – 2nd line
- migraine prophylaxis
- anaesthesia:
  - sedative:
    - premed – but also helps with post op agitation esp in kids
    - ↓post op delirium if ketamine based anaesthesia
    - MAC sparing effect intra-op
  - analgesia:
    - opioid sparing effect
    - many diff routes: PO, IV, patch, neuraxial (esp caudals), with Las in periph blocks
  - blunting of CVS/neuroendocrine response eg to surg, intubation
  - anti-shivering
  - long term M&M benefit post op – similar to ßBs
  - Useful peri-op in addicts

Adverse Reactions

- SEs:
  - dry mouth
  - headaches
  - constipation, urinary retention
  - ↓sex drive
  - withdrawal can ⇒ HTN crisis

Cautions/Contraindications

- caution in
  - elderly
  - impaired AVN/SAN function
  - Hx depression
  - Raynauds
- contra in:
  - sick sinus
  - heart block

Interactions
- ↑sensitivity to IV catecholamines & indirect acting sympathomimetics eg ephedrine
- B blockers:
  - ↓↓bp & ↓HR
- TCAs:
  - ↓anti-HTN effect of clonidine

Dexmedetomidine
Chemical
- =S-stereoisomer of medetomidine
- an imidazole
Mechanism of Action
- more potent than clonidine
- greater selectivity for α2 receptors: α2 1600:1 α1
- full agonist
Effects
- same as clonidine
Uses
- IV infusion for sedation
- withdrawal form dubstnace dependence
- sedative for delecate procedures:
  - awake craniotomies
  - AFOI
  - vocal fold injuries
Presentation
- IV only
Pharmacokinetics
- extensive 1st pass liver metab
- VD 1.33 L/kg
- 94% PPB (albumin & aag)
- T1/2distr 6mins
- t1/2elim 2 hrs

Methyldopa
- covered in Adrenergic drugs section (under 4. Other drugs affecting noradrenergic neurons)
- summary:
  - mechanism of action multifactorial:
    - less selective α2 agonist > α1 (10:1)
    - MAO unable to metabolise it ⇒ ↑conc in neurone ⇒ displacement of NA from vesicle ⇒ ↑ed NA MAO metabolism

Ganglion Blockers

- rarely used due to side effects

Trimetaphan

Chemical

- = quaternary ammonium compound

Presentation

- pale yellow solution – used to induce hypotensive analgesia
- oral route not used anymore

Mechanism of Action

- 2 main:
  - competitive antagonist at all nicotinic ganglionic receptors incld at adrenal cortex
  - direct vasoD effect on periph vessels
  - (histamine release – but likely not significant contribution to ↓bp)
- it has no central effects

Effects

- CVS –
  - rapid hypotesion via ↓afterload & ↓preload
  - +/- reflex tachycardia
- CNS –
  - no direct effect on CBF as long as autoregulatory pressures not exceeded
  - does not cross bbb
  - cerebral metabolic rate unaffected
- resp: histamine ⇒ bronchospasm
- parasympathetic:
  - parasymp ganglion blockade ⇒ periph anticholinergic like side effects:
    ↳ [blind as a bat, red as a beet, hot as hell, dry as a bone, the bowel & bladder lose their tone, and the heart runs alone]
- misc:
  - inhibits P-ChE ⇒ prolongs depolarising muscle relaxants
    ↳also prolongs NDNMBs ?mechanism

Noradrenergic Neurone Blockers

Guanethidine

Mechanism of Action

- gains access to adrenergic neurone via uptake 1 (neuronal) transport mechanism
- Following IV admin – see triphasic response
  - initial ↓bp : via direct vasoD of arterioles
  - then ↑bp : via displacement of NA from nerve terminal
  - steady state = ↓bp: prevention of release of what little NA is left in nerve terminal

  ↳not seen orally
- does not alter secretion of catecholamines from adrenals

Effects

- CVS:
  - hypotension
  - post hypotension common as blocks compensatory rise in symp tone
  - fluid retention may occur ⇒ oedema
- GUT – diarrhoea
- misc – failure to ejaculate
- long term use ⇒ upregulation of adrenoceptors ⇒ pts very sensitive to direct sympathomimetics

Uses

- prev used as antiHTN
- currently only used for control of sympathetically mediated chronic pain

  ↳ regional blocks for chronic pain

Pharmacokinetics

- OBA 50%
- PPB 0%
- dose not cross bbb
- t1/2 elim many days
- hepatic metabolism
- renal excretion

Interactions

- drugs which block uptake 1 prevent action:
  - TCAs
  - cocaine

Reserpine

Chemical

- naturally occurring alkaloid

Mechanism of Action

- central & periph action:
  - prevents NA uptake from cytoplasm into vesicles
  - NA then metab by MAO
  - (serotonin also affected & depleted)

Effects

- CVS:
  - ↓bp – 2nd to ↓CO & ↓SVR
  - less postural hypotension
  - nasal congestion a problem
- CNS:
  - crosses bbb⇒ depression, lethargy & nightmares

    ↳NA & serotonin affect
  - extrapyramidal SEs
  - ↓MAC

- GIT:
  - diarrhoea & ↑gastric acid
- misc: sex dysfunction, hyperprolactinaemia, gynaecomastia

Uses

- Rx refractory HTN failed to respond to ßBs or diuretics
- no longer really used

Pharmacokinetics

- liver metab
- excretion:
  - unchanged drug via bile (most of the drug)
  - renal (metabolites)
- t1/2 life many days
- crosses placenta, bbb, breast milk

Interactions

- altered sensitivity to exogenous sympathomimetics:
  - direct acting = ↑sensitiity
  - indirect acting = ↓sensitivity (depleted NA stores)

Metirosine

- = competitive inhibitor of tyrosine hydroxylase
- ∴ prevents synthesis of catecholamines
- only used in management of phaeochromocytoma
- side effects:
  - severe diarrhoea
  - sedation
  - extrapyramidal effects
  - hypersensivity reactions

Vasodilators

- Direct acting VDs:
  - cardiac glycosides
  - Ca channel blockers
  - K channel activators
  - misc VDs
- indirect acting VDs:
  - central acting adrenergic inhibitors
  - ACEIs & ARBs
  - aldosterone receptor antagonists

ACEIs

- drugs to target RAAS system
  ↳renin, angiotensin, aldosterone system
- impt for physicians, less so for anaesthetists
- should be stopped peri-operatively due to risk of peri-op hypotension

Physiology Summary

- see physiology section: Renal>factor affecting ECF volume
- factors which will cause juxtaglomerular apparatus to ↑renin release:
  - ↑SNS outflow – ß1 effect on renal symp fibres
  - ↓renal perfusion
  - ↓Na & Cl delivered to macula densa
  - ↓ATII – preventing –ve feedback loop
- renin (80min t1/2) splits angiotensinogen into decapeptide ATI
- ACE converts ATI to ATII (and inactivates bradykinin)
- ATII is broken down in kidney & liver to:
  - ATIII & ATIV – which have some activity
  - other inactive metabolites
- ATII:
  - has 2 receptors:
    - AT_1
    - AT_2

    ↳ATII has stronger affinity for AT_1
- ATII effects:
  - profound vasoC –
    - x5 of NA
    - directly & indirectly via central mechanisms
  - Blockade uptake-1 of NA ⇒ ↑ed SNS activity
  - ↑thirst, ↑ADH, ↑ACTH
  - ↑release of aldosterone from adrenal cortex
  - ↓renin release
  - ↓ed GFR
  - adverse CVS effects:
    - ↑vascular & cardiac hypertrophy
    - inflammation
    - fibrosis
  - ↓insulin sensitivity & ↓insulin secretion

MOA

- competitively block ACE ⇒ ↓ATII
- ∴ effects are mediated via less ATII

Effects

- CVS:
  - sig ↓SVR – may lead to ↑in CO in heart failure pts
    - ↳ ↓preload (↓Na & H2O retention) & ↓afterload (vasoD)
      - ↳ afterload affect > preload
  - HR unaffected or +/- mild tachy
    - ↳ baroreflexes unaffected
  - transient hypotension at start of Rx ∴ start low in hosp & titrate up
  - no rebound HTN – as opposed to clonidine
- renal:
  - if baseline ↓renal perfusion: see ↓↓ed renal perfusion ⇒ +/- renal failure (↑creat & urea)
    - via loss of: ATII norm vasoC efferent arteriole (in presence of poor renal perfusion)
      - ↳∴ don't use in presence of renal art stenosis
  - if baseline norm renal perfusion: renal efferent vasoD ⇒ ↑GFR ⇒ ↑UO
- metabolic:
  - ↓ed aldosterone levels ⇒
    - ↓-ve feedback on renin production ⇒ ↑renin levels
    - ↑K

Pharmacokinetics

- 3 main groups based on kinetics:
  - gp 1 = captopril = active drug which is metabolised to active metabolites
  - gp 2 = enalopril, ramipril = prodrugs: hepatic metabolism to diacid moiety activates them
  - gp 3 = lisinopril, quinapril = active drug which is not metabolised and exreted unchanged renally
- duration mostly 24hrs
- onset action 1 hr

Uses

- reverse endothelial dysfunction & atherolsclerosis
- HTN esp in DM
- heart failure – all grades
- Diabetic nephropathy in type I
- LVF post MI

Adverse Reactions

- ACEI cough:
  - ~10-20%
  - more in women, non smokers, Chinese
  - hours to months to develop
  - MOA:
    - ACE also involved in metab of bradykinin
    - ACEI inhibits peptidyl dipeptidase ⇒ accumulation of bradykinin & substance P ⇒ cough
- los of taste
- skin rashs
- rare:
  - angio-oedema – 0.2% more common in blacks
  - agranulocytosis
  - thrombocytopaenia

Cautions/Contraindications

- avoid in liver impairement except lisinopril/quinapril)
- not for pregnancy
- caution in:
  - SLE/scleroderma
  - angiooedema
  - ↑K

- renal art stenosis

Interactions

- avoid diuretics, ACEI & NSAIDs ⇒ triple whammy effect ⇒ worsening renal impairement
- avoid combo with other drugs which may ⇒ ↑K
  ↳eg K sparing diuretics
- loops:
  - 1st dose ↓bp
  - ⇒ renal impairement
- lithium:
  - ↓excretion of lithium ⇒ ↑risk tox
- NSAIDs ⇒ ↑risk ↑K & reverse ↓ ACEI antiHTN effects

Captopril

Pharmacokinetics

- OBA 65% 25% PPB
- 50% oxidised in liver to active metabolites
- excreted in urine
- t1/2 elim 4 hrs (↑ed with renal impairement)
- onset 15-30mins, peak 1-2hrs, duration 6-10hrs

Enalopril

- = prodrug: hydrolysed in liver & kidney ⇒ enaloprilat (active metabolite)
- Can be given IV
- long lasting effects via tight binding to ACE:
  - t1/2 elim 4-8 hrs which ↑s in prolonged use to 11hrs
  - duration of action 18-30hrs

Lisinopril

- similar drug to enalopril but active drug which is not metabolised

Angiotensin II Receptor Antagonists (ARAs)

- eg losartan, candesartan
- advantages over ACEIs:
  - blockade of AT_1 receptor = specific way of preventing adverse effects of ATII seen in heart failure & HTN
    ↳ esp as ATII may be synthesised by non-ACE pathways
  - AT_2 receptor not blocked – may possess cardioprotective properties
  - lower incidence of cough & angioedema
    ↳10% pts on ACEI unable to tolerate them

Losartan

Chemical

- = substituted imidazole compound

MOA

- block angiotensin II (AT_1) receptor ∴
  - ↓VC
  - ↓aldosterone
- actually see ↑ed levels of circulating ATII cos:
  - blocks –ve feedback of ATII on renin ⇒ ↑renin secretion ⇒ ↑ATII

  ↳ no clinical impact due to robust AT_1 block
- avoid problems with:
  - ↑K (ATII levels are high ∴ aldosterone levels norm/↑ed)
  - bradykinin accumulation (ACEI not blocked)

Pharmacokinetics

- OBA 30% (well absorbed but sig 1st pass metab)
- PPB 99%
- metab to
    - active carboxylic acid metabolite
    - inactive other compounds
        (↳ candesartan & valsartan minimally metabolised & excreted unchanged)
- t1/2 elim 2hrs (t/12 elim of active metabolite = 7hrs)
- 10% excreted in unchanged active form in urine
- inactive metab excreted via urine & bile

Uses

- same as ACEI where ACEI not tolerated due to SEs
- also ARBs ⇒ ↓end organ damage to:
    - kidney
    - brain
    - heart

Adverse Reactions

- see ACEI

Cautions/Contraindications

Interactions

see ACEI

Nitrovasodilators

- 2 main drugs:
  - sodium nitroprusside (SNP)
  - glyceryl trinitrate (GTN)
- both are NO donors ⇒ vaso D via NO

Sodium Nitroprusside

Chemical

- $Na_2[Fe(CN)_5NO]$
- = inorganic complex
- functions as a prodrug

Presentation

- administered as 0.01% solution in 5% dextrose
- must be freshly prepared
- faint orange solution
- if exposed to light ⇒ cyanide formation ⇒ turns dark brown ∴ discard!!

MOA

- potent & rapid acting VD ⇒ ↓bp
- action on venous & arterial system
- 1 molecule of drug with 1 molecule of Hb ⇒
  - 1 metHaemoglobin
  - 5 cyanide ions
  - 4 nitric oxide – active substance
    ↳this then:
    - activates guanylate cyclase: ↑cGMP ⇒ PK ⇒ VasoD of arterioles + venules/veins

Effects

- CVS:
  - rapid ↓bp due to vasoD or arterial & venous system
  - reflex tachy (baroreceptor reflex)
    ↳in heart failure pts = ↑CO with no tachy, and ↓myocardial wall tension ⇒ ↓O2 consumption
  - ?↑inotropy – may somewhat offset bp lowering effects
  - coronary steel = diversion of blood flow from ischaemic areas (already max dilated) to non-ischaemic areas (new max dilation)
- CNS:
  - controversy
  - ↑ICP by:
    - direct cerebral vasoD ⇒ ↑CBF
    - but cerebral autoreg maintained & also offset by ↓systemic bp
- resp: antagonises hypoxic pulmon vasoC (HPV) via non-selective vasoD
  ↳ this may ⇒ ↑shunt ⇒ ↓PaO2
- endocrine:
  - ↑plasma catecholamines levels
  - ↑renin levels
- GIT: paralytic ileus has been reported ?caused by SNP
- platelets – impaired by SNP in high doses
-

Pharmacokinetics

- rapid onset of action – mins post IV administration
- half life 2mins
- duration of effect 1-20mins post dose

M

[in rbc]

- metabolism starts with transfer of electron from the iron (Fe++ = ferrous) of oxyHb to SNP ⇒ unstable SNP radical (non enzymatic process)
- unstable SNP radical releases
  - 5 cyanide (CN) ions via dissociation
  - metHb (Fe+++ = ferric)
  - NO
- 1 CN reacts with metHb (high affinity for CN) ⇒ cyanmetHb (non-toxic)

[in liver/kidneys]

- remaining CN-ions are either:
  - converted to thiocynate by rhodenase enzymes
    ↳rate of conversion is dependant on availability of a sulphur donor to rhodenase enzyme

[systemic]

  - combines with hydroxycobalamin (vit b12) ⇒ cyanocobalamin
    - cyanocobalamin = non toxic store of CN which can be excreted in urine
  - Any free CN's may cause cyanide toxicity:
    - bind to cytochrome oxidase C ∴ impair aerobic respiration ⇒ tissue hypoxia

↳ amount of CNs released from SNP depends on dose administered

- thiocynate:
  - fate:
    - (mionr) in rbc: thiocyanate oxidase converts it back to CN ion
    - (most) excreted slowly by kidneys (t1/2 2days or 7 days in AKI)
  - can accumulate in prolonged Rx or renal failure
  - toxic side effects:
    - plasma conc >10mg/dl = skeletal mm weakness, confusion
    - prolonged ↑plasma conc = hypothyroidism via iodide ion uptake trapping
- excreted by kidneys

Uses

- rapid onset eg need for ↓bp in HTN emerg or surgery
- short term as infusion only
- common in cardiac theatre

Adverse Reactions/Toxicity

- SEs:
  - sweating
  - abdo cramps
  - hypothyroid
  - mm twitching
- SEs toxic metab (thiocynate):
  - thiocynate = x100 less toxic than CN ions
  - usually only a problem in:
    - prolonged infusion
    - renal impairement
    - people getting prophylactic sodium thiosulphate (see below)
  - signs:
    - ataxia
    - blurred vision
    - tinnitus
    - delirium
    - LOC

↳haemodialysis antidote

- SE cyanide toxicity (CN ion toxicity):

- more likely if:
  - hypothermia
  - renal/hepatic failure
  - vit B12 deficiency
- signs:
  - met acidosis
  - ↑ScvO2
  - tachy arrhythmias
  - ↓reflex
  - sweating
  - wide dilated pupils
  - coma
- Rx:
  - stop infusion
  - dicobalt edetate (IVI)– chelates CN ions
  - sodium thiosulphate (150mg/kg IV)– provides additional sulphur gps to convert CN ⇒ thiocynate (rhodenase system)
    ↳ can be used as prophylaxis
  - nitrites: sodium nitrite or amyl nitrite:
    - converts oxyHb to metHb
    - metHb has higher affinity for CN than CN for cytochrome oxidase
  - hydroxycobalamin (vitB12) –
    - promotes CN ⇒ cyanocobalamin
    - only useful as prophylaxis not for acute toxicity

- cyanide toxicity more life threatening than thiocynate

Cautions/Contraindications

- caution in
  - stroke, IHD
  - liver/kidney disease
  - vit b12 deficiency

Interactions

- additive effect on ↓bp with:
  - other anti-HTNs
  - volatile anaesthetics
  - –ve inotropes

Dose

- HTN emerg: dose 0.3mcg/kg/min to max 10mcg/kg/min in 5% glucose
- can give concurrent ßB to blunt reflex tachy meaning less SNP
- if SNP approaching max dose should monitor ABGs for met acidosis
- must protect from light

Nitrates - Glyceryl Trinitrate

Chemical

- = organic nitrate

Presentation

- varied: spray, patch, tablets, IV, buccal prep
- diluted usually to 0.01% solution
- gets greatly absorped by polyvinyl chloride (PVC) ie lines & bags
  ↳ must be very careful to change lines after infusion stopped or use polyethylene sets
- GTN may explode if heated ∴ remove patches prior to DC cardioversion

MOA

- activates vascular soluble guanylyl cyclase
  ↳precise method how unclear, thought:
  - metabolism of GTN ⇒ ↑NO ⇒ activates guanylyl cyclase ⇒ ↑cGMP ⇒ ↓Ca into smooth mm cell & ↑Ca into SER ∴ ↓↓Ca cytoplasmic levels ⇒ dephosphorylation of myosin light chain ⇒ mm relaxation & VD
- dose related:
  - [low] = therapeutic doses <2mcg/kg/min)(:
    - venodilation with little effect on arterial resistance
    - ⇒ ↓preload ⇒ ↓LVEDV ⇒ ↓myocardial wall tension ⇒ ↓O2 demand
      ↳ postural hypotensive effects
  - [high]:
    - ↓arterial resistance
    - ↓o2 consumption by heart – (↓CO & ↓periph resistance)
    - dilation of coronary vessels ⇒ ↑o2 delivery to myocardium
- note tolerance develops within 48hrs:
  - ?due to depletion of sulphydryl gps in vascular mm
  - daily drug free period of few hrs prevents tolerance

Effects

- mediated via NO effects
- CVS:
  - hypotension more dependant on posture & blood volume than SNP
  - PVR ↓ed = direct affect
  - dilates larger coronary arteries ∴ not steal affect as with SNP
  - does not affect platelets
- anti-anginal –
  - (mostly) from ↓in myocardial O2 demand
  - (some) vasoD of coronary arteries ⇒ ↑flow to ischaemic areas esp in vasospasm (Prinzmetal)
- bilay tract = relaxation
- CNS: cerebral vasodilator:
  - headache common
  - less ↑ICP compared to SNP
- metHb – due to nitrite metabolite
- resp:
  - non-selective pulmonary vasodilator ∴HPV antagonised ⇒ shunting ⇒ ↓PaO2
    ↳ same as SNP
- uterus: causes rapid uterine relaxation eg for C section
    ↳ 50-100mcg IV or spray

Uses

- for controlled hypotension
- unstable angina
- heart failure

Pharmacokinetics

- OBA <5% due to high 1st pass metab
- S/L effects seen within 3mins & last 30-60mins
- rapidly metabolised in liver:
    - hepatic nitrate reductase: GTN ⇒
        ↳ requires tissue thiols (R-SH)
        - glycerol dinitrate = 10% activity of parent drug
        - nitrite (NO2-)
    - nitric oxide synthetase: Nitrite ⇒ NO
        ↳ under certain conditions this metabolism can induce metHb (Fe++ ⇒ Fe+++)
- it is NO that confers activity
- excretion from kidneys

Interactions

- use with other anti-HTNs & vasodilators (eg sildenafil) ⇒ ↑post hypotension

SEs

- presyncope – postural hypotension
- ↓bp
- headache
- N&V
- ↑HR
- facial flushing

Cautions & Contrainidications

- contra in:
    - cardiomyopathy
    - hypotension/hypovolaemia
    - AS or MS
    - severe anaemia
    - ↑ICP/glaucoma

Dosage

- sublingual tabs – 300-600mcg every 5 mins to max 1800mcg
- linguial spray - 400-800mcg
- IV infusion – 5-10mcg/min ↑ed by 5mcg/min every 5mins until desired response

Isosorbide Dinitrate (ISDN) & Mononitrate (ISMN)

- ISDN prepared with lactose & mannitol to ↓risk of explosion
- well absorbed
- extensive 1st pass metab in liver ⇒
    - isosorbide 2-mononitrate
    - isosorbide 5-mononitrate (ISMN)
    ↳ both equally active
- ISMN undergoes no 1st pass metabolism: OBA 100%
- ISMN t1/2 longer at 4.5hrs

K Channel Activators

Nicorandil

Chemical

- = nicotinamidoethyl nitrate
- K channel activator with nitrate moiety

Presentation

- tablets

MOA

- K channel action [heart & arterioles]:
  - intracellular ATP ⇒ K channel close ⇒ smooth mm cell depolarise ⇒ contraction
  - K channel activators ⇒ antagonise ATP preventing closure of K channel ⇒ K moves out cell causing hyperpolarisation membrane ⇒ closure of Ca channels ⇒ less Ca available for myocardial contraction ⇒ relaxation
- Nitrate like action [venous system]:
  - nitrate moiety of drug acts like GTN ⇒ ↑cGMP ⇒ venous relaxation ⇒ ↓preload

Effects

- CVS:
  - venodilation & arterial vasoD ⇒ ↓pre & after load ⇒ ↓bp
  - coronary art vasoD – without steal phenomenon
  - ↑CO – if heart failure
  - supresses torsades de pointes assoc with long QTc
  - not assoc with tolerance
  - contractility & AV conduction not affected
- CNS: headaches – usually initially only
- metabolic – no affect on lipids/glucose
- haematological – inhibits in vitro ADP-induced platelet aggregation (similar to nitrates)
- giant apthous ulcers have been reported

Pharmacokinetics

- rapid absorb – max cons 30-60mins
- limited PPB
- OBA 75% ∴ little 1st pass metab
- metab by denitration ⇒
- excreted in urine – 80% unchanged
- t1/2elim = 1hr (actions last up to 12hrs)

Uses

- alternative to long acting nitrates for angina

Cautions/Contraindications

- ↓dose in severe liver impairement
- contraindicated in:
  - ↓bp
  - LVF

Dose

- 5mg bd ⇒ ↑10-20mg bd after 1 week

Ca Channel Blockers

Ca Channel Types

- diff types of channel exist:
  - L type:
    - widespread in CVS system
    - responsible for:
      - plateau phase of cardiac AP
      - depolarisation of pacemaker AP
    - triggers internal release of Ca
    - regulated by cAMP dependant protein kinase
  - T type:
    - structurally similar to L type
    - present in:
      - cardiac cells which lack a T tubule system ie pacemaker cells
      - vascular smooth mm

      ↳ ie not present in ventricular myocardium
    - responsible for prepotential of pacemaker AP
  - N type = only found in nerve cells
  - P type
- CCBs:
  - specifically block only L-type channels
  - variable affinity for L type channels in diff locations:
    - myocardium
    - nodal pacemakers
    - vasc smooth mm
- role of calcium in muscle contraction:
  - skeletal mm:
    - Ca released from intracellular stores in SR
    - release from SR triggered by Ca entering through transverse tubules

    ↳ ∴ CCBs don't affect contraction
  - Cardiac mm:
    - Ca released from intracellular stores in SR
    - release from SR triggered by Ca entry through Ca channels

    ↳ ∴ CCBs affect contraction
  - Smooth mm:
    - Ca from i/c stores triggered by
      - Ca entry through Ca channels
      - cell receptors

    ↳ ∴ CCBs affect contraction but slightly diff mechanism to cardiac mm

Subtypes

- class 1 = phenyl-al-kyl-amines
  - eg verapamil
  - ↑pacemaker specific with less vascular VD effect
- class 2 = dihydro-pyridines
  - eg nifedipine, amlodipine, nimodpine
  - minimal cardiac pacemaker effect; ↑↑vasc VD effects
- class 3 = benzo-thiaz-epines
  - eg diltiazem
  - actions at both: pacemaker & vascular effects

Table 15.3. Main cardiovascular effects of some Ca^{2+} channel antagonists.

	Blood pressure	Heart rate	AV conduction time	Myocardial contractility	Peripheral and coronary artery vasodilation	relex SNS stim
Verapamil	↓	↓	↑	↓↓	↑	0/↑
Nifedipine	↓	→↑	→↑	→↑	↑↑↑	↑↑
Diltiazem	↓	↓	↑	↓	↑↑	0/↑

MOA

- diverse chemical structures
- all block inward movement of Ca through L type Ca channels of cardiac & smooth mm cell membranes:
  - nifedipine – reduces number of active channels
  - verapamil + diltiazem – reduce conductivity + kinetics of reactivation of channels
  - all = ↑ effective refractory period

Effects on Myocardium

- block Ca influx during plateau phase of cardiac AP
- ↓Ca [in] ⇒ ↓release of Ca from sarcoplasmic reticulum ⇒ ↓↓Ca[in] ⇒ ↓excitation-coupling which required to allow cross bridge formation between actin & myosin
- ↓cross bridges within sarcomere ⇒ ↓force of contraction ⇒ ↓inotropic effect

Effects on SAN & AVN

- depolarisation (phase 0) of pacemaker potential caused by Ca influx
- block Ca influx across SA node ⇒ ↓rate of depolarisation ⇒ ↓automaticity ⇒ ↓HR
- ↓Ca influx across AVN cell membrane ⇒ ↓speed AVN conduction & ↑refractory time
  ↳= -ve dromotropic effect

Effects on Vasc Smooth Mm

- effect
  - coronary
    - ↑coronary dilation ⇒ ↑o2 delivery
  - peripheral vessels:
    - VD ⇒ ↓periph reistance ⇒ ↓afterload & ↓bp ⇒ ↓o2 demand myocardium

Pharmacokinetics

Table 15.2. Various pharmacological properties of some Ca^{2+} channel antagonists.

	Absorbed (%)	Oral bioavail-ability (%)	Protein binding (%)	Active metabolites	Clearance	Elimination half-life (h)
Verapamil	95	20	90	yes	renal , 20% bile	6–12
Nifedipine	95	60	95	no	renal	2–5
Diltiazem	95	50	75	yes	60% hepatic, 40% renal	3–6

Interactions

- common involvement of CP450 enzymes imply extensive interactions
  ↳enzyme inhibitors eg erythromycin & grape fruit juice ⇒ ↑plasma levels
- examples:
  - volatiles:

        - ↑ed myocardial depression & ↑periph vasoD
        - can be tolerated – unless pre-existing LV dysfunction
    - mm relxants:
        - ⇒ ↑effect of depolarising & NDNMBs
        - may be caused by ↓presynaptic release of Ach (Mg like effect)
    - Las:
        - D-verapamil: potent LA effects ∴ risk of toxicity with regionals
    - K containing solutions:
        - risk of hyperkalaemia: CCB ⇒ slowed inward K movement
    - Dantrolene &CCBs = assoc with myocardial depression & hyperkalaemia
    - BBlockers –
        - ↑risk of bradycardia
        - verapamil & BB avoid due to risk of heart block
    - Carbamazepine – Ca blockers ⇒ ↑levels of carbamazepine
    - Digoxin –
        - CCBs ⇒ ↑levels of dig
    - platelets: Ca mediated functions opposed

SEs

- constipation
- gingival hyperplasia (in 1st 9months of Rx)
  ↳stop drug 1-4wks improvement

Cautions & Contrainidications

- contraindication:
    - SVT with WPW!!!
- caution in
    - heart failure, bradycardia, hypotension, ACS
      ↳extreme caution if congestive heart failure
    - liver/renal failure - ↓dose
    - elderly –
        - presyncope & falls
        - ↑plasma half life
- slow withdrawal – rebound syndrome

Dosage

very variable depending on drug & prep

Verapamil

Chemical

- = prodrug
- =racemic mixture
- synthetic derivative of papaverine

Pharmacokinetics

- liver metab:
    - demethylation ⇒ nor-verapamil (active: sig anti-arrhythmic properties)

Mechanism of Action

- S isomer = specific Ca channel blocking action with affinity for SAN & AVN
- R isomer = fast Na channel blocker ⇒ LA activity

Effects

- CVS:
    - predominant effect = node blocker
        - direct depressant SAN
        - -ve dromotrope AVN

↳ ↓HR
- lesser effect =
  - -ve inotropy
  - periph vasoD
  - mild coronary vasoD
  - less reflex tachycardia (∴better in IHD)

- CNS: cerebral vasoD

Interactions
- chronic use of verapamil ⇒ potentiation of muscle relaxants

Cautions
- pts with:
  - impaired LV function ⇒ heart block & cardiac failure
  - WPW ⇒ VF

Uses
- predominantly used for arrhythmias – esp SVTs – rate control +/- rhythm control
- angina
- HTN – limited by –ve inotropic properties

Nifedipine

Presentation
- capsules – can give contents sublingually (5-10mins onset)
- tablets – immediate or slow release
- 15-20mins onset via oral route

Mechanism of Action
- ↑ed affinity for vascular smooth muscle
- ↓number of slow Ca channels

Effects
- CVS:
  - ↓tone in
    - periph ⇒ ↓SVR ⇒ ↓bp
    - coronary arteries ⇒ ↑coronary art blood flow
  - reflex ↑HR & contractility
    ↳ these may worsen o2 supply/demand
  - no real effect at nodes

Uses
- prophylaxis & Rx of angina
- HTN
- Raynauds syndrome

Pharmacokinetics
- as table prev
- no active metabolites

Adverse Reactions
- abrupt discontinuation ⇒ coronary art spasm
- reflex tachy
- hypotension

Nimodipine

- = more lipid soluble analogue of nifedipine ∴ can penetrate bbb
- used in prevention & Rx of cerebral vasospasm

Diltiazem

Effects

- CVS: (generally similar to verapamil)
  - central cardiac affects:
    - prolongs AV conduction time
    - ↓ed contractility (less than verapamil)
  - vasc effects:
    - ↓SVR ⇒ ↓bp
    - reflex tachy usually not seen
    - ↑coronary blood flow

Uses

- prophylaxis & Rx angina & HTN
- rate control in SVT

Pharmacokinetics

- hepatic metabolism ⇒ active metabolie = des-acetyl-diltiazem
- urinary excretion:
  - 40% in unchanged form

Interactions

- BBs – less likely to cause –ve inotropy (than verapamil) as less cardiodepressant effects

Diuretics as VDs

- See separate section

Summary

- main effect by ↓ing plasma volume ie long term control of bp
- thiazides:
  - has direct periph vasodilator effect at doses far lower than diuretic action
  - ↓interstitial volume ⇒ ↑vasc compliance
  - potentiate anti-HTN effects of other antiHTNs
  - concurrent NSAIDs counteract anti-HTN & diuretic effect:
    - NSAIDs ⇒ ↓PGs
    - PGs vital in homeostasis of renal blood flow, GFR, tubular ion transport
- furosemide – initial direct vasoD effect via ↓cAMP

Other VD Drugs

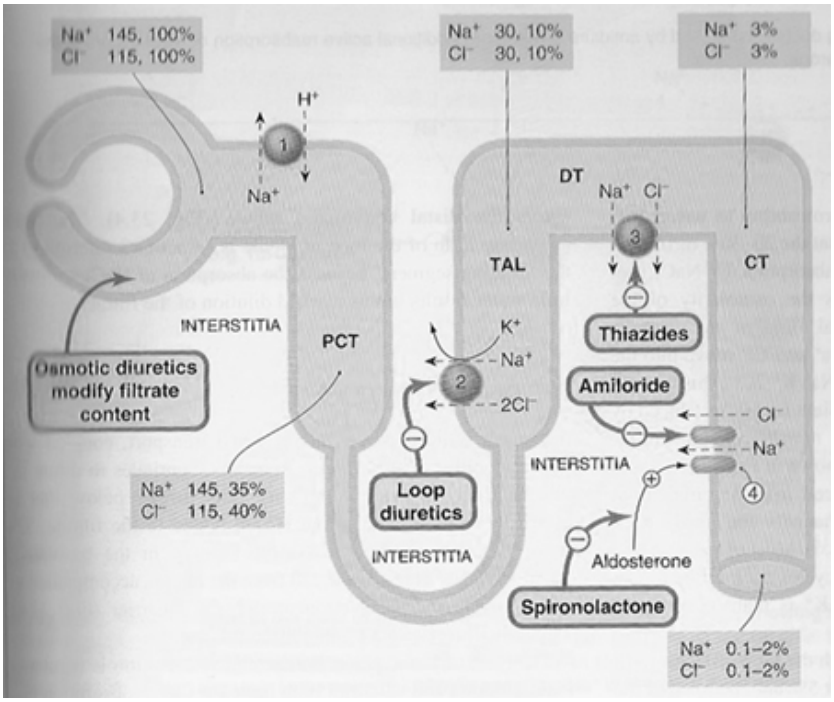
Ketanserin

- mechanism of action = selective competive antagonist of
  - 5-HT at periph 5-HT_2 receptors
  - α1 receptors ⇒ vasoD
  - histamine-1 receptors ⇒ Rx bronchoconstriction
  - dopamine receptors ⇒ ↓plt aggregation
- used in:
  - carcinoid syndrome
  - anti-HTN
  - Raynauds
  - Migraine

Diuretics

- cause a net loss of Na & water from body
- primary effect is to decrease Na + Cl reabsorption from filtrate ⇒ water loss moves with Na loss
- classification:
  - direct - action on nephron cells:
    ↳ can subclassify by site of action:
    - thick ALH = loops
    - early distal tubule = thiazides
    - CDs = K sparing diuretics
  - indirect – modify content of filtrate:
    - osmotics
    - carbonic anhydrase inhibitors
  - others:
    - alcohol – inhibits ADH
    - water – inhibits ADH
    - V2 receptor antagonists – antagonises ADH action at collecting ducts
    - xanthines:
      - ↑GFR
      - ↓tubular reabsorption of Na
    - dopamine receptor agonists:
      - D1 stim ⇒ inhibition Na reabsorption
      - dopamine also stim ß1 ⇒ ↑CO ⇒ ↑renal perfusion
        ↳ although studies show no clinical benefit in vivo

Physiology - Summary



- Normally a very large proportion of Na & water is reabsorbed ∴ only need actual small change in percentage to ⇒ large excretion:
  - normal =
    - 99.4% Na reabsorbed
    - 99.4% water
    - 99.2% Cl
- Sites of Na reabsorption:

- PCT = 65%
- asc LOH = 25%
- DCT = 9-10%

↳ = 99.4%

Loop Diuretics

Furosemide

Chemical

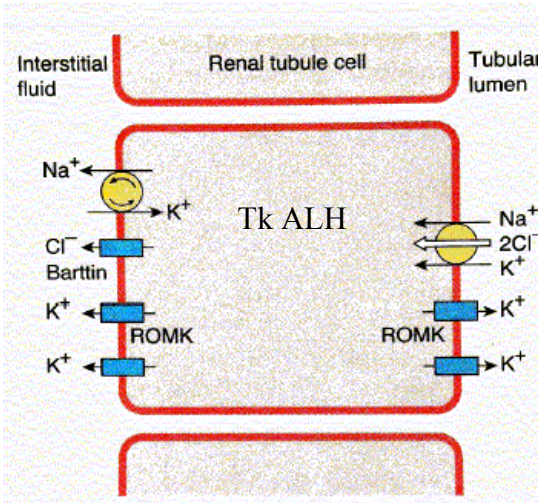
- very potent drugs
- 15-25% or original filtered Na potentially excretable
  ↳ie a high ceiling
- = a sulfamoylbenzoic acid

MOA

- site of action inside thick ascending loop of Henle
- loops inhibit Na-K-2Cl cotransporter (NKCC) isoform 2 in Thick ALH by binding to Cl binding site
  ↳transporter needs all 3 ions to be bound to be active
- NKCC =
  - absorptive transporter specific to Thick ALH luminal membrane
  - moves ions into epithelial cells from lumen
  - sets up electrochemical gradient which drives reabsorption of Ca & Mg into epithelial cells
- ∴ furosemide blocking of NKCC ⇒
  - excretion of Na, K, Cl:
    - water moves with Na due to ↓toniciy of interstitium
    - ↑solute delivered to distal nephron ⇒ ↑osmotic pressure inside tubule ⇒ ↓water reabsorption ⇒ ↑water excretion
  - excretion of Ca & Mg
  - acute ↑uric acid excretion but chronically ↓uric acid excretion

  ↳prevents 15-25% reabsorption of Na/Cl
  ↳greatest effect all diuretics
- also has direct venodilation effect prior to onset of diuresis:
  - MOA not fully understood but include ↓responsiveness to:
    - ATII
    - NA
- prolonged use can lead to loop resistance:
  - ?rebound ↑Na reabsorption of Na in distal nephron

  ↳overcome by:
    - fluid & Na restriction,
    - ↑doses,
    - thiazide combo – blocks distal tubule reabsorb
    - IV doses



Pharmacokinetics

A

- absorption 60-70%
- OBA 40-70%

D

- acidic drugs
- high PPB 96%
- site of action = inside tubular lumen in thick ascending limb ie not plasma
- drug is not filtered but requires active secretion via organic anion transporter OAT3>OAT1
  ↳ in proximal tubule
- drug in tubular lumen ∴ excreted via urine unchanged

M

- drug which isn't secreted into/excreted by urine is metabolised by liver (ph 1 glucuronidation)
- then excreted via kidney

E

- excretion:
  - 50% dose unchanged
  - 50% conjugated with glucuronic acid in kidney
- peak action 1hr (oral), 30mins (IV)
- t1/2 ~90mins (↑ed in renal failure)
- duration 3-6hrs

Uses

- Rx of oedema assoc with:
  - heart failure
  - cirrhosis
  - renal impairement
  - nephrotic syndrome
  - adjunct acute pulmon oedema
  - severe ↑Ca

Adverse Reactions

- electrolyte disturbance:
  - ↓K =
    - in distal tubule principle cell secretes K
    - rate limiting step is concentration gradient – depends on flow of distal tubule
    - ∴ loops ⇒ ↑Na & H20 presented to distal tubule ⇒ ↑flow ⇒ ↑K able to be secreted into tubule due to washout
  - ↓Ca & Mg ⇒ bone loss
- metabolic alkalosis:
  - loss of Na, Cl, K & volume depletion ⇒ stimulation of
    - ↑ed H via type A intercalated cells
    - new HCO3 generation
- hypovolaemis & hypotension – esp in elderly
- other:
  - nausea, allergy
  - ↑LDL & ↑triglycerides
  - high IV dose ⇒ ↑risk ototoxicty eg tinnitus, vertigo, deafness
    ↳esp if used with aminoglycosides also

Cautions/Contraindications

- caution:
  - DM
  - gout
  - hearing impairment
  - ↓K
- contra:
  - severe Na & fluid depletion

Interactions

- NDNMBs:
  - [low doses] ⇒ potentiate NDNMBs by
    - ↓cAMP ⇒ ↓Ach release
    - hypokalaemia
  - [high doses >1mg/kg] ⇒ antagonise NDNMBs by inhibiting PDE ⇒ ↑cAMP ⇒ ↑Ach release
- ARBs & ACEIs: severe 1st dose hypotension

- Aminoglycosides:
  - ↑risk ototoxicity & renal toxicity
  - care in elderly
  - combo not advised
- dig: diuretic may ⇒ ↓K & ↓Mg ⇒ ↑risk dig toxicity
- lithium: ↓renal clearance ⇒ ↑lithium tox
- NSAIDs:
  - ↓effect loops
  - predispose to renal failure if hypovolaemia
- thiazides: +/- profound diuresis & electrolyte disturbance

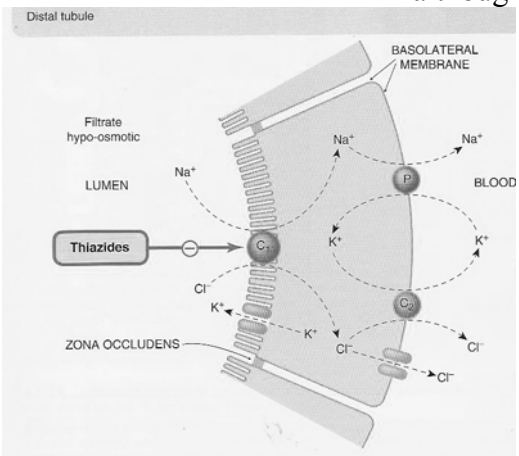
Thiazides

- main = bendrofluazide
- moderately potent

MOA

[renal effects]

- inhibit active reabsorption of Na & Cl in early distal tubule
  ↳ remember distal tubule releatively impermeable to water
- bind to Cl site of Na-CL symporter on luminal membrane
- Na-Cl symporter:
  - uses electrochemical gradient of Na to move Cl into epithelial cell against its gradient
  - also ↑excretion of K – similar mechanism to furosemide
  - 5% of sodium load reabsorbed in this method
  - ∴ inhibition ⇒ ↑excretion of Na & Cl in urine
    ↳although 5% less potent than loops



- additional effects:
  - ↓excretion of uric acid :
    - thiazides compete with uric acid for organic acid transporters (OATs) in prox tubule
    - ⇒ ↑serum uric acid due to ↓ed secretion
  - ↓excretion of Ca
  - ↑excretion of K:
    - ↓ECF volume ⇒ ↑renin ⇒ ↑aldosterone ⇒ ↑K loss
    - ↑Na load presented to distal tubule ie ↑ed washout ⇒ ↑K secretion
  - ↑excretion Mg
  - chronic use ⇒ ↓periph resistance via action on blood vessels

[extra-renal effects]

- vasodilation:
  - early cause of ↓bp = due to ↓blood volume
  - late cause of ↓bp = direct action on blood vessels

↳ eg diazoxide = non diuretic thiazide which powerful vasoD via ↑K permeability ⇒ hyperpolarisation ⇒ vasoD

- hyperglycaemia:
  - ↑K permeability of cell membrane of pancreatic ß cells ⇒ ↓insulin release

Pharmacokinetics

- well absorbed
- active secretion to site of action in tubular fluid (same as loops) via OATs
- onset action 1-2hrs
- max effect 4-6hrs
- duration action 8-12hrs
- usually excreted unchanged in kidneys

Uses

- mild/mod HTN
- oedema from failure/cirrhosis

Adverse Reactions

- generally large therapeutic index so rare
- ↓K:
  - seen in 15-60%
  - usually in 1st month with higher doses
  - concern in pts taking
    - dig
    - cirrhosis ⇒ encephalopathy

  ↳use lowest dose, coadminister K sparing diuretic, K supplements (great care in elderly)
- ↑uric acid –
    - caused as described prev (↑competition for organic acid secretory pump in prox tubule)
  - effect reversible when drug stopped
  - ↑risk gout
- hyperglycaemia/impaired gluc tolerance:
  - often in elderly
  - ? MOA - ?↓insulin secretion
- hypochloraemic alkalosis
- high dose ⇒
  - ↑LDL/triglycerides; ↓HDL
- minor:
  - mm cramp
  - rash
  - blurred vision
  - male impotence

Cautions/Contraindications

- caution in:
  - type I DM
  - gout
  - renal/hepatic impairement
  - dyslipidaemia
- contra in:
  - Addisons

Interactions

- same as loops

Spironlactone

- limited diuretic action
- = a prodrug

MOA

- specific competitive antagonist for intracellular aldosterone receptor:
  - spiro-receptor complex fails to bind DNA
  - ∴ no transcription/translation ⇒ ↓aldosterone effects:
    - ↓Na reabsorption (Na excrete) & ↓K secretion (K remains)
      ↳ ie K sparing diuretic effect
- effect directly related to amount of circ aldosterone
- does not effect tubule transport of Na/Cl
- additional effects seen:
  - ↓H ion secretion (type A intercalated cells) ie ⇒ acidosis
  - ↓uric acid secretion

Pharmacokinetics

- absorb 30-70%
- extensively metab to active canrenone
  ↳ responsible for its actions
- t1/2 elim:
  - spiro = 10mins
  - canrenone = 16hrs
- onset action 1day

Adverse Reactions

- spiro – structurally similar to progesterone ∴ chronic use ⇒
  - gynaecomastia
  - ↓libido
  - impotence
  - menstrual irreg
- others:
  - GIT disturbances
  - ↑K
  - met acidosis

Amiloride

- limited diuretic action

MOA

- act on late distal tubule & collecting duct:
  - inhibit Na reabsorb & K secretion on luminal membrane
  - blocks Na channels where aldosterone produces main effects
  - blockade of Na ⇒ ↓Na/H exchange ⇒ ↓H secretion ⇒ alkalinsation of urine
    ↳ ⇒ ↑Na excretion

Pharmacokinetics

- absorbtion – poor 15%-25%
- excreted mostly unchanged in urine
- onset action 1-2hrs, peak at 6hrs. duration 24hrs
-

Uses

- limited diuretic efficacy byself
- usually used in combo with loop or thiazide
- spiro also indicated for
  - heart failure as aldosterone antagonist

- primary hyperaldosteronism
- hirsuitism in femals

Adverse Reactions

- both drugs incl:
  - include ↑K
  - ↓Na & ↓Cl
  - met acidosis - rare
  - constipation
  - impotence

Cautions/Contraindications

- contra:
  - renal failure & ↑K
  - preg:
    - spiron ⇒ feminisation of male fetus
    - amiloride ⇒ elec chem. disturbances of fetus
- caution:
  - type I DM
  - elderly

Interactions

- same as loops & thiazides
- cyclosporine & NSAIDs:
  - ↑risk ↑K

Osmotic Diuretics

- eg mannitol
- pharmacologically inactive
- freely filtered, incompletely or not completely reabsorbed by tubule

Effects/MOA

- main effects exerted in parts of nephron which is freely permeable to H20 ie
  - PCT,
  - descending LOH,
  - collecting ducts
- diuresis by adding a non-reabsorbable solute to solutes already in tubular fluid ⇒
  - ↓passive water reabsorb
  - ↑amount of water in tubule fluid ⇒ ↓conc of Na ⇒ ↑back diffusion of Na across leaky paracellular junctions of PCT cells ⇒ ↓total Na & Cl reabsorb

    ↳∴NET = large ↑water excretion, ↑Na exceretion (but smaller amount relative to water)
- ↑K secretion & excretion:
  - via ↑flow to DCT ⇒ washout
  - similar to loops & thiazides
- free radical scavenger

Uses

- now used only really for
  - cerebral oedema – 0.25-0.5g/kg 6hrly
  - acute ↑IOP or intraocular surg – 0.5 -1g/kg
- historical theory to prevent ARF:
  - in ARF: ↓GFR ∴ compensatory complete reabsorption Na & water ⇒ drying up of distal nephron

    ↳ counteracted by osmotics

Adverse Reactions

- transient expansion of ECF

- transient hyponatraemia – 2nd to absorption of H20 from intracellular compartment ie dilutional hyponatraemia
- headache, N&V

Acetazolamide

- = (non competitive) carbonic anhydrase inhibitor

Mechanism

- inhibits CA at:
  - inside PCT cells
  - brush border (lumen) of PCT cells
- (remember: HCO3 is filtered and excreted (with ↑proportion filtered))
- results of CA inhibition:
  - ↓H ions available for excretion ⇒ ↓HCO3 reabsorption (ie ↑HCO3 excretion)
    ↳ ⇒ metabolic acidosis & alkaline urine
  - Na & water excretion slightly ↑ed ⇒ ↑drive for K secretion in DCT
    ↳ ∴↑flow of alkaline urine with serum **hyperchloraemic acidosis**
- process is self limiting:
  - depletion of intracellular HCO3 ⇒ serum HCO3 falls ⇒ ↓filtered HCO3 ⇒ less target for drug to work

Pharmacokinetics

- OBA >95%
- highly protein bound
- excreted unchanged in urine

Uses

- rarely used as diuretic
- acute mountain sickness: counteracts resp alkalosis
- acute glaucoma: inhibits aqueous humour production

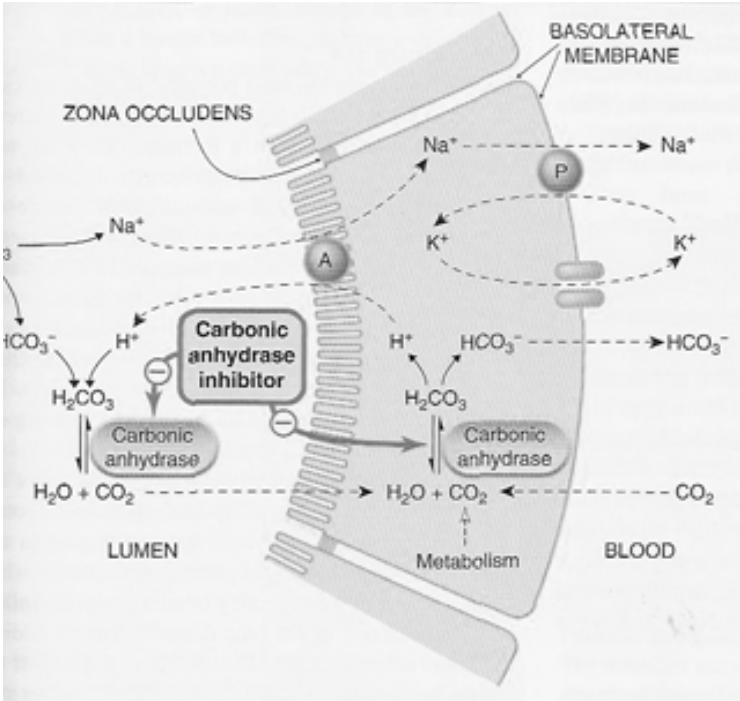


Fig. 23.10 Renal mechanisms for conserving base showing the action of carbonic anhydrase inhibitors. Sodium ions are absorbed and H^+ secreted at the luminal surface by an antiport mechanism (A). Most bicarbonate in the filtrate is 'reabsorbed' in this way in the proximal tubule. In the distal tubule, bicarbonate is added to the plasma, and monobasic phosphate or ammonium chloride is added to the urine (not shown). The primary active transport mechanism is the Na^+ pump (P). Potassium ions pass out of the cell through potassium channels. (Amiloride inhibits the Na^+/H^+ exchange or antiport, but this is not a major factor in its diuretic action.) Note that the diagram is simplified; consequently, the stoichiometry is not accurate; e.g. each time the sodium pump works, it exchanges $3Na^+$ for $2K^+$. (Adapted from Hendry & Ellory, 1988.)

Signs of Electrolyte Imbalance with Diuretics

- ↓Na:
  - lethargy
  - disorientation
  - ↑mm tone
  - seizures ⇒ coma
- ↓K:
  - mm weakness
  - abnormal ECG ie long PR, flat T waves, prolonged QT, U waves
  - post hypotension
  - flaccid paralysis
- ↓Ca:
  - irritable
  - vomit
  - mm tetany
  - ↑mm reflexs
  - cardiac arrhythmias – prolong QT
  - seizures
- ↓Mg:
  - N&V
  - lethargy
  - mm weakness
  - loss deep tendon reflexs
  - tremors/tetany
- ↑K (K sparing diuretics):
  - N&V
  - diarrhoea
  - mm weakness
  - ECG changes: wide QRS, absent Ps, tented T waves

Anti-Arrhythmic Drugs

Mechanisms of Cardiac Arrhythmias

- enhances automaticity:
  - eg ischaemia ⇒
    - pathological damage to conducting fibres of cardiac mm:
      - ⇒ unstable RMP ⇒ spont depolarisation during diastole ie before SAN
    - myocardial mm cell assumes elec characteristics similar to pacemaker cells
  - hypokalaemia ⇒ unstable phase 4
- re-entry + reciprocating mechanisms:
  - common cause of A + V arrhythmias
  - from anatomical sites which able to change rates of conduction or use different pathways
    - impulse can pass down alternate pathway with diff conduction time & refractory periods
    - impulses can be blocked
  - eg AV bundle, terminal Purkinje
  - damaged atrial/ventricular mm
- pathological after potentials:
  - ischaemia ⇒ pathological changes ⇒ spontaneous after-potentials after AP
  - these may reach threshold potential ⇒ depolarisation
  - ?related to Ca or Na entry through ion channels
- heart blockade:
  - from damage to AV node or ventricular conduction system
    ↳ usually 2nd to ischaemia

Classification

- Vaughan Williams ie mechanism of action
- clinical : conditions drugs more effective against:
  - narrow complex tachy: adenosine, ßBs, CCBs, digoxin
  - broad complex tachy: amiodarone, procainamide, lignocaine, bretylium

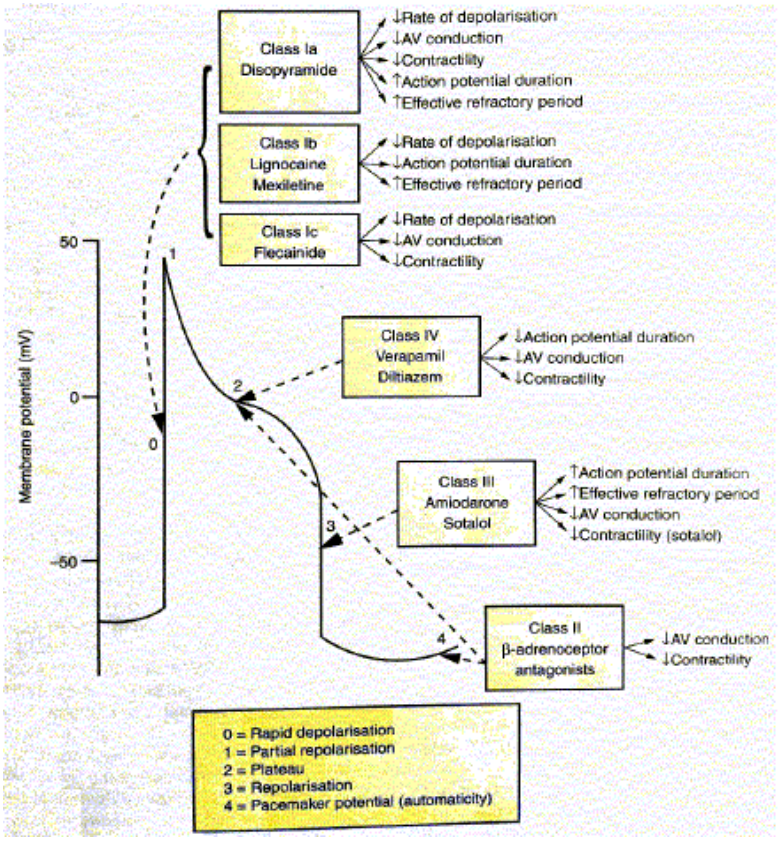
Vaughan Williams Classification of AADs

Classes

"some block potassium channels"

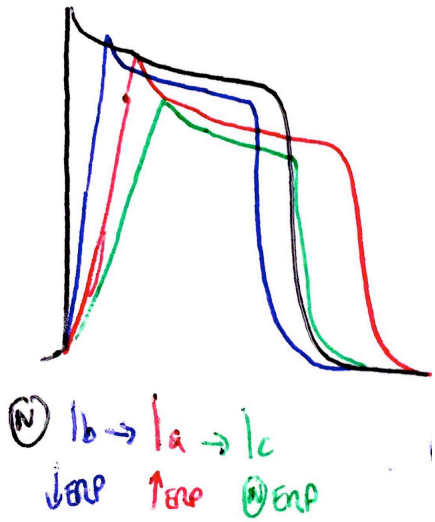
- different classes:
  - Class I "Some" = S = Sodium channel blockers
    - bind to Na channel when open or refractory
      ↳∴ more channel open more it is blocked
      ↳∴ slow rate of depolarisation of ph 0 & ph4
    - subclasses:
      - Class IA “Double Quarter Pounder” (Disopyramide, Quinidine, Procainamide)
        - lengthen AP duration
      - Class IB “Lettuce, Tomato, Mayo” (Lidocaine, Tocainide, Mexilitine),
        - fast dissociation ie shortern AP duration
        - bind to open Na channel in phase 0 ∴ many channels blocked during max depolarisation
      - Class IC “More Fries Please” (Moricizine, Flecainide, Propafenone)
        - also inhibit His-Purkinje system
  - class II "Block" = B =Beta blockers:
    - ↓slope of phase 4 of SAN & conducting tissue
    - prolong effective refractory period (ERP) of AV conduction tissues
    - shortens AP duration & ERP of Purkinje
  - Class III "Potassium" = Potassium channel blockers

        - ↑duration of AP
        - ↑ERP
        - prolongs phase 3 of muscle & conduction cells
        - "A Big Dog Is Scary" (Amiodarone, Bretylium, Dofetilide, Ibutilide, Sotalol).
    - Class IV “channels” = C =Calcium blockers
        - IV Ca blockers: "Very Nice Drugs" (verapamil, nifedipine, diltiazem)
        - blocks slow inward Ca (L type)
        - ↓phase 2 & ph 3 esp in AV node
    - Class V: cardiac glycosides



- unclassified by this system:
    - adenosine
    - Mg
- general uses:
    - restore haemodynamic stability
    - prevent life threatening arrythmias
    - prevention sudden cardiac death
    - controlling vent rate
    - prevent VTE eg AF
- all anti-arrhtymics intrinsicly are also pro-arrthymic

Class I – Na channel Blockers



Class 1a - Procainamide

- usage has declined due to assoc with mortality in chronic use

Use

- re-introduced in ACLS gudielines in stable VT (better than lignocaine)

MOA

- electrophysiology changes:
    - blocks Na entry ∴ slower rate of depolarisation ph0
    - ↑threshold potential for excitation
    - surpasses re-entry: directly prolongs refractory period of all heart cells (relative to AP)
    - anticholinergic effect – may antagonise an ↑in vagal tone
- result is:
    - ↓impulse conduction,
    - delayed repolarisation of atria, ventricles & Purkinje finbres
        ↳∴ ↑↑effective refractory period
    - ↓abnormal/ectopic pacemaker activity
    - inhibition of vagal action on SAN & AVN
        - risk of tachycardia
        - ∴ can give AV node blockers concurrently
- ECG: ↑QT, ↑QRS, ↑PR

Kinetics

- OBA 85%
- metab:
    - partly metabolised:
        - liver & plasma: hydrolysed
        - liver only: acetylated ⇒ N-acetyl-procainamide ⇒ renal excretion
- partly excreted unchanged in urine
- t1/2 elim 3-4hrs

Adverse Reactions

- cVS:
    - ↑QRS ⇒ risk of torsade
    - hypotension
- GIT
- SLE type syndrome with chronic Rx

Class 1b – Lignocaine (Anti-arrhythmic)

- differs to Ia drugs as doesn't affect conduction velocity

- useful for vent arrythmias
- high incidence of adverse effects limited their use

MOA

- electrophysiology:
  - ph 0: Na blocking ⇒ prolongs time to depolarisation
  - ph3: short AP: quicker repolarisation due to Ca & K channel block
    ↳ esp in Purkinje fibres ie good at preventing re-entry tachys
  - ph4: depresses diastolic depolrisation
  - ↑threshold for depolarisation
  - little effect on AVN

Uses

- for vent tachys (broad complex) esp if induced by MI or surgery
- blocks open inactivated Na channels
- no effect on vagal activity/CO/contractility/SAN
  ↳∴ little use in SVTs

Pharmacokinetics

- IV only (OBA30%)
- Vd 0.8-2 L/kg
- PPB 60-80% pKa 7.9
- lipid soluble
- onset 1min
- half life 1.5 hours
- metab by liver ∴ ↑half life in
  - liver disease
  - heart failure ie stagnant flow through liver
  - drugs which ↓liver blood flow

Adverse Reactions

- mild:
  - dizziness
  - N&V
  - tinnitus
  - visual disturbance
- toxic:
  - seizures – serum level 5-10mcg/ml
    ↳ convulsive threshold ↓ed if hypoxic, ↑K, acidosis
  - resp depression
  - cardiac collapse – levels >10mcg/ml

Cautions/Contraindications

- caution liver/kidney impairement: risk of accumulation of active metabolites
- avoid:
  - lignocaine hypersensitivity
  - complete heart block
  - sinus brady
  - stokes adams syndrome

Interactions

- ↑risk of toxicity with concurrent use of :
  - B blockers
  - cimetidine

  ↳inihibit metabolism

Dose

- 75-100mg IV bolus
- 2-4mg/min infusion

- at therapeutic levels little effect on HR, bp, contractility or central toxicity

1b - Mexilitene

- very similar to lignocaine
- orally active (OBA 90%)
- side effects common: nystagmus, tremor, nausea ∴ low therapeutic index
- sometimes used in chronic pain when +ve response to lignocaine infusion

Class 1c - Flecainide

Chemical

- = fluorinated LA analogue of procainamide

MOA

- electrophysiological:
  - ph 0 - Na channel blocking ⇒ slower depolarisation
  - no effect on AP or ERP
  - prolongs conduction in all junctional tissues ∴ ↓conduction in
    - intra atrial
    - nodal
    - intraventricular tissues
- –ve inotropic effects ⇒ if prev impaired LV may cause failure
- no anticholinergic properties

Uses

- atrial, junctional, vent arrhythmias eg SVTs, VEBs, VT or prophylaxis against
- is effective against WPW/accessory pathways in narrow complex tachys
- oral dosing

Pharmacokinetics

- well absorbed orally
- PPB 35-45%
- 50% hepatic metab
- renally excreted 45% unchanged
- onset of action 1-6hrs
- half life 12-24hrs ie od dosing

Adverse Reactions

- particular risk of proarrhythmic effect especially if:
  - poor LVF
  - sustained vent arrhythmia
- can aggravate heart failure (-ve inotropy)
- mild:
  - blurred vision
  - dizzy
  - tremor

Cautions/Contraindications

- severe caution in
  - heart failure
  - ↓↑K
  - renal impairement
- contraindicated:
  - post MI
  - block
  - cardiogenic shock

Interactions

- coadministration with other antiarrhythmics ⇒ ↑adverse cardiac effects

- if diuretic induced ↓K ⇒ ↑risk of arrhythmias

Dose

- oral 50-100mg bd ↑ing 50mg every 4 days to max 400mg

Class II - B Blockers

- control cardiac arrhythmias caused by excessive symp activity

MOA

- electrophysiologic effects:
  - ↓slope of ph 4 in pacemaker cells ie ↓HR
  - ↑ERP in AVN ie effective against SVTs
  - ↓ERP & ↓AP in Purkinje fibres ∴ ↓re-entry tachycardias
  - ↓CO via ↓HR & ↓ionotropy
  - most have membrane stabilising properties – except atenolol & nadolol

  ↳ NB sotalol included in class 3
- only anti-arrthymic to show ↓mortality post MI

Uses

- examples:
  - atrial tachys PSVT or sinus tachy ie where arrhythmia due to ↑SNS activity or catecholamines
  - AF /- dig – aim to surpress rapid ventricular response
  - **must avoid in WPW** ⇒ force conduction down acc pathway by blocking AV node
  - post MI – anti angina & anti-arrhythmic properties
- esmolol esp useful:
  - rapid onset & offset
  - Rx of SVT, diagnosis of flutter
  - trial of Rx where ßB relatively contraindicated – if good response can use longer acting version

Class III – K Channel Blockers

- major drugs are amiodarone & sotalol

  ↳quite different actions but grouped as both prolong effective refractory period by prolonging AP in atria, vent & AVN

III - Sotalol

- = βblocker which also blocks K channels
- =racemic mixture:
  - D isomer = class III K blocking activity
  - L isomer = class II (ßB) & class III activity
- used in Rx & prevention of atrial & serious vent arrhythmias

  ↳not used for standard ßB indications
- OBA 100%
- not protein bound
- not metabolised
- excretion:
  - 90% unchanged renally
  - 10% unchanged bilary
- additive depressant effects if used with other drugs ⇒
  - brady
  - AV block
  - ↑risk heart failure
- caution if diuretic induced ↓K ⇒ additive cardiac effect
- side effects:
  - may precipitate torsades in 2% when used for AF or SVT
  - prolonged QTc
  - hypokalaemia

- both IV and oral

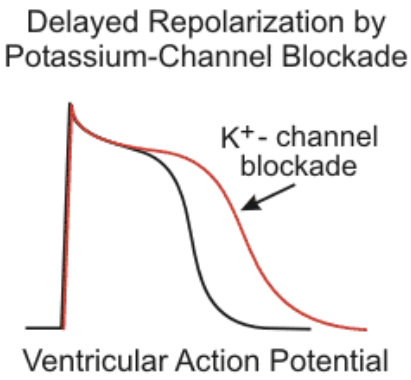
III – Amiodarone

Chemical

- = a benzofuran derivative
- has structural thyroxine
- highly lipid soluble

MOA

- electrophysiological properties of all classes:
  - main = K channels (III effect):
    - ↑repolarisation in conducting system & myocardium ⇒ ↑AP + ↑ERP
  - Na channels (I effect)
  - Ca channels (IV effect)
  - B receptors (II effect)
- causes:
  - ↑refractory period of all tissues through direct effect
  - ↓automaticity of myocytes esp ventricular
  - initial affects when given IV is not class III but is prolonged AV conduction
  - ECG: prolonged QT
- visual effect on cardiac AP:



↳ but NB amiodarone also has effects via all other classes ie
  - Ca channel blockade (short plateau)
  - Sodium channel – class 1a effect ie ↑ERP
  - B blocker – slow phase 4 ie ↓HR
- main active metabolite desethylamiodarone (DEA):
  - accumulates in chronic dosing
  - ⇒ rate of depolarisation during phase 0 becomes increasingly slower

Uses

- ideal in arrhythmias assoc with accessory pathways eg WPW
- can be used in any other arrhythmia where standard drugs not working
- (AF – shoud be CVS stable & <48hrs)
- ALS

Pharmacokinetics

- large interindividual variability in bioavailability, plasma conc, half life
- differences between single dose & chronic dosing

A

- OBA 60-80% - little 1st pass metab

D

- large Vd = 70L/kg due to:
  - extensive tissue/protein binding

- accumulation in organs
- but is highly protein bound 96%

↳ steady state in plasma after several weeks

- onset of action days to weeks even with loading doses

M

- liver metab
- main metab = N-des-ethyl-amiodarone (DEA)

↳ active & accumulates with chronic Rx

E

- main excretion into bile (some enterohepatic recirculation)
- minimal renal excretion
- biphasic elimination half life:
  - initial- 2-10days
  - terminal half life 26-107 days
- t1/2elim 28d average
- (DEA half life 60days)
- onset 2-7days of orally, why need IV loading
- effects persist for 4-6weeks after stopping

Adverse Reactions

- CVS: = a non-competitive α&ß blocker ie class 2 effect:
  - bradycardia – mild unless used in combo with other node blockers eg CCBs, ßB, dig, halothane

    ↳ is resistant to atropine
  - minimal direct depressant effects on myocardium
  - vasoD – α blocking effects ⇒ ↓SVR

    ↳ ∴ ↓SVT & ↓HR can ⇒ ↓↓MAP
  - torsades due to ↑QT – although les than other class III drugs

  ↳ all above exacerbate by concurrent GA
- Lung toxicity 3-9% - may kill if missed
  - Interstitial pneumonitis
  - Lung fibrosis +/- alveolitis in 5-15% on chronic Rx

    ↳2 patterns:
    - slow onset with infiltrates on CXR
    - acute onset with cough, SOB, hypoxia – looks like pneumonia
  - post op pts ↑risk of developing ARDS – esp if on high dose FiO2
  - BOOP – bronchiolitis obliterans organising pneumonia
- phototoxicity:
  - = UVA skin reaction
  - blue-grey skin discolouration may occur
- skin disorders:
  - photosensitivity
  - rash: erythema nodosum
  - slate grey may rarely persist on discontinuation
- Thyroid dysfunction (2%):
  - ↑↓thyroid – amoidarone = iodinated drug with resemblance to thyroxine
- Neurotoxicity (up to 40% chronic dosing)
  - Periph neuropathy prox motor weakness & distal sensory loss
  - Sleep disturbance (nightmares),
  - ataxia
  - fine resting tremor (Worse in elderly)
- Liver:
  - enzyme induction
  - asymptomatic abnormal LFTs – in 20%

- hepatitis possible
- eyes: corneal microdeposits – reversible & generally asymptomatic

Cautions/Contraindications

- caution in
  - heart failure
  - liver failure
  - thyroid impairement
  - avoid if any heart block or bradycardia

Interactions

- inhibits multiple CP450 enzymes
- multiple interactions
  - Markedly ↑dig levels & additive effect on SAN/AVN – thus reduce dig or stop
  - ⇒ ↑phenytoin levels
  - Rifampicin incr amiodraone level
  - Avoid use with class I vaughan Williams agents – otherwise ↓dose of class I 30-50%
  - flecanide – inhibits its metabolism ∴ ↓dose flecanide
  - Warfarin – inhibits it metabolism ∴↓dose

Class IV – Calcium Channel Blockers (CCBs)

see CCB section

Summary

- Electrophysiological:
  - verapamil (l-isomer): Nodal blocker via prolong conduction & ↑ERP
    ↳ inhibits Ca ion flux in ph2 & ph4
  - verapamil (D-isomer) : Membrane stabiliser – effect on fast Na channels
  - nifedipine: no sig effects on node
- heart effects –diff degrees see table)
  - –ve chronotropy
  - dromotropy – both ↓ except nifedipine which has no effect
  - inotroy
  - reflex tachy (nifedipine)
- vasomotor: ↓Ca entry ⇒ vasoD

Table 15.3. Main cardiovascular effects of some Ca^{2+} channel antagonists.

	Blood pressure	Heart rate	AV conduction time	Myocardial contractility	Peripheral and coronary artery vasodilation	relex SNS stim
Verapamil	↓	↓	↑	↓↓	↑	0/↑
Nifedipine	↓	→↑	→↑	→↑	↑↑↑	↑↑
Diltiazem	↓	↓	↑	↓	↑↑	0/↑

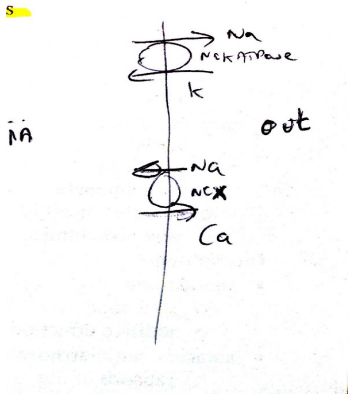
Uses

- HTN – little/no effect in normotensives
- antiarrhythmic: esp narrow complex tachys
  - verapamil 75-150mcg/kg ie 5-10mg
  - should avoid in accessory pathways ie WPW
- coronary vasospasm – nifedpine
- exercise induced angina – need better balance of O2 supply vs demand
- cerebral art vasospasm =
  - nimodipine drug of choice

- typically 4-14days post SAH
- spasm ?due to influx of Ca ions ⇒ contraction of smooth mm in large cerebral arteries

Class V – Cardiac Glycosides (Digoxin)

- ↓K, ↓Mg ⇒ ↑dig levels
- ↑Ca ⇒ ↑dig levels



Chemical

- one of 3 digitalis glycosides derived from foxglove leaves (digitalis lanata)
  ↳ other 2 = oubain + digitoxin
- chemically = glycoside ie consists of:
  - sugar = digitoxose
  - aglycone = digitoxigenin
- pharmacological + therapeutic effects due to digitoxigenin

MOA

- main effects on heart:
  - ↑inotropy
  - ↓AV conduction
  - ↓HR
  - anti-arhythmic
- direct effects:
  - inotropic effect:
    - inhibits membrane NaKATPase
      ↳ action to Na out; K in; during repolarisation
    - ↑Na [in] ⇒ inhibit Ca expulsion via NCX ⇒ ↑Ca uptake by SR
    - ↑Ca levels in SR ⇒
      - ↑excitation-contraction coupling during contraction ⇒ ↑inotropy
  - ↑ERP of AVN & Hiss bundle **but** ↓ERP of ventricular mm cells
    ↳ due to ↑Ca [in]

  ↳ digoxin doesn't appear to have any benefit in normal hearts
- indirect effects via ↑vagal affects: (∴ antagonised by atropine):
  ↳ via direct effect on central vagal nuclei ⇒↑efferent vagal activity
  - ↓rate of depolarisation ph4 in SAN ⇒ bradycardia
  - ↓atrial refractory period ie ↑chance of atrial arrhythmias
  - ↑ERP of AV node & Hiss bundle
  - ↓sensitivity of SAN & AVN to sympathetic activity

Uses

- AF & flutter – esp if heart failure:
  - direct ↑ERP of AVN & Hiss bundle ⇒ ↓conductivity ⇒ ↓vent rate ∴ ↑diastolic filling time ⇒ improved O2 balance
  - (but may ↑chance of atrial arrhythmias – indirect ↓atrial ERP)
- Heart failure – note if in sinus then +ve inotropy effect is **not** maintained in long term
- paroxysmal SVT: indirect ↑vagal tone ⇒ ↓HR ⇒ may convert to sinus

Pharmacokinetics

A

- absorption influenced by:
  - formation
  - intestinal efflux transporter P-gp ⇒ ↓s absorption
    ↳∴ coadministration quinidine (P-gp inhibitor) ⇒ ↑dig levels
- OBA 75%
- max serum conc within 30-60mins ⇒ effects take hrs

D

- Large Vd 10 L/kg although ↑conc in cardiac & skeletal mm

↳conc in tissues generally higher than plasma conc

- PPB 25%

M

- not hepatic metabolised

E

- excretion:
  - ~20% bilary excretion
  - 80% renal unchanged drug:
    - filtered & secreted in kidneys
      ↳by renal P-gp transporter
- half life:
  - t1/2elim 36hrs
    ↳∴ od dosing and steady state in 5days
  - impaired renal function ⇒ half life 3-5days
- elderly:
  - ↓elimination 2nd to renal effects
  - ↓volume of distribution

  ↳∴ lower doses required

Adverse Reactions

- dig has low therapeutic index (ED50/LD50)
- ↑ mild:
  - anorexia & Gi disturbance
  - CNS effects – visual disturbances, nightmares, drowsiness, agitation
- skin rash – occasional
- gynaecomastia - occasional
- ↑ plasma concentrations ⇒ CVS effects
  - bradycardia
  - AV conduction so slowed ⇒ heart block
- toxic concentrations:
  - ↑sympathethic activity & direct ↑automacity ⇒ ↑ rate spont depolarisation ⇒ dig induced ectopic pacemakers
  - any type of arrhythmia can be produced:
    - vent premature extrasystoles
    - bigeminy (2 beats & a pause)
    - atrial arrhythmias less common
    - any type of block

    ↳∴avoid in VT & PVBs, VT, AV block
- electrolyte disturbances ↑risk of toxicity:
  - ↓K level:
    - K normally competes with dig for binding to NA-K-ATPase pump
      ↳↓K ⇒ ↑dig binding ⇒ ↑excitability
    - low K [out] ⇒ synergistic effect direct to ↑ectopic pacemaker activity
  - ↓Mg ⇒ ↑risk toxicity
  - ↑Ca with dig present ⇒ sinus brady, AV block, ectopics
- signs of dig toxicity:
  - anorexia
  - N&V
  - abdo pain

Cautions/Contraindications

- caution in:
  - renal impairement
  - thyroid –

        - ↑thyroid ⇒ ↓dig action
        - ↓thyroid ⇒ ↑dig action
    - electrolytes:
        - ↓K, ↓Mg ⇒ ↑dig levels
        - ↓Ca ⇒ ↓dig levels
    - ACS
- contraindicated:
    - WPW
    - pericarditis
    - corpulmonale
    - complete heart block
    - vent arrhyhtmias

Interactions

- amiodarone:
    - ↑dig conc
    - additive effect on slowing cardiac conductions
- antacids, antidiarrhoeals, bile acid binding resin, macrolides:
    - ↓absorb of dig
        - ↳∴ separate administration of drugs
- Ca channel blockers:
    - ↑plasma dig level
    - additive effect ↓AV conduction & HR
- K depeleting drugs eg steroids, loops, thiazide:
    - ↑lowering of K ⇒ ↑chance dig toxicity
        - ↳enhance oral K & monitor UEs
- Quinine: ↑dig conc
- spironlactone: ↑dig conc
- St Johns Wort: ↓dig conc
- suxamethonium: risk of dangerous arrhythmias eg brady's

Dose

- narrow therapeutic range
- people can be toxic even in range
- alter dose based on:
    - renal function
    - clinical response
    - plasma level
- loading: 250-500mcg for 3x4 doses 4-6 hourly
- maintenance: 125-250mcg daily

Monitorring of Plasma Conc

- narrow range:
    - <1ng/ml = ineefective
    - >2.5ng/ml = toxic
- if heart failure 0.5-1 should be target
- blood should be taken 6-8 hours after last oral dose or immed prior to next dose

Treatment of Dig Poisoning

- if toxic with renal failure ⇒ half life 3-5days need Rx early
- strategies
    - normalise electrolytes: ie aim high normal K & Mg, decr Ca
    - Phenytoin has a role
    - Digibind

Digibind

- Rx with bovine dig specific immune antigen-bining fragment (Fab)

- bind dig molecules in plasma preventing them from being active ⇒ conc gradient to draw dig out of tissue ⇒ ↓tissue level
- dig-fragment complex accumulates to plasma & excreted by kidney
- post IV dose should see improvement in 15-30mins
- half life of dig Fab 15-20hrs
- need to monitor as withdrawal of dig ⇒ :
  - ↓CO
  - heart failure
  - ↓K
  - ↑HR if AF
- one vial of antibody binds 500mcg dig

  ↳calculate from plasma level or amount ingested:

  oral: body load (mg) = dose ingested (mg) x 0.8

  plasma level: body load (mg) = $\frac{\text{dig conc (ng/ml) x 5 L/kg x body weight (kg)}}{1000}$

  calculate antibody dose:

  dose (no of vials) = body load (mg) / 0.5 (mg/vial)

Unclassified- Adenosine

Chemical

- = endogenous nucleoside consisting of
  - purine base (adenine) linked to
  - pentose sudar (D-ribose)
- is produced by:
  - during normal metabolic activity of various intracellular enzymes on high energy phosphates (AMP, ADP, ATP)
  - conversion of s-adeno-syl-homo-cysteine ⇒ adenosine

Effects/MOA

- cellular protective effects:
  - vasoD via NO effect on A2 receptors:
    - coronary dilator ie metabolic autoregulation
    - peripheral dilation ie flushing, headaches, ↓MAP
  - inhibition of Ca flux
  - release of excitatory neutransmitters eg glutamate
  - K channel activation ⇒ hyperpolarisation ⇒ selective AVN effect:
    - inhibit AV conduction
    - ↑AV node refractory peroid
  - ↑energy production via glucose transport
- cardiac – via mediation with A1 receptor ⇒ ↓cAMP
  - –ve inotropy
  - –ve chronotropy:
    - ↓SAN automaticity ⇒ ↓HR
    - ↓AVN conuductivity: prolongs conduction
    - ↓accessory pathway conductivity
- other:
  - bronchoconstriction
  - direct activation of carotid boday ⇒ ↑MV
  - renal afferent arteriolar constriction

Uses

- Cardiovert
  - 10% of flutters

  - 90% AVRT & AVRNT
- may cause transient ↑rate in WPW so try to avoid!
- induce temporary asystole in endoluminal repair of AAA
- can be used with broad complex tachycardia
- hypotensive anaesthesia (50-300mcg/kg/min)

Pharmacokinetics

- used with IV bolus
- immediate onset
- action terminated rapidly ~20secs by uptake into rbcs & vascular ECs
- metabolised to
  - inosine ⇒ uric acid
  - Adenosine monphosphate (AMP)

Adverse Reactions

- mild:
  - SOB
  - facial flushing
  - parasthesia in arms
- pot serious:
  - transient arrhythmias eg
    - vent ectopics
    - sinus brady
    - sinus tachy
    - CP – coronary steal

Cautions/Contraindications

- caution in asthma
- contra:
  - adenosine hypersensitivity
  - 2^{nd} & 3^{rd} AV block
  - sick sinus syndrome
- NB not contraindicated in 1^{st} deg block

Interactions

- caffeine & theophylline competitively antagonise effects
- dipyridamole additive effect
  ↳inhibits uptake of adenosine into rbcs ∴ blocks redistribution & metabolism

Dose

- 3mg>6mg>12mg

Unclassified – Magnesium

- 35-40% Mg salts found in cardiac & skeletal mm
- ↓Mg assoc with variety of arrhythmias – esp if assoc with ↓K

MOA

- methods:
  - Mg is cofactor for Na/K/ATPase
    - ∴↓Mg ⇒ intracellular K depletion
    - need to replace Mg before K other can't intracellularly replenish
  - inhibits L type Ca channels ⇒ ↓Ca influx in phase 2 of AP
    ↳potential to shortern QT interval
  - blocks K channels ⇒ ↓efflux of K
    ↳potential to lengthen QT interval
  - ↓early after-depolarisations
- counterbalancing K & Ca channel effects thought to terminate torsades de pointes indep of QT interval

Pharmacokinetics
- renally cleared

Uses
- essentially = myocyte stabiliser for any arrhythmia:
  - torsades de points
  - digoxin induced arrhythmias
  - MFAT
- severe asthma
- eclampsia

Adverse Reactions
- ↑Mg incl:
  - loss of deep tendon reflexs
  - resp depression from neuromuscular blockade
  - flushing/headache
  - diplopia
  - dry mouth
  - pulmon oedema

Cautions/Contraindications
- renal impairement

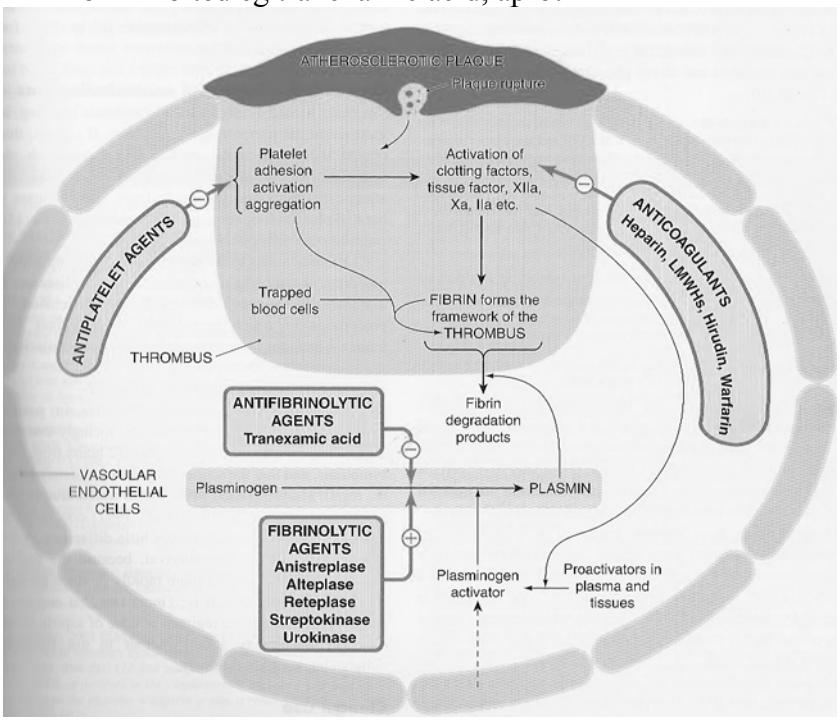
Interactions
- aminoglycosides ⇒ ↑↑risk of resp depression due to neuromuscular blockade

WPW Syndrome
- = congen accessory pathway between atria & ventricles
- conducts more rapidly than AV node but has a long ERP
- ECG findings:
  - short PR
  - wide QRS with delat waves:
    - type A = delta wave in v1 ∴ L heart
    - type B = delta wave elsewhere ∴ R heart
- presents with SVT like pattern
  ↳ suspect if very young, HP >300, resting delta waves
- periop Rx:
  - continue anti-arrhythmic Rx peri-op (usually flecainide or sotalol)
  - avoid drugs causing
    - ↑HR eg atropine, ketamine, pancuronium
    - ↑conduction acc pathways eg adenosine, ßBs, CCBs, digoxin
- Rx of any arrhythmias:
  - avoid: adenosine, ßB, CCBs, digoxin
  - use:
    - if <48hrs & CVS stable: amiodarone, flecainide, procainamide
    - >48hrs – anticoag first ie like AF
    - unstable ⇒ cardiovert

Clotting Drugs

MOA Drugs on Coagulation & Platelets

- heparins: potentiating the naturally occurring inhibition of coagulation:
  - esp F10a & thrombin
- Coumarins: vit K antagonism ⇒ suppression of synthesis of vit K dependant clotting factors
  ↳ 2,7,9,10 & protein C
  - eg warfarin
- antiplatelet function eg aspirin, clopidogrel
- fibrinolytic pathway:
  - enhanced eg t-PA, streptokinase, urokinase
  - inhibited eg tranexamic acid, aprotinin



Heparins

Unfractionated Heparin (UFH)

Chemical

- naturally occurring substance which derived from animal sources:
  - bovine lung = more allergies
  - porcine intestine = less allergies
- as from animals leads to variability in potency
  ↳ ∴ drug measured against standardised assay & reported in no of active units
- = complex proteoglycan of repeating disaccharide (sugar) units attached to core protein
- moelcules have wide range of molecular weights ie 5000-40,000
  ↳LMWH 4000-6000 units
- formed endogenously in large amounts in body:
  - mast cells in liver,
  - lungs,
  - intestinal mucosa

Presentation

- strongly acidic with high protein binding
- electronegatively charged

MOA

- does not have fibrinolytic activity
  ↳∴ no dissolution of existing clots but can prevent extension
- @physiological pH
  - drug contains large number of anionic (-ve charge) groups
  - essential for action
  - also mechanism of neutralisation with basic substances eg protamine

1. Anticoagulant effects:

- heparin binds directly to coag factors and facilitates their reaction with AT-3
- ↑s action of heparin cofactor 2 which ⇒ inactivation of thrombin
- enhances activity of TFPI x2-4
- [low dose]:
  - binds reversibly to antithrombin III in plasma ⇒
    - x1000 enhancement of inactivation of thrombin (2a) & F10a
      ↳ UFH anti 10a:2a = 1:1
      ↳LMWH anti 10a:2a = 4:1 to 2:1
- [higher dose]:
  - suppression of other activated clotting factors:
    - mediated via AT-3
    - inactivation of 9a, 11a, 12a
    - ∴ see further suppression of thrombin synthesis
  - ↓platelet aggregation
    - MOA with AT-3

**** explanation of effect on coag cascade *****

- inactivation of factor X ⇒ block of intrinsic & extrinsic pathways ⇒ ↓ conversion of prothrombin to thrombin
- the effect of ↓ed activated thrombin (II) means
  - ↓fibrin formation
  - ↓ed thrombin induced activation of factor V & VIII
    ↳VIII is a fibrin stabilising factor ∴ ↓stable clots
- fibrin assoc with venous thrombi ∴ heparin targeted to venous system

****

2. vWF effects

- heparin binds & inhibits vWF
- ∴ further antiplatelet effect
  ↳ in addition to effects at high heparin doses

3. Other Effects

- ↓serum triglycerides:
  - activation of lipoprotein lipase in tissues ⇒ ↑FFAs
  - can interefer with plasma protein binding of some drugs eg phenytoin, propanolol

Pharmacokinetics

A

- large molecular weight & polar (water soluble):
  - no Gi absorption
  - does not cross placenta
- onset of action
  - IV injection – immediate
  - s/c – 1-2hrs

D

- bound to:
  - AT-3 – 33%
  - albumin

  - fibrinogen
- does not cross bbb or placenta
- Vd =
  - 0.04 – 0.1 L/kg
  - ~ vascular volume (70ml/kg)
  - ∴ one compartment kinestics

M/E

- rapid:
  - desulphated & depolymerized by heparinises in :
    - liver
    - kidneys
    - tissue (endothelial) - macrophague system
- meatb is saturable ⇒ disproportionate ↑ in anticoag effect with ↑ed doses
  ↳ renal pathway – not saturable ∴ liver impairement has large effect compared to renal injury
- half life dose dependant due to saturable clearance mechanisms
  ↳av 1-6hrs
  ↳ speed of elim is ↓ed in hypothermia eg CPBypass
- metabolites are inactive & renal excreted
- Cl = 0.5-2ml/kg/min
- t1/2 elim 90mins
- duration of action after single dose 4-6hrs ie time to wait before doing neuraxial techniques
- not removed by haemodialysis due to size of molecules
- monitor action/dosage with APTT
- heparin resistance seen in:
  - AT III deficiency – long term Rx ⇒ ↓AT3 activity by 10-20%
  - ↑hep clearance
  - ↑hep binding proteins
  - ↑level of VIII & fibrinogen

Uses

- prophylactic to prevent VTE eg DIC, surgery, heart surgery
- acute arterial occlusion eg ACS
- immediate onset of action & reversal if required

Adverse Reactions

- excessive bleeding:
  ↳↓ed risk with LMWHs
  - ↑ed risk if vit K deficiency or concurrent anti-plt Rx
- hypersensitivity reactions:
  - type 1 IgE mediated
  - eg bronchospasm/anaphylaxis
- thrombocytopaenia:
  - anaphylactoid reaction – involves alternative complement pathway
  - HITS
    - = heparin induced thrombocytopaenia
    - if concurrent thrombosis = HITTS
    - 1-6% incidence (much less with LMWH)
    - present 4-14 days after 2nd exposure to heparin
    - more frequent with bovine lung heparin
    - 2 types:
      - type 1:
        - transient/self limiting ↓platelets to ~50
        - = direct heparin induced plt agglutination ie non immune mechanism
      - type 2:

    - platelet ↓ to ~10 & assoc with thromboembolic phenomena
    - immune mediated plt aggregation by IgG & IgM antibodies
    - development of antibodies to platelets following 1st heparin exposure. ie occurs on next exposure
    - = type II hypersensitivity reaction
    - usually resolves rapidly on stopping heparin (can last for 2/12)
    - must avoid UFH forever, but can use LMWH (with caution)
- thrombosis:
    - prolonged Rx ⇒
        - ↓AT-3 activity
        - ↓plasmin activity
- ↑K:
    - ↑risk if have problems with K homeostasis
    - MOA:
        - inhibition of final step in pathway for production of aldoseterone
        - ↓number and affinity for AT II receptors ⇒↓aldosterone secretion
- chronic use of heparin >1month (eg pregnancy):
    - ↓bone density in 30% pts
    - ?MOA - ?↓osteoblasts ↑osteoclasts

    ↳LMWH less risk

Cautions/Contraindications

- caution in:
    - asthma
    - Hx of allergies
    - mod liver impairement ie altered levels of coag factors
- contra:
    - bleeding tendancies
    - sever HTN
    - peptic ulcers
    - women recent childbirth

Interactions

- aspirin, platelet inhibitors & NSAIDs:
    - large dose of aspirin ⇒ hypoprothrombinaemia
    - ↑risk GI bleeding
- dipyridamole – risk of bleeding
- thrombolytics

Monitoring

- causes:
    - ↑APTT
    - ↑TT
    - ↑whole blood clotting time (9-12mins)
    - ↑ACT (activated clotting time)
        - = bedside test – use routinely in cardiac theatre
        - normal = 100-140sec
        - usually aim for x3-4 pre-heparin value
- INR = normal

Dose

- international units = 1 IU heparin will prevent 1ml of citrated sheep plasma from clotting for 1hr after adding 0.2ml 1:100 $CaCl_2$ (Ca added to reverse citrate)
- heparin sodium contains 120U/mg

    ↳ for ease 1mg heparin = 100 IU eg 5000 U = 50mg
- loading doses = 70U/kg ~ 5000U

- infusions 15u/kg/hr ~ 1000-2000 U/hr

LMWH

Chemical

- produced by fractionising heparin to exclude molecules >10 000 D

Mechanism of Action

- coag cascade effect:
  - has no direct effect on thrombin inhibition (via AT-3)
    ↳ unable to bind AT-3 & thrombin simultaneously
      ↳ because anti-2a activity is directly proportional to chain length
      ↳ ie anti1a activity isnt
  - exerts it effect (via AT-3) directly on factor 10a
      ↳ also via 9a, 11a, 12a – but minor
  - ∴ LMWH = more specific for inhibiting 10a:2a (4:1 to 2:1)
- ↓vWF binding ⇒ ↓effect on platelet function ∴ fewer haemorrhagic complications
- = safe & same effect as heparin in prophylaxis of DVT + PE

Pharmacokinetics

(compared to UFH)

- only 10% PPB ∴ ↑bioavailability
- ↓ed dosing requirements
- does not ↑vasc permeability
- longer duration of action:
  - ↓ed liver metab
  - less affinity for endothelial cells & macrophagues

  ↳∴ no rapid degredation
- t1/2 elim 4-5hrs
- some hepatic conjugation
- excreted via kidneys predominantly ∴ levels ↑in renal failure
- longer half life 3-6hours
- partially reversible with proatmine sulphate

Neuraxial Blocks

- need to wait longer than UFH
- prophylactic dosing:
  - neuraxial blocks 12hr after LMWH dose
  - post block need to wait 2-6hrs (longer the better)
- treatment dosing (1mg/kg): wait at least 24hr prior to procedure

Monitoring

- does not effect APTT, PT ∴ no need to monitor
- means some difficulty in assessing coag profile prior to procedures

Adverse Effects

- thrombocytopaenia less common ~0.6% & ↓bone effects

Protamine Sulphate

Chemical

- = highly basic compound
- prepared from fish sperm
- = mixture of low mw cationic proteins

Mechanism of Action

- heparin neutralising effect:
  - basic nature ⇒ neutralisation of heparin by forming complexs with highly acidic heparin

  - ⇒ formation of stable inactive salt
- effect on LMWHs:
  - only neutralises anti-2a effect ie doesn't effect 10a action
    (↳ which confers the majority of their action)
- intrinsic anticoagulation effect:
  - only in high doses
  - inhibits formation & activity of thromboplastin

Uses

- neutralises effects of heparin
- prolongs action of insulin

Pharmacokinetics

Adverse Reactions

- CVS:
  - complement activation ⇒
    - myocardial depression
    - bradycardia
    - hypotension

    ↳ give slow IV to ↓risk
- SOB & flushing
- hypersensitivity reactions – higher risk if diabetic or fish allergies
- anaphylactoid reactions
- bleeding – overdose
- pulmonary hypertension – due to complement activation & TXA2 release
-

Dose

- dose adjusted according to:
  - amount of hep given
  - time elapsed since hep given
  - ACT
- 10mg protamine neutralises 10mg or 1000units of heparin
- max dose = 50mg slow push every 10mins

Coumarin Anticoagulants

- dicoumarol = 1st used in 1940s
- warfarin = racemic synthetic analogue of dicoumarol

Warfarin

Chemical

- =racemic drug with equal concentrations of s- & r- warf

MOA

- primary action is to antagonise the action of vit K
- vit K dependant coag factors = 2,7,9,10 & protein C & S
  - coag factor activity:
    - produced in liver
    - their activation requires carboxylation – vit K required as a cofactor
    - once carboxylated: factors have 2 carboxyl gps ⇒ can chelate Ca ⇒ able to bind to phospholipids membranes ⇒ pro-coagulant effect

  ↳ protein C & S also vit K dependant for activity
  - vit K as a cofactor:
    - gets oxidised as part of coag factor activation reaction
    - needs to reduced again to be re-activated

      ↳ achieved by enzyme vit K reductase

  - warfarin inhibits diaphorase ⇒ depletion of active vit K ⇒ depletion of activated coag factors ⇒ anticoagulation
- NADH = another cofactor in reduction of vit K
- in vivo:
  - warf clearly not effective against already active coag factors
  - ∴ takes time for activated circulated factors to be removed from plasma according to half lives
  - half lives range 5-60 hrs (quick to slow: protein C&S⇒7⇒9⇒10⇒2)
  - ∴ protein C&S have shortest half life ∴ initially warf = procoagulant
  - therapeutic effect starts @12hrs, max response 48-72 hrs

Pharmacokinetics

A

- high lipid solubility:
  - 100% oral bioavailability
  - ∴ rapid absorption
    - peak plasma conc 3-9hrs

D

- high protein bound 99% - mainly albumin
- Vd 0.1-0.16L/kg ie one compartment model (vascular) due to high PPB
- cross placenta easily – not iven 1st & 3rd trimester (generally avoid completely in preg ⇒ heparin)

M

- metab completely in liver: phase 1 and phase 2
- s- warf:
  - metab by liver CYp450
  - accounts for large variability in warf dosing
- r- warf:
  - metab by CYp450
  - relatively predicatable metab

E

- metabolites excrted in faces & urine
- duration action 2-5days
- Cl 3.2-3.8 ml/kg/min ie slow
  ↳ reasons for slow offset of warf action:
    - slow clearance
    - slow production of new coag factors
- t1/2 elim = 35hrs

Uses

- DVT & PE Rx and prophylaxis
- VTE prophylaxis assoc with AF, MI, heart valves

Factors in Variability in Response to Warf

- availability:
  - condition which ↓s availability of vit K ⇒ enhanced warf:
    - diet
    - ↓synthesis
    - ↓absorption – obstructive jaundice
    - Abx – altered vit K absorption
  - liver disease: ↑warf due to ↓synthesis of clotting factors
  - metabolic rate:
    - fever/hyperthyroid ⇒ ↑breakdown of coag factors
    - myxoedema ⇒ ↓breakdown of factors
- pharmacogenetic:
  - hereditary –
    - ?resistant forms of enzyme diaphorase

        - congenital AT3 deficiency ⇒ severe reactions to warf
- drug interactions:
    - enhanced warf effects:
        - NSAIDs + aspirin:
            - low dose = antiplatelet effect ⇒ ↑bleeding time
            - large dose ⇒ ↓prothrombin synthesis
        - paracetamol – high dose ⇒ x10 ↑risk of INR >6
        - competition for protein binding sites +/- metabolising enzymes:
            - amiodarone
            - cimetidine
            - chloramphenicol
            - disulfram
            - erhtyromycin/tetracyclines/sulpha's
            - ketoconazole
            - metronidazole
        - alcohol – prolongs clearance of warf
    - decreased effects:
        - liver enzyme inducers:
            - barbituates
            - OCP
            - carbamazepine
            - rifampicin
            - phenytoin

Adverse Reactions

- haemorrhage
- skin necrosis:
    - uncommon
    - occurs soon after starting Rx due to low protein C&S levels ie hypercoaguable state
- hypersensitivity
- GIT upset
- alopecia
- anorexia
- leucopenia
- warf withdrawal – during 1st few days:
    - factor 7 & 9 ↑ more rapidly than C&S ⇒ hypercoagulable state
- preg :
    - 1st high risk teratogenicity in
    - 2nd/3rd CNS abnormalities

    ↳use LMWH – doesn't cross placenta

Cautions/Contraindications

- caution:
    - oedema
    - hyperlipidaemia
    - high risk falls
    - poor compliance
- contra:
    - bleeding risk any cause
    - blood disorder
    - severe DMs
    - vit C or K defiicincy
    - pericarditis

- should not interchange brands

Interactions

- numerous
- ↑INR:
    - alcohol
    - amiodarone
    - simvastatin
    - thiazides
    - aspirin
    - Abx incl metronidazole, macrolides, quinolones
    - propanalol
    - valproate
    - allopurinol
- ↓INR:
    - phenytoin
    - azathioprine
    - carbamazepine
    - haloperidol
    - rifampicin
    - vit K

Dose

- 5mg for 2 days then adjust according to INR

Management Bleeding

- Synthetic clotting factors used 1st line over FFP
  ↳ prothrombinex (2,9,10)
- vit K
    - = phyto-mena-dione:
    - 1mg = reversal of effects within 12hrs
    - 10mg = prevent re-warfarinisation due to saturation of liver stores
- presurg:
    - stop warf 3-6 days prior aiming
        - low risk surg: INR <1.5
        - high risk surg & neuraxial block <1.2
    - high risk pts can have heparin bridging

Antiplatelet Agents

- platelets play important role in genesis of arterial thrombosis
  ↳ role in venous thrombosis is less clear
  ↳ ∴ role is to prevent arterial thrombo-embolic disease eg MI, stroke
- specific cox 2 inhbitors do not alter platelet function ∴ should only be used in pts needing anti-inflam Rx

Aspirin (Acetyl-salicylic Acid)

- 4 effects:
    - analgesic – peripheral ↓inflammation ⇒ ↓sensitisation of nociceptors
    - antipyretic - ↓PGE1 & ↓PGE2
    - anti-inflam – COX inhibition
    - antiplatelet – see below
    - metabolic role (in toxic dose) – uncouples oxidative phosphorylation

MOA

- = a non specific COX inhibitor ⇒ ↓peripheral production of prostaglandins & thromboxane
- CVS specifically:
    - platelet actions:

- irreversible inhibition of platelet COX by irreversible acetylation of the active site of the enzyme
- ⇒ ↓thromboxane A_2 in platelets
  ↳ TXA_2 causes ↑ADP release ⇒ VasoC & ↑platelet aggregation
  ↳∴ aspirin ⇒ vasoD & ↓platelet aggregation
- effect lasts for life of platelet (approx 3-5/7)
- occurs at very low doses of aspirin

o endothelial action:
- ↓endothelial PGI2 (prostacycline) production:
  - PGI2 role (opposite to TXA2) ie vasoD & ↓platelet aggregation
  - ∴ ↓PGI2 ⇒ vasoC & ↑platelet aggregation
    ↳ but NET effect is of TXA2 inhibition (vasoD & ↓aggregation) because of:
    - endothelium able to remanufacture more PGI2 (platelet not)
      ↳ because endothelium has a nucleus & able to remanufacture COX
    - aspirin (especially at low dose) more selective for TXA2 inhibition
- proposed that diseased patients have a dysfunctional endothelium ∴ baseline low PGI2 production ∴ use of aspirin helps to restore correct equilibrium

Pharmacokinetics

A

- rapid absorb from stomach & intestine
  ↳is acidic (pKA =3)
- may see some salicylate ion trapping in alkaline mucosal cells ⇒ prevent reach systemic circulation
- peak levels
  - of acetylsalicylic acid within 20-40mins

D

- salicylate:
  - wide volume of distribution into all body tissues
  - 85% protein bound – mostly to albumin

M

- aspirin rapid hyrdolysed by intestinal & hepatic esterases to
  - acetic acid
  - salicylate (active component)
    ↳ peak level 2-4hrs
- further hepatic metab:
  - glycine conjugation: salicylate ⇒ salicyluric acid
    ↳ saturatable step which ⇒ zero order kinetics
  - salicyluric acid ⇒ glucuronide derivatives

E

- metabolites excreted via urine (enhanced under alkaline conditions)
- t1/2 elim depends on whether 1st or zero order kinetics

Monitoring

- salicylate levels:
  - 28mg/l anti-pyrexic level
  - 100mg/l anti-inflam
  - >200mg/l toxic

Uses

- are safe to give preop in regard to neuraxial anaesthesia
- in most surgery (non high risk) aspirin does not need to be stopped
  ↳ ↑risk of cardiac morbidity x2-4 if stopped in high risk pt
- pain & primary/secondary prevention ACS/stroke

Adverse Reactions

- inhibition of gastric protection: ↓PGE1 & E group production
- renal impairement: ↓PGE1 & ↓PGE3 & PGI2 ⇒ unable to vasodilate afferent vessels to ↑GFR ⇒ ↓GFR & impairment
- smooth mm effects:
  - inhibit vasodilation
  - inhibit bronchodilation (↓PGE2)
- closure of PDA: ↓PGE1 & ↓PGE2
- Reyes syndrome:
  - uncommon
  - problem in paeds
  - features =
    - widespread mitochondrial damage
    - fatty changes ⇒ hepatic failure
    - encephalopathy with cerebral oedema
  - mortality up to 40%
  - ∴ only give aspirin to <12s when truly indicated eg Stills disease (juvenile arthritis)

Cautions/Contraindications

- caution in:
  - heart failure & HTN
  - renal/liver disease
  - bleeding tendancy
  - GI probs eg ulcer
  - late pregnancy
- never <18yrs esp if fever ⇒ Reyes: severe liver damage & encephalopathy

Interactions

- with any antiplatelet
- anti-HTNs – aspirin ⇒ ↑HTN & impair renal function
- other NSAIDs - ↑risk GI ulceration
- steroids ⇒ ↓salicylate conc & effect
- valproate – aspirin ⇒ ↑valproate levels

Toxic Dose

- MOA – uncouples oxidative phosphorylation
- ingestion levels:
  - 150mg/kg ⇒ mild toxicity
  - 500mg/kg ⇒ severe & poss fatal
- features from toxic dose:
  - tinnitus
  - vertigo
  - ↑↓glucose
  - hypervent
  - ↓GCS ⇒ coma
  - agitation & tremor – severe as has penetrated bbb
  - resp alkalosis ⇒ met acidosis
- Acid base disturbance
  - Adults:
    - early: resp alkalosis
    - later: met acid
    - progressive acidosis, ↓K, dehydration
  - Small children: acidosis predominates
    ↳assoc with confusion/coma

- early management
    - early <1hr & >4.5g ingested (15tab) ⇒Gastric lavvage
    - activated charcoal
        ↳can give 2nd dose of charcoal if levels still climbing

- Rx based on levels:
    - therapeutic <300mg/l
    - Mild 450mg/l adults (350 kid) – only need ↑oral fluids
    - Mod >450 adults –
        - IV fluids
        - Sodium bicarbonate
    - Severe >750mg/L or CNS features or acidosis
        - May need urgent haemodialysis esp if level >1000 or ↓ing GCS
        - Sodium bicarbonate
        - Repeated activated charcoal via NG tube
        - IPPV with paralysis may help
        - Give IV glucose to deliver gluc to brain

Dipyridamole

MOA

- ↓platelet aggregation by 2 mechanisms:
    - reversible inhibition of platelet phosphodiesterase (isoenzyme 5):
        - ⇒ ↑platelet cAMP ⇒ sequestration of calcium in cytolsol + ↓phospholipase activity ⇒ ↓Thromboxane A2 creation ⇒ ↓platelet aggregation
    - inhibits adenosine uptake by rbcs ⇒ ↑↑serum adenosine ⇒ inhibits ADP induced platelet aggregation

Uses

- used
    - prosthetic valves: with other anticoagulants
    - TIAs – alone or with aspirin

Peri-Op

- stop ~24hrs preop (incl neuraxial)

Low Molecular Weight Dextrans

Chemical

- = polysaccharides which contain long chains of glucose units
- produced by a fermentation of sucrose medium with a bacterium
- the glucose polymers have MWs from 10-50kDa

Presentation

- dextran 40 =
    - 10% solution in 5%dex or N saline
    - contains glucans with av MW 40kDa
    - slightly higher osmotic pressure than plasma
- dextran 70:
    - 6% solution in 5% dex or N saline
    - Av glucan MW 70 KDa
    - osmotic pressure same as plasma

MOA

- in vitro = no effect on platelets
- in vivo:
    - ↑bleeding time
    - polymerization of fibrin impaired
    - ↓platelet function
        ↳ dex 70 ⇒ acquired vWillebrand state
    - [dex 40]: ↓plasma viscocity, ↓agglutination of rbcs ⇒ enhanced flow in small vessels

Adverse Reactions
- volume overload
- can interfere with X matching
- anaphylactoid reactions
- hypersensitivity
- bleeding problems

Thi-eno-pyridine Derivatives – eg Clopidogrel
MOA
- =prodrugs
- active metabolites:
    - block ADP receptors on platelet membranes ∴ blocking
        - activation
        - degranulation
        - aggregation
        - ↓binding fibrinogen to GP2b/3a
- effect is irreversible

PeriOp
- stop 7 days prior to op incl neuraxial

Glycoprotein 2b/3a receptor blockers
- eg tirofiban, abciximab
- commonly used in ACS

MOA
- abciximab =
    - monoclonal antibody that binds avidly to GP2b/3a
    - possesses greatest anti-platelet activity
    - 24-48hrs to return to norm aggregation
- tirofiban =
    - reversible non-peptide antagonist of Gp2b/3a receptor
    - 4-8hrs to return to norm aggregation
- blockage of receptor⇒
    - ↓platelet aggregatioj
    - prevent attachement to platelet of:
        - fibrinogen
        - vWF
        - other adhesive molecules
- drugs do not prevent platelet adhesion or secretion of mediators

Monitoring
- ACT
- plt count

Adverse Reactions
- bleeding
- acute severe thrombocytopaenia = class effect
    ↳ esp if used in combo with clopidogrel

PeriOp
- drugs are contraindicated 4 weeks preop
- avoid neuraxial until return of norm platelet function
- can reverse effects with transfusion if emerg surgery

Other Anti Platelet Drugs
- prostacycline (PGI2) ⇒ vasoD & ↓platelet aggregation
- biguanides
- clorofibrate

- dazoxiben – selective inhibitor of TXA2 synthesis
  ↳ although only effective combined with aspirin

Pro-Platelet Drugs

Desmopressin

- aka DDAVP or desamino-d-arginin-vaso pressin

Chemical

- synthetic polypeptide structurally related to arginine vasopressin

MOA

- causes dose dependant ↑in:
  - F8
  - plasminogen activator
  - F8 related antigen
  - vWF activity
    - via
      - V2 receptor mediated release from endothelial cells
      - ↑vWF release from platelets
    - causes ↑in:
      - plt/subendothelial interaction
      - plt/plt interactions
  - improved platelet retention
  - ↑expression of GP1b receptor on plt
  - enhanced procoagulant activity

Uses

- haemostatic functions:
  - bleeding from:
    - haemophilia:
      - f8 activity can ↑by 300-400%
      - in haemophilia A need to have baseline f8 >5%
    - vWDisease:
      - avoid in type 2B as can cause thrombosis or thrombocytopaenia
    - uraemia
    - antiplatelet drugs
    - plt dysfunction post op
  - effect on platelets lasts ~3hrs
  - tachyphylaxis if used more than once in 48hr period
- prophylactic use in vWD:
  - intranasal 2hrs, IVI 30mins preop
  - can cause ADH like hyponatraemia & fluid overload
  - no proven benefit in blood loss in otherwise healthy people
- non-haematological uses:
  - enuresis
  - neurogenic diabetes insipidis

Pharmacokinetics

- bioavailability intranasally ~4% with peak plasma levels at 45mins
- post dose ↑f8 & vWF within 30mins – peak 90min to 3hrs
- metab unknown
- t1/2elim ~75min
  ↳ biphasic ↓ in plasma levels

Drugs Acting on Fibrinolytic Pathway

Fibrinolytic Inhibitors

- synthetic lysine analogues eg aprotinin
- lysine analogues eg
  - aminocaproic acid
  - tranexamic acid – x10 more potent than ACA

Synthetic Lysine Analogues

- eg aprotinin
- = proteolytic enzyme inhibitor
- forms reversible enzyme inhibiting complex with:
  - plasmin
  - trypsin
  - kallikrines (tissue + plasma)
- used clinically:
  - life threatening haemorrhage due to hyperplamsinaemia eg tPA antidote
  - acute pancreatitis
  - post CPB, TURP, liver transplant
  - prevention of post
- monitor with ACT
- rarely causes thrombophlebitis & hypersensitivity reactions

Lysine Analogues

MOA

- competitive inhibitors of conversion of plasminogen ⇒ plasmin
- 3 major mechanisms:
  - ↓spliting of fibrin:
    - bind to lysine binding sites of plasminogen & plasmin
    - once bound ⇒ displaces plasminogen from fibrin ∴ inhibiting ability to split fibrinogen
  - protection of fibrin from plasmin degredation – by binding to fibrin
  - TXA & ACA preferentially to clot bound tPA (compared to circulating) ⇒ inhibit cleavage of plasminogen :
    - ∴aprotinin better at inhibiting systemic fibrinolysis where high tPA levels ⇒
      - high level fibrin degredation products
      - high systemic plasmin levels and
      - ↑ed bleeding times

Uses

- antidotes to overdose with fibrinolytic agents eg tPA
- Rx in pathological states assoc with hyperfibrinolytic activity:
  - obstetric pathology – HELLP syndrome
  - prostatic surgery
  - haemorrhage disorders incl menorrhagia
  - haemophilia – haem A – give prior to dental extractions
  - hereditary angioedema
  - major trauma

Adverse Reactions

- [ACA]: IV prep may cause:
  - hypotension
  - arrhythmias
  - DIC & fatal thrombus formation
- [both]:
  - GIT & N&V
  - failure of fibrinolytic system to remove clots ⇒ renal, hepatic, cardiac lesions

- NB use periop is not assoc with ↑risk of DVTs

Pharmacokinetics

- excreted renally (95% unchanged)

Fibrinolytic Activators (Thrombolytics)

- Rx acute thromboembolic disorders
- drugs include:
  - tissue plasminogen activator eg alteplase
    ↳made from recombinant DNA technology
  - streptokinase – made from cultures of β-haemolytic streptococci
  - urokinase
- all convert plasminogen ⇒ plasmin
- plasmin dissolves fibrin clots wherever drug can reach

Streptokinase

- = enzyme produced by group C ß-haemolytic streptococci

MOA

- it forms a complex with plasminogen
- complex then facilitiates conversion of further plasminogen ⇒ plasmin
- complex can then be lysed

Pharmacokinetics

- IV loading dose – this usually sufficient to neutralise any antibodies which are present from previous exposure to streptococcal infection
- streptokinase-antibody complex is cleared rapidly
- streptokinase-plamsinogen complex degraded to a number of smaller fragments during this action

Uses

- used to dissolve arterial & venous clots

Adverse Reactions

- haemorrhage – contraindicated in patients who have a risk of serious bleeding which outweighs benefits eg recent stroke, severe hypertension, active internal bleeding
  ↳ SK does not distinguish between thrombus & haemostatic plug
- CVS: may precipitate reperfusion arrhythmias & hypotension
- allergic reaction: very antigenic

Cautions/Contraindications

- absolute contra:
  - active internal bleeding
  - <1month major trauma/surgery
  - <6month stoke
  - bleeding disorder
  - haemorrhagic retinopathy
  - prior brain bleed or Ca
  - endocarditis
  - HTN >180/110

Interactions

- oral anticoagulants or heparin:
  - ↑risk bleeding
- antiplatlets:
  - ↑bleed

Urokinase

- = a globulin
- converts plasminogen to plasmin in a 2 stage reaction
- used in local thrombolytic procedures eg AV shunts to lyse clots

↳ unable to use systemically due to very high bleeding risks

- now made recombinantly to produce pro-urokinase

Alteplase

- = recombinant tissue plasminogen activator (t-PA)
- = glycoprotein which has higher affinity for plasminogen bound to fibrin (compared to circulating plasminogen) ⇒ conversion plasminogen to plasmin
- ∴ even at high serum t-PA levels see very little plasmin in general circulation – is all tissue bound
  ↳ ∴ see ↓ed systemic fibrinolysis than with streptokinase

ANZ Periop Guidelines 2005

RISK ASSESSMENT				
Category	**Medical Patients**	**VTE PROPHYLAXIS**	**Surgical Patients**	**VTE PROPHYLAXIS**
HIGH	Age>60years Ischaemic stroke History of VTE Decompensated cardiac failure Active cancer Acute on chronic lung disease Acute on chronic inflammatory disease	Low Dose Unfractionated Heparin or LWMH or GCS &/or IPC if heparin contraindicated	Orthopaedic surgery of pelvis, hip or lower limb Multiple trauma Major surgery, age>60years Major surgery, age 40-60 years with cancer or history of VTE or other risk factors	LMW Heparin or Fondaparinux* AND GCS &/or IPC
MODERATE			Major surgery, age 40-60 years without additional risk factors Minor surgery, age >60years Minor surgery, age 40-60years with history of VTE or on oestrogen therapy or with other risk factors	Low Dose Unfractionated Heparin or LMWH
LOW			Major surgery, age 16-40years with no other risk factors Minor surgery, age16-60years with no other risk factors	Consider GCS

(GCS = graduated compression stockings, IPC = intermittent pneumatic compression)

Coagulation in Sepsis

- see suppression of mechanisms which limit excessive activation of coag cascade ie ↓fibrinolytic system
- ∴ see ↑ed coagulation ie ↑ed laying down of fibrin
- derangement mediated by proinflam cytokines eg TNF-α, IL1 & IL6
- regulation of thrombin formation involves:
  - protein C
    ↳ activated protein C ⇒ ↓factor 5a & 8a ⇒ ↓thrombosis & ↑fibrinolysis
      ↳ part of rationale behind activated protein C in sepsis (although withdrawn as dangerous)
  - antithrombin
  - tissue pathway inhibitor
- IL6 & thrombin = principle mediator of coag problems in sepsis –
- IL6 & thrombin cause:
  - ↑release of plasminogen activator inhibitor 1 (from plts & endothelium)
  - activation of 'thrombin activatable fibrinolysis inhibitor' which ⇒ ↓activity of plasmin

Coag Tests

APTT

- measure of overall activity of intrinsic pathway
- normal 26-39
- prolonged test ≈
  - deficiency one or more intrinsic coag factors
  - presence of lupus type coag inhibitor
  - heparin
- target with heparin 50-90sec

- not effected by LMWH

PT

- overall activity extrinsic pathway
- clotting time used to measure INR
  ↳removes variation of reagent brand or testing lab
- prolonged test ≈
  - deficiency of extrinsic coag factor
  - lupus coag inhibitor
  - warfarin

Neuromuscular Blocking Agents

- NMBs part of the triag of anaesthesia:
  - amnesia
  - analgesia
  - areflexia - somatic – (NMBs) & autonomic

Somatic Nervous System

- aka voluntary ns
- primary motor area of cerebral cortex initiate voluntary movement
- impulse through UMN which decussate in medulla oblongata
- UMN terminate in ant grey horn of spinal cord at each spinal segment
- often interneurons which then connect to LMN
- LMN = final common pathway which connects CNS to skeletal mm

Mechanisms to Block Neuromuscular Transmission

- CNS:
  - brain volatiles – work at different levels
  - spinal cord level – LA's ie spinal/epidural
- PNS: LA blockade of motor nerves
- NMJ:
  - presynaptic:
    - CCB's
    - antibiotics – metronidazole, tetracyclines
    - Mg
    - botulinism
  - postsynaptic:
    - depolarising agents
    - NDNMBs
- Muscle:
  - dantrolene
  - volatiles

Indications for Use

- absolute:
  - essential that pt doesn't move at all eg neurosurg, retinal eye surg
- relative:
  - high priority:
    - RSI
    - abdo relaxation for laparotomy
    - laproscopic surgery
  - lower priority eg facilitate ventilation

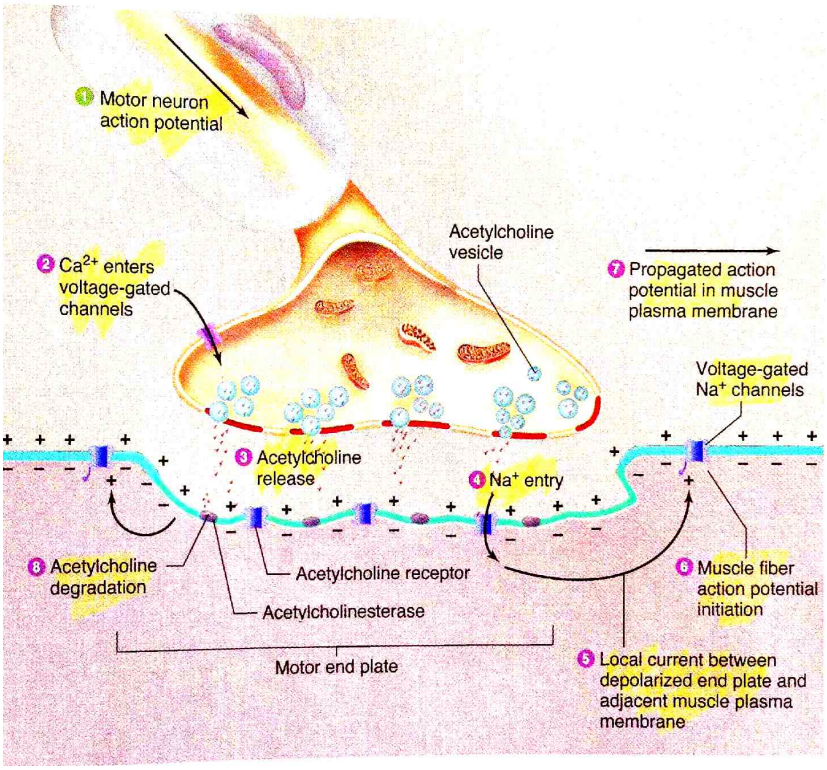
NeuroMuscular Junction (copied directly from physiology notes)

- 1 nerve fibre ends on each end plate
- no convergence or mutliple inputs
- endfeet contain many small clear vesicles
- @NMJ motor neuron divides into cluster of synaptic end bulbs (terminal buttons) containing Ach
- motor neuron is myelinated until start of button
- synaptic cleft ~50-70nm wide, filled with ECF
- post synaptic membrane = motor end plate:
  - folded into longitudinal gutters

- has junctional folds which conceal orifices to secondary clefts
- orifices:
  - lie opposite lie opposite release points for Ach
  - contain high concentrations of acetylcholinesterase (true AchE)

- NMJ norm in centre of mm fibres
- impulses radiate out from NMJ over mm

Activation of NMJ



- AP arrives at motor end plate
- ↑permeability of endings to Ca ⟹ enter of Ca into neurone through pre-synaptic membrane
- ⟹ ↑↑excocytosis of small clear Ach containing vesicles
- Ach diffuses across cleft to muscle-type nicotinic Ach rceptors
- receptors concentrated on junctional folds on MEP
- binding Ach to post junctional nicotinic receptor:
  - receptor has 5 subunits with ion channel in centre:
    - α x2
    - β
    - δ (delta)
    - ε (epsilon)
  - bulk of receptor faces extracellularly
  - 2 molecules of Ach bind onto each (ie both) α subunit ⇒ channel opens ⇒
    - Na & Ca move into cell
    - K flow out of cell

    ↳ ⟹ depolarising of Motor Endplate potential towards threshold (-90mV to -60mV) ⟹ if threshold achieved ⟹ depolarisation of muscle membrane ⟹ depolarising AP through muscle ⟹ mm contraction

    ↳ current sink by local potential depolairses adjacent mm membrane to threshold level
- hydrolysis of Ach by acetylcholinesterase:
  - occurs within 1ms
  - Ach ⟹
    - acetate
    - choline -

- then actively reuptake into nerve ending
- combined with acetyl-coenzyme A (from mitochondria) ⟹ Ach
  ↳ catalysed by choline acteyl transferase (CAT)

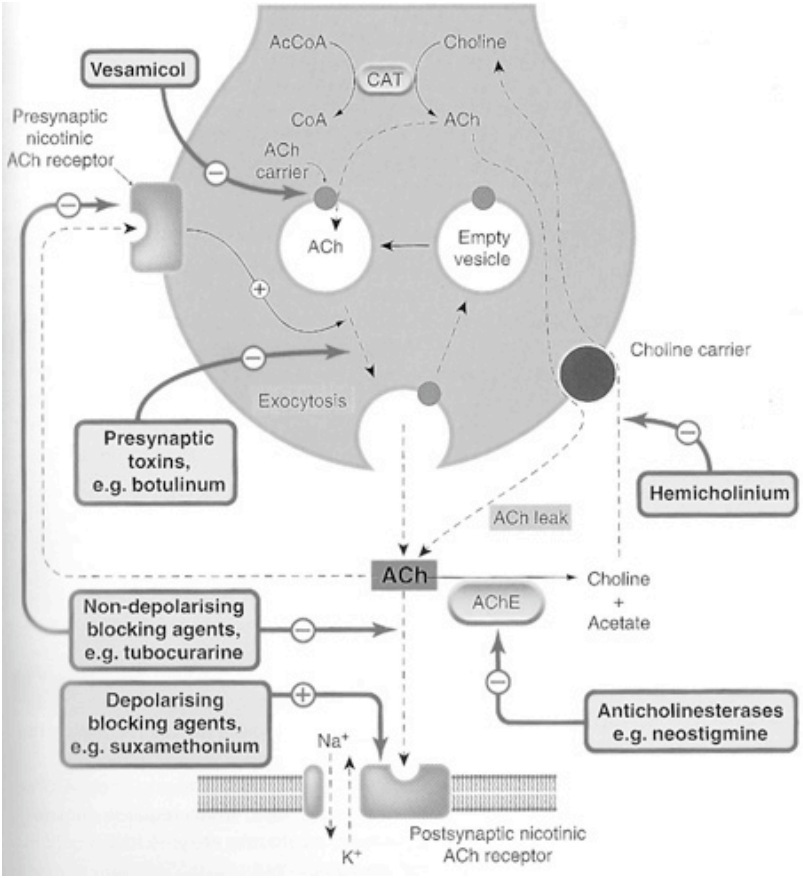


Fig. 10.2 Events and sites of drug action at a nicotinic cholinergic synapse. Acetycholine (ACh) is shown acting postsynaptically on a nicotinic receptor controlling a cation channel (e.g. at the neuromuscular or ganglionic synapse), and also on a presynaptic nicotine receptor, which acts to facilitate ACh release during sustained synaptic activity. The nerve terminal also contains acetylcholinesterase (not shown); when this is inhibited, the amount of free ACh, and the rate of leakage of ACh via the choline carrier, are increased. Under normal conditions, this leakage of ACh is insignificant. At muscarinic cholinergic junctions (e.g. heart, smooth muscle, exocrine glands), both postsynaptic and presynaptic (inhibitory) receptors are of the muscarinic type. (AcCoA, acetyl coenzyme A; CoA, coenzyme A; CAT, choline acetyltransferase; AChE, acetylcholinesterase.)

End Plate potential

- av human end plate contains 15-40million Ach receptors
- each nerve impulse causes emptying of ~60 Ach vesicles
- each vesicle contains ~10,000 ACh molecules

↳ ∴ each Ap enough to produce full end plate potential with x10 redundancy

- minature end plate potential
  - = at rest see small packets of Ach released
  - cause 0.5mV depolarising spike
  - size of packets of Ach released varies depending on Ca/Mg:
    - ↑Ca ⟹ ↑Ach packet release
    - ↓Mg ⟹ ↑Ach packet release

Other Ach Receptors

- postjunctional - as above
- prejunctional:
  - nicotinic Ach receptors
  - control an ion channel specific for Na
  - respond to released Ach
  - function to mobilise more Ach storage vesciles to active zone of junction ready for release
  - ∴ function ad part of +ve feedback loop
  - most likely involved in fade phenomenon of NDNMBlockade
- extrajunctional:
  - normally only present in small numbers
  - can proliferate in:
    - denervation

        - burns
        - some muscle diseases
    - contain a γ (gamma) subunit instead of ε (epsilon)
        - ↳ as seen in fetal receptors
    - minature end plate potentials maintain normal concentrations of Ach receptors on postsynaptic membrane

↳ with denervation this basal Ach release is abolished ⟹ proliferation of extrajunctional receptors

Monitoring Neuromuscular Junction

- different ways of assessing NMJ:
    - clinical:
        - suggestion of ~50% occupied:
            - sustained head lift ~5sec
            - -ve insp effort of > -40cmH20
        - should only be used as an adjunct to PNS due to variability of drug responses
    - experimental:
        - patch clamping with glass micropipette:
            - tip placed into lipid of membrane
            - electronic apparatus arranged so that current flows through channel of receptor
    - peripheral nerve stimulation:
        - standard of care
        - ANZCA: PNS must be available for every pt who receves a NMB
        - especially useful in:
            - long surg where intermittent bolus NMB given
            - elderly
            - pt with altered PK's
            - concurrent drugs given which interact with NMBs
            - patient factors ie ↑ed sensitivity to NMBs

Peripheral Nerve Stimulator

- neuromuscular function assessed by evaluating response of muscle to supramaximal elec stimulation of an accessible periphera motor nerve
- response of whole muscle dependa on number of muscle fibres activated/blocked
- supramax stimulus (SMS) needed cos:
    - eliminates variation in muscle response caused by partial depolarisation of nerve
    - ∴ see simulatenous depolarisation of all nerve fibres
    - need current 20-60mA
- can calculate SMS required:
    - determine initial threshold for stimulation = ITS
    - ITS x 2.5 = SMS
- can ↓ current needed by placing +ve (red) electrode proximal; black distal (or over nerve)
- are targeting nerves not mm directly
- sites for electrode placement:
    - ulnar nerve:
        - Ax thumb adduction
        - more sensitive than diaphragm + vocal cords to NMBs
    - facial nerve – tend to underestimate blockade
        ↳direct muscle stim & facial mm's relatively insensitive to NMBs
    - tibial nerve –
        - place behind medial malleolus
        - Ax plantarflexion of big toe
    - common peroneal n:

        - lat to neck of fibula
        - Ax foot dorsiflexion
- desirable features of a PNS:
    - produce unipolar square waveform 0.2 – 0.3 msec duration
    - constant current output – despite changes in skin resistance
    - linear adjustment current output from 0.1-10mA
    - easily read current display
    - clearly marked polarity
    - small, portable, robust, battery operated
    - diff patterns of stimulation

Patterns of Stimulation

- single pulses = 1-2Hz
- tetanic =
    - 50-100Hz for 3-5secs
    - tetany occurs when frequency >30Hz ⇒ contractions fused into 1
    - can repeat >5-10mins
    - use single pulses post tetanic stimulation
- train of four:
    - used to assess **recovery** from blockade
    - = x4 0.1msec pulses at 2Hz
    - TOF count = number of palpable twitches
    - TOF ratio = force of 4th twitch/force of 1st twitch (T_4/T_1)
    - may repeat Ax every 10-15secs
- double burst stimulation (DBS):
    - used to assess **recovery** from blockade **manually**
    - 2 short tetanic stimulations eg 50Hz (= x3 0.2ms stimuli burst 0.75sec apart)
    - more sensitive for detection of fade than TOF
- post tetanic count (PTC):
    - used to assess **intensity** of blockade
    - best used when degree of receptor bock >95% ie TOF = no twitches
    - relies on mechanism of post tetanic potentiation (see below)
    - procedure:
        - 5 sec of tetany at 50Hz; wait 3 secs ⇒ then 10 equal supramax stimuli are delivered at 1Hz
        - count number of twitches
    - must wait >5-10mins for **any** further PNS testing – if repeated sooner can antagonise NDNMB
    - PTC:
        - number of twitches indicates length of time to recovery of TOFC=1 depending on NDNMB ie PTC =4:
            - atracurium = 8mins
            - pancuronium = 16mins
        - PTC 8-9 usually = 1st twitch of TOF returning

Assessment of Muscle Response to Stimulation

- visual
- manual/tactile
- mechanical:
    - reflects
        - NM transmission &
        - muscle contractility
    - uses pressure transducer or accelerometry (piezo-electric ceramic wafer)
- electrical:
    - only NM transmission Ax'ed via EMG response with 2 surface/needle electrodes
    - ∴ more specific than mechanical assessment

Observed Responses

- normal NMJ function:
  - TOF/single pulses = equal twitches
  - tetanic =
    - sustained tetanic contraction
    - post tetanic potentiation –
      - = subsequent twitches post tetany are larger
- depolarising NMB:
  - TOF/single pulses/tetany:
    - TOFR = 1
    - decreased amplitude of response to all stimuli – TOF & tetany
    - no fade seen
    - no post tetanic potentiation
  - can see phase 2 block:
    - with repeated or high doses of sux
    - shows characteristics of NDNMB ie fade
- NDNMB:
  - single pulses = progressive ↓ing amplitude of twitches with eventual disappearance
  - TOF =
    - progressive ↓in TOF responses with eventual disappearance
    - 0 twitches = 90-100% block
    - 1 twitch = 80-90% block
    - 2 twitch = 75-80% block
    - 3 twitch = 70-75% block
    - 4 twitch = <70% block

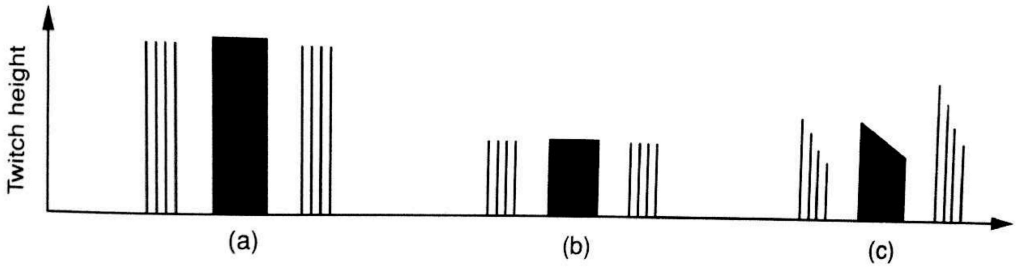


Figure 11.3. Types of neuromuscular block in response to a train-of-four, tetanic stimulus, repeat train-of-four. (a) Control, no muscle relaxant present; (b) partial depolarizing block, reduced but equal twitch height, no post-tetanic facilitation; (c) partial non-depolarizing block, reducing twitch height, fade on tetanic stimulation, post-tetanic facilitation.

- recommend:
  - TOFC 1 or less for intubation
  - TOFC 1-2 for maintenance
  - TOFC 2 or above needed for reversal
  - TOFR 0.7-0.8 needed for adequate maintenance of spontaneous ventilation
- fade:
  - seen with:
    - NDNMB
    - sux phase 2 block during TOF
    - tetany
  - mechanism behind =
    - prejunctional n-Ach receptor blockade causes ↓Ach release with repetitive stimulation
    - with blockade present need more Ach to achieve muscle MEP threshold potential
    - repeated stimulation unmasks this decline in Ach release
- post tetanic potentiation:

  - = ↑ed amplitutde of twitch post period of tetany
  - to demonstrate:
    - tetany > ~ 3 sec delay > subsequent supramax stimulus > twitch amplitude potentiation (↑ed amplitude)
  - mechanism thought:
    - ↑synthesis & release of Ach from terminal bouton OR
      ↳possible due to pre-synaptic Ach receptor stimulation
    - ↑ed Ca in synaptic terminal
  - large amounts of Ach can of course overcome NDNMB due to competitive nature
- ways of determining residual blockade (list most sensitive ⇒ least sensitive):
  - No fade in PTC of 20 (= *most sensitive*) ⇒ 50% of receptors blocked
  - Head lift for 5 sec (*most useful clinically*) ⇒ ~ 50% blockade
  - Insp force > - 40 cm H2O ⇒ ~ 50%
  - No fade with DBS ⇒ 60 – 70% blocked
  - No fade with TOF ⇒ 50 - 60 % blocked

Neuromuscular Blocking Drugs

- 2 types:
  - non depolarising (aka competitive) drugs:
    - block action of Ach at
      - postsynaptic nicotinic
      - presynaptic nicotinic ⇒ blocks normal feedback loop which ⇒ ↑Ach under conditions of enhanced stimulation
    - action can be reversed by anticholinesterase
    - subclassification:
      - chemical:
        - aminosteroids eg pancuronium, vecuronium, rocuronium
        - benzyl-iso-quinolines eg mivacurium, etc
        - phenolic esters: gallamine
        - toxiferine: alcuronium
      - duration of action:
        - short – mivacurium
        - intermediate – atracurium, roc, vec
        - long - pancuronium
  - depolarising drugs:
    - nicotinic receptor agonists ⇒ maintain depolairsed state of motor end plate ∴ no further APs
    - eg suxamethonium

Ideal NMB:

- pharmaceutical:
  - easy to use – solution vs powder
  - non glass ampoule
  - cheap
  - stablelong shelf life – no refrigigeration needed
  - non irritant
  - compatible with other drugs
  - no preservatives
  - steralisable
- pharmacokinetics:
  - not cross BBB/placenta
  - non saturable, organ-indep elimination

    - no active metabolites
    - no accumulation
- pharmacodynamics:
    - non-depolarising block
    - rapid onset (1 circulation time) + offset
    - reversible
    - action confined to NMJ
    - CVS stable
    - no MH potential
    - no toxicity/wide therapeutic index
    - duration of action suitable for surg needs

Structure-Activity Relationships

- Quaternary N+ ⇒ binds to receptor (α subunit)
- quaternary structures:
    - mono quaternary = dTc, Vec, Roc
    - Bisquaternary = panc, atrac, miv, sux
    - trisquaternary = gallamine
- closest to Ach:
    - = pancuonium ∴ side effects:
        - plasma ChE antagonist
        - M2 blockade
        - ↓MAC
- gallamine = selective M2 blocker
- leptocurare
    - = long thin flexible structure
    - eg six
    - agonist at n-Ach receptors
- pachycurares:
    - = bulky and rigid structure
    - = antagonists at n-Ach
    - eg NDNMBs
- isomers: atracurium, cis-atracurium, mivacurium all ismoers with unique properties
- change in structure:
    - pancuronium without $-CH_3$ = vecuronium
      ↳ means is less like Ach ∴ ↓ed SE's BUT ↑lipophilic ∴ ↑liver metabolism
    - distance between bisquaternary ammoniums is impt:
        - 5-6 C atoms = ganglion blockade eg hexamethonium
        - 10C atoms : NMJ antagonist

Phase 2 vs Phase 1 Block

	Phase 1 block	Phase 2 block (~NDNMB)
Fasciculations	+	-
ChE inhibitors	enhances	antagonizes
NDNMB's	antagonizes/reverse	additive/enhance
TOFR	> 0.7	< 0.7
Fade	no	Y
Tetany	sustained response	diminishing contraction
PT facilitation	no	Y
Quinidine	+	-
Mustard cytotoxics	+	-

Phase 2 Block

- only theories for cause:
  - ↑NaKATPase ⇒ hyperpolarisation of post synaptic membrane
  - ↓synthesis of Ach
  - post synaptic receptor desensitisation

Non Depolarising Blocking Drugs

- 2 mol of Ach required to active post junctional receptor (x1 bind to each α subunit)
- only 1 NDNMB mol combine with n-AcH receptor ⇒ non functional ion channel
  - combines with 1 or both α subunits
  - prevents Ach binding
  - no conformational change in receptor
- at high doses NDNMB may also 'block' channel
- some NDNMB's may show preference for 1 of the α subunits
  ↳may explain synergism with certain combo's of NDNMBs
- antagonism wll (virtually) never by complete & always reversible
- ~80% receptors need blocking to prevent NMJ transmission
  ↳= margin of safety of NMJ transmission
- Unaffected receptors have norm ion fluxes ∴ summation of receptor effects must meet threshold (-50mV) ⇒ AP at MEP
- characteristics of NDNMB's (and phase 2 block of sux):
  - tetanic fae
  - TOFR <0.7)
  - potentiation of other NDNMBs
  - antagonism of depolarising blockers
  - post tetanic facilitation
  - reversibility with anticholinesterases
- order of onset: small muscles (eye, larynx) ⇒ limbs ⇒ trunk ⇒ diaphragm
  ↳recovery is generally opposite order
- rapid blockade with motor weakness ⇒ total flaccid paralysis
- can cause histamine release from mast cells:
  - flushing & rash ⇒ anaphylactic reaction
  - not due to receptor action but acidic nature of drug
  - risk varies inbetween drugs
- classifications:
  - chemical:
    - aminosteroid compounds – vecuronium, rocuronium, pancuronium

        - benzylisoquinolines – atracurium, mivacurium, tubocurarine
    - duration of action:
        - short – mivacurium
        - intermediate – atracurium
        - long – pancuronium
- all NDNMBs = polar ie hydrophilic ⇒ unable to cross lipid membranes easily ⇒ small Vd

Factors Effecting Onset of Action

- patient factors:
    - cardiac output & circulation time – will effect speed of delivery of drug to effect site
        - circulation time infant = 24secs; adolescent = 1min
          ↳∴ speed of onset in infant = 40% of adolescent
    - skeletal mm blood flow - ↑regional flow here ⇒ ↑speed of onset
    - capillary permeability –
        - all NBMs are ionised & confined to ECF
        - access NMJ via fenestrations in capillaries at NMJ
    - muscle sensitivity – diff mms have diff sensitivities due to:
        - diff fibre composition ie fast / slow twitch fibres
        - density of recptors
    - pathological factors:
        - myasthenia pts have ↓ed NMJ receptors ⇒ less to block ⇒ ↑ed rapid onset
        - atypical P-ChE – will metabolise less sux on way to NMJ ⇒ ↑ed relative dose delivered with quicker onset
- drug factors:
    - route of admin – IV vs IM
    - MOA – NDNMBs slower onset vs sux as antagonists
    - potency – NDNMBs:
        - potency of agent is inv. proportional to speed of onset
        - roc = least potent ∴ quickest onset
        - explained: large no of molecules need to be administered ⇒ ↑ed diffusion gradient for entry into NMJ
    - priming:
        - = ¼ intubating dose ⇒ subclinical blockade of NMJ ⇒ fewer to be blocked before clinical paralysis
        - ∴ obviously ↑speed of onset but dangerous
    - other drugs:
        - volatiles –↑speed of onset by 25% compared to using TIVA
          ↳also enhance amplitude of relaxants effect

Factors Effecting Duration of Action

Drug interactions

- Abx:
    - MOA:
        - ↓pre junctional release of Ach - ?via competition with Ca influx
        - post junctional stabilisation of membrane
    - eg aminoglycosides, tetracycline, metronidazole
      ↳can reverse gent effect with neostigmine & Ca
- CCB's ⇒ ↑duration of action - ?prevent entry of Ca into presynaptic membrane ⇒ ↓release of Ach
- antiarrhythmics:
    - eg quinidine & lignocaine
    - prolongs all muscle relaxants
    - ↓prejunctional release of Ach
- diuretics (frusemide):

  - dual effect:
    - low dose (1mg/kg) - ↑duration : ↓prejunctional release
    - high dose: ↓duration: ↑c-AMP ⇒ ↑Ach release
- LA's: prolong duration:
  - ↓nerve AP
  - stabilises post junctional membrane
  - directly depresses muscle fibres

  ↳via Na channel effects
- Anti-epileptic Rx / antipsychotics:
  - lithium ⇒ potentiates NDNMBs (Na channel effect)
  - chronic phenytoin & carbamazepime ⇒ ↓duration via ↑ed metab
- Ganglion blockers eg gallamine:
  - ↑block by ↓mm block flow
- Volatiles & IV induction agents:
  - ↑duration in dose dependant fashion

    ↳iso>des>sev>enfl>hal>N2O
  - depression of somatic reflexes in CNS ⇒ ↓ Ach release at NMJ
- dantrolene: ↑duration
- combo of diff NDNMBs : ↑ed duration of action reflects diff principle sites of action ie diff α subunit pref
- Mg sulphate (or hypermagnaseamia) ⇒ ↑duration of block:
  - ↓ed Ach release by
    - competition with Ca
    - stabilisation of post junctional membrane

    ↳ Mg at supranormal levels eg pre-eclampsia can cause apnoea by similar mechanisms

Non Drug/Physiological Factors

- temp – hypothermia:
  - ↓metab & ↓clearance ⇒ ↑duration of action of panc & vec
  - ↓Hoffman elimination ⇒ ↑duration of atrac
- electrolytes:
  - acute ↓K ⇒ resting membrane potential more –ve (ie further to reach threshold) ∴ ↑ed block

    ↳note depolarising relaxants are antagonised
  - acute ↑K ⇒↓ed block ie opposites
- acid base:
  - resp acidosis ⇒ ↑block
  - all other changes show unpredictable responses
- thermal/burn injury: resistance to NDNBs

The Aminosteroid NDNMBs

- the '–oniums'
- 1st was pancuronium (1960s)
- now vecuronium, rocuronium et al

Pancuronium

Chemical

- bisquaternary aminosteroid
- no hormonal activity

Presentation

- clear colourless solution
- 4mg in 2ml usually plastic amps

MOA

- non depolarising competitive blockade of nicitonic receptors at motor end plate

- interruption requires >70% of N receptors; blockade >95%

Pharmacokinetics

D

- into ECF
- low Vd = 0.25L/kg
- PPB 10-40%

M

- liver metabolism = variable 10-40%
- de-acetylation to diff versions of dihydroxy-pancuronium:
    - 3 = 50% of activity of panc
    - 17
    - 3,17

E

- highly water soluble ∴ urinary excretion begins immed
- clearances:
    - **80% renal unchanged**
    - rest hepatic metab ⇒ bilary excretion (5-10%)

∴ ↑↑↑duration in renal failure

- t1/2 distribution = 10mins
- t1/2 elim = 130mins

Adverse Reactions

- autonomic effects:
    - sympathomimetic – via prevents NA reuptake at post-ganglionic nerve endings
    - vagolytic (M2 block)

    ↳mean slight ↑HR, ↑CO, ↑bp

    ↳handy in cardiac anaesthesia where can offset opioid bradycardia problems
- ↑intragastric pressure ⇒ risk of vomiting
- anaphylactoid reaction small risk (1 in 10,000)

    ↳histamine release
- P-ChE inhibition – has closet structure to Ach of all muscle relxants

Cautions/Contraindications

- care in:
    - HTN
    - liver/kidney failure

Interactions

- additive effect with:
    - inhalational anaesthetics
    - sux
    - aminoglycosides (also cause blockade themselves)
    - benzo's
    - Ca channel blockers
    - lithium
    - propanaolol
- ↓effect with:
    - adrenaline
    - carbamazepine
    - anticholinesterase agents eg neostigmine
    - high dose steroids
    - Ca, Na, K salts

Dose

- ED95 = 0.07mg/kg
- intubating dose = 0.1mg/kg

- onset 3-5mins
- duration 40-60mins
- recovery index 15-22mins

Vecuronium Bromide

Chemical

- synthesised in 1970's
- = monoquaternary aminosteroid (⇒ becomes bisquaternary at pH 7.4)
- no hormonal activity
- compared to panc:
    - **lacks** a methyl gp on N-atom of A-ring
    - contains a tertiary amine (like d-Tc)
    - result is:
        - unstable in solution – comes as a powder
        - more lipophilic ⇒ shorter duration of action due to more efficient metab & clearance

Presentation

- white powder (acetate gps at pos 3 + 17 undergo hydrolysis in solution)
- 4mg/amp as well as:
    - 8.3mg citric acid
    - 6.5mg disodium phosphate
    - 24mg mannitol

    ↳should dissolve it in water for administration
- decomposes 1-2% at 24deg C when reconstituted & stored in light

Pharmacokinetics

D

- mainly distributes to ECF
- fits 2 compartment model
- Vd = 0.28l/kg
- PPB <20%

M

- hepatic metab 20-30%:
    - similar metab to panc
    - de-acetylation to dihydroxy-vecuronium: 3 + 17 +3,17
        - 3-hydroxy :
            - like panc version has sig muscle relaxant properties
            - but unlike panc version
                - has v short half life:
                    - little significance if norm renal function
                - more lipid soluble ⇒ ↑proportion excreted in bile
- 50% of initial dose sequestered within liver in 30mins

E

- renal excretion 15-25%
- bilary excretion 40-75%

    ↳cirrhosis ⇒ ↓cl & ↑t1/2 but accumulation unlikely
- t1/2 distr = 7.5mins
- t1/2 elim = 71mins
- cl = 4ml/kg/min

Adverse Reactions

- much more cardiovascularly stable
- less likely allergic responses – due to monoquaternary structure
- critical illness myopathy – if used for prolonged duration

Dose
- ED95 = 0.05mg/kg
- intub dose 0.1mg/kg
- onset 3-5mins
- duration 20-35mins after bolus; 25% top ups = 10-20mins
- continuous infusion 1-2ug/kg/min

Pipecuronium
- = long acting blocker developed to have duration of panc but less CVS side effects
- bisquaternary structure
- intbubation dose 0.14mg/kg
- similar pharmacokinetics to panc

Rocuronium Bromide
Chemical
- monoquaternary aminosteroid related to vecuronium (structurally diff at only 4 positions)
- advantage is rapid onset ∴ ↓ed potency
  ↳low potency means must give higher dose ∴ ↑ed conc gradient plasma:NMJ ⇒ faster onset
- no hormonal activity
- resembles vec – but hydroxyl gp instead of acetyl gp in A ring of steroid nucleus

Presentation
- in glass amps 50mg/5mls
- very slow degredation at room temp

Pharmacokinetics
D
- ECF distribution mainly
- Vd = 0.16 l/kg
- PPB <20%

M
- hepatic metab 10-20%
- renal excretion 10-25%
  ↳∴ mostly excreted unchanged in bile>urine

E
- bilary excretion 50-70% ⇒ ↑duration in hepato-bilary disease
- T12 dist = 1.6mins
- t1/2 elim = 100mins
- Cl 4ml/kg/min

Adverse Reactions
- vagal blockade ⇒ slight ↑HR & ↑bp
  ↳ but minimal clinical effects
- pain on injection

Dose
- ED95 = 0.3mg/kg
- intubation = 0.6 -1.2mg/kg
- infusion 0.3-0.6mg/kg/hr
- onset: 0.45mg/kg = 90secs, 1.2mg/kg = 55secs
- duration = same as vec

The Benzyl-iso-Quinolines NDNMBs

- the '-uriums'
- histamine releasing potential:
  - dTc>atracurium>mivacurium>cisatracurium

Atracurium Besylate

- intermediate acting NDNMB
- 1st used 1980's

Chemical

- bisquaternary nitrogenous plant derivative with 10 geometric isomers (4 chiral centres)
  (↳1 of these = cis-atracurium)

Presentation

- commercial prep adjusted with ben-zene-sulfonic acid
  ↳ ↓s pH to 3.25 to prevent invitro degredation
  ↳∴ should not mix with alkaline Rx
- stored at 2-8 degrees
- at room temp ↓activity ~5%/month
- amps 25mg/2.5 or 50mg/5mls

Pharmacokinetics

D

- ECF main distribution
- Vd = 0.01 L/kg
- PPB <20%

M

- unique metabolism 2 major forms:
  - 50 % Hoffman elimination:
    - at body temp & pH = spontaneous breakdown to
      - laudanosine (inactive metabolite at NMJ – see below)
      - quaternary monoacrylate
    - acidosis & ↓temp slow process
  - 50% direct ester hydrolysis by non specific plasma esterases to:
      - quaternary alcohol
      - quaternary acid
      - laudanosine
    - acidic conditions ⇒ ↑speed of this pathway (opposite to Hoffman)
      ↳but not seen at human clinical conditions
- atracurium = organ independent elimination
- laudanosine =
  - tertiary amine – similar to atropine ∴ does cross bbb
  - major metabolite of both metabolic pathways of atracurium:
    - Hoffman ⇒ 2 mols of laudanosine / molecule of atrac
    - ester hydrolysis ⇒ 1 mol laudanosine / molecule of atrac
  - T1/2 ~2hrs – double in ARF
  - is **not** active at NMJ but is active elsewhere:
    - CNS stimulation –
      - epileptiform changes in dogs but unlikely sig in humans at clinical doses
      - may ↑MAC required
    - vasodilation

E

- ideal for renal/hepatobilary impairement

- t1/2 elim = 20min

Adverse Reactions

- histamine release - localised or generalised (bronchospasms, ↓bp)
- minmum CVS side effects
- critical illness myopathy – similar to vec

Dose

- ED95 0.2mg/kg
- intubate dose 0.5mg
- onset 1.5-3mins
- duration 20-30mins
- cont infusion 0.3-0.6mg/kg/hr

Cisatracurium

- one of the 10 stereo-isomers of atracurium (15% of total)

Chemical

- bisquaternary compound
- pale yellow-greenish acidic solution
- 2mg/ml or 5mg/ml vials stored at 4deg in fridge
- no preservative

Pharmacokinetics

D

- Vd 0.15 L/Kg

M

- Different to atracurium:
    - only see Hoffman elimination ie tiny/no direct ester hydrolysis
        ↳ as atracurium: metabolites are inactive at NMJ

E

- renal – 16% excreted unchanged
- t1/2 elim = 40mins

Dose

- x3-5 more potent than atracurium ⇒ ∴ slower onset but can ↑dose as ↓ed histamine release
- ED95 0.05mg/kg
- intubate dose 0.15mg/kg
- onset 3-5mins
- only real benefit > atracurium is ↓ed histamine release

Mivacurium

- short acting NDNMB eveloped in 80-90s
- main advantage is short duration of action

Chemical

- benzyl-iso-quinoline derivative
- bisquaternary ammonium related to atracurium
- a geometric isomer – prepared as 3 isomers:
    - cis-trans 36%
    - trans-trans 58%
    - cis-cis 6% -
        - has 10% of potency of other 2 isomers
        - is **not** metabolised
        - **half life is x10** other 2 isomers

Presentation
- glass ampoules 10mg/5mls
- shelf life 18months when stored <25deg

Pharmacokinetics
M
- hydrolysed by P-ChE – 88% the rate of sux
  ↳∴abnormal response if abnormal P-ChE
- some liver microsomal enzyme hydrolysis as well

E
- efficient clearance means well suited for day surg/short procedures
- if end stage liver disease may see ↑↑duration of action
  ↳due to ↓P-ChE
- neostigmine ⇒ prolonged blockade
  ↳ if want to reverse need t use FFP

Adverse Reactions
- histamine release – less than atracurium
- minimal CVS SEs

Dose
- ED95 0.08mg/kg
- intubation dose 0.1-0.2mg/kg
- onset 2-3mins
- duration 12-20mins
- continuous infusion ~8ug/kg/min

Older/Other NDNMBs
Tubocurarine (dTc)
- historical drug
- curare = generic term for various alkaloids from plant species Chondrodendron
  ↳used on poisoned arrows of South American Indians
- dTc 1st used in 1940s
- = monoquaternay, benzylisoquinoline
- adverse reactions:
  - cardiovascular:
    - causes greatest degree of
      - autonomic ganglion blockade
      - histamine release

      ↳∴ ↓bp, unlikely to cause tachycardia, protects against arrhythmias
  - gut - ↑ed salivation
  - anaphylaxis

Doxacurium
- introduced in 90's in USA
- = most potent MR available
- bisquaternary benzylisoquinoline
- no clear advantage over newer drugs
- very variable onset & duration
- ED95 = 0.03mg/kg
- may take up to 10mins for max effect
- duration 30-90 mins
- minimal histamine release

Gallamine

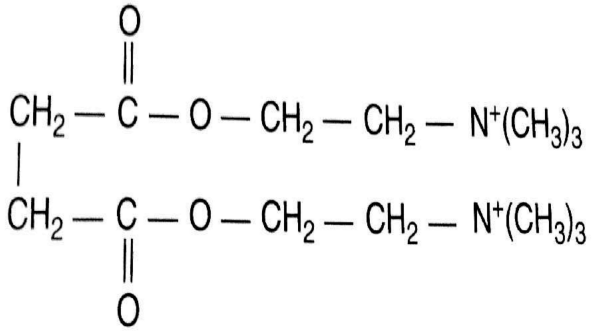
- introduced in 1947 as 1st synthetic muscle relaxant
- only current role is to limit sux fasciculations
- selectively blocks cardiac muscarininc receptors & activate SNS ⇒ tachycardia
- excreted unchanged by kidneys ∴ renal failure ⇒ ↑duration of action
- opposite to other NDNMBs: alkalosis ⇒ ↑ed duration of action and vice versa

Drug	Onset time (min)	Half-life (min)	Vol. of distribution (l/kg)	Clearance (ml/kg/min)	Clinical duration of action (min)	Route of elimination	Histamine release	Autonomic effects
Alcuronium	3–5	180–200	0.1–0.3	1.5	20–40	Renal	±	–
Atracurium	1.5–2	20	0.16–0.18	5.5–6.0	20–30	Hofmann degradation + plasma hydrolysis	+	–
Cisatracurium	1–1.5	100	0.23	3.9	30–40	Renal + hepatic	–	–
Dimethyl tubocurarine (metocurine)	3–5	345	0.5	1.0	90–120	Renal	+	Weak ganglion blockade
Doxacurium	4–5	85–100	0.2	2.2–2.6	100–200	Renal + hepatic	–	–
Fazadinium	0.5–1.5	40–80	0.2	4.0	40–60	Renal	–	Muscarinic + ganglion blockade
Gallamine	1–2	160	0.25	1.2	20–30	Renal	–	Muscarinic blockade
Mivacurium	1.5–2	2–5	—	—	10–15	Plasma cholinesterase + hepatic	±	–
Pancuronium	2–3	120–140	0.25–0.3	1.8	40–60	Renal + hepatic	–	Weak muscarinic blockade + sympathomimetic action
Pipecuronium	2.5–3	140	0.3	2.5	90–120	Renal + hepatic	–	–
Rapacuronium	0.5–3.5	28	0.29	6–11	6–30	Renal + hepatic	++	–
Rocuronium	2	22–29	0.12–0.16	4.7–5.7	30	As for atracurium	–	±
Tubocurarine	3–5	150–190	0.5–0.6	2–3	30–50	Renal + hepatic	++	Ganglion blockade
Vecuronium	1.5–2	55–70	0.27	5.2	20–30	Renal + hepatic	–	–
Suxamethonium	0.5–1.5	2.5	—	—	2–5	Plasma cholinesterase	+	Muscarinic + ganglionic stimulation

Depolarising Blocking Drugs

Suxamethonium

Chemical



= 2 molecules of Ach
= a leptocurare (long flexable molecule)

Presentation

- clear fluid 50mg/ml suxamethonium chloride
- stored at 4 deg C (shelf life 15/12)
- at room temp stable for 2 weeks ⇒ spontaneous hydrolysis

MOA

- agonist of N receptors on motor end plate
- binds to α subints x2
- ⇒ persistent stim & maintenance of depolarisation of MEP
- Na channels remain inactivated but open ∴ no further response to elec stimulus
- during onset of action see mm fasiculations:
  - as each MEP is depolarised ⇒ local AP to motor units without total mm contraction
  - partly mediated by presynaptic effects of ↑ed Ach
  - x1 fasciculation/Motor unit then blockade
- depolarisation is prolonged compared to Ach as is hydrolysed slower:
  - AchE in cleft on Ach = milli seconds
  - plasma ChE – very little present in cleft. Sux must diffuse away from cleft into ECF for P-ChE to occur ∴ takes longer
- short acting mm relaxant
- reversal by anticholinesterase not possible:
  - will prolong depolarisation
- phase 2 block:
  - repeated, high or continuous dosing
  - ?due to receptor desensitisation or Na channel block
  - clinically = same as NDNMB's

Pharmacokinetics

A

- IV or IM/sl in emergency when IV access not possible

D:

- into ECF
- initial rapid distribution ⇒ short onset & duration:
  - onset 30-60secs
  - duration 3-5mins
- ?extent of PPB
- pKa 13
- MW 400 Da ∴ v small molecule ∴ able to move quickly to effect site

M:

- 80% hydrolysed by butyrylcholinesterase (aka plasma-cholinesterase) before reaching NMJ to
  - choline
  - succinyl monocholine
    - has 1/20 – 1/50th activity of sux
    - unknown SE's
    - this active metabolite further hydrolysed to inactive ⇒ choline & succinic acid

  ↳if atypical pseudo-cholinesterase see extended blockade
- T1/2 elim ~ 0.5 – 1min

E

- 2-10% unchanged in urine

Uses

- brief mm relaxation eg
  - ECT
  - tracheal intubation
  - surg procedures

Adverse Reactions

- immediately life threatening:
  - MH
  - anaphylaxis
- serious/potentially life threatening:
  - ↑serum K:
    - release of K from MEP
    - expect ↑K ~0.5mmol/l but can be up to 4-5mmol/l:
      - caution in
        - burns esp 3rd degree – effect lasts 24hrs – 6months
        - muscle trauma
        - UMN lesion
        - denervation eg recent paraplegia – from 96hrs to 6 months
  - muscarinic side effects:
    - brady-arrhythmias:
      - watch with digoxin & BB's
      - esp seen with a second dose within 5mins
      - use repetitive doses in kids with caution
    - ↑bronchial secretions (incl hypersalivation) & ↑bronchial tone
    - GIT:
      - ↑gastric secretions
      - ↑intragastric pressure 10cmH20 but also see ↑LES pressure ∴ no change in reflux risk if patent LES
    - ↑uterine tone

    ↳could pre-treat with atropine
  - ↑ICP – from fasciculations, transient and not that impt
  - ↑Intra-occular pressure
    - transient 5-10mins of 10mmHg
    - if concurrent use thiopentone then no change in IOP
    - unknown mechanism of sux ↑IOP
    - avoid in
      - penetrating eye injury
      - eye surg if anterior chamber needs to be opened
    - BUT coughing on intubation ↑IOP x4 ∴ use sux of roc
  - myoglobinuria – esp in paeds from fasciculations
  - prolonged contraction:
    - myotonia dystonica + congenital

        - masseter spasm – warming sign of MH
- bothersome:
    - tachyphylaxis/phase 2 block
    - prolonged relaxation aka sux apnoea:
        - low pseudo-cholinesterase levels eg liver disease or congenitally low levels:
        - abnormal pseudo-cholinesterase – congen
    - myalgias –
        - from fasciculations
        - more in women/young who mobilise rapidly post op

Cautions/Contraindications

- care if:
    - electrolyte disturbance
    - low pseudo-C levels
    - renal disease
    - digoxin
- contraindicated:
    - malignant hyperthermia or FH
    - extensive burns or multiple trauma
    - Muscular dystrophy – MH like response

Interactions

- antagonism/↓duration of action:
    - NDNMBs
    - abnormal receptors eg myasthenia
- additive effect ie prolonged duration or ↑effect
    - ↓quantity of P-ChE – need level <75% ⇒ prolonged sux action
        - anticholinesterases ie neostigmine, insectisides
        - severe liver disease
        - drugs – metoclopramide, ester LA's, cyclophosphamide
        - oestrogen ie pregnancy:
            - ↓P-AchE 25% (can ↓by 35% in 1st week post partum)
              ↳but offset by ↑Vd of sux so intubating dose = same
    - ↓quality of P-ChE:
        - genetic causes – see sux apnoea
        - pregnancy ↓activity by 25%
        - plasmapheresis/bypass

      ↳other drugs also effected by abnormal P-ChE = mivacurium, ester LA's
      ↳ not effected =
      remi – metab by non-specific tissue
      esmolol metab by rbc ChE's
    - other drugs: act on P-ChE either directly, substrate or inhibitor:
        - lignocaine
        - non penicillin Abx
        - βblockers
        - lithium
        - metoclopramide, ketamine
        - OCP
        - neostigmine
- metoclopramide - ↓s inactivation of sux ⇒ prolonged NMJ blockade

Dose

- 1.5 – 2 mg/kg IV (5-10mg/kg IM)
- ED90 = 0.27mg/kg
- not to conscious person

Plasma cholinesterase Deficiency aka Sux Apnoea

- Aka pseudo-cholineterase deficiency
- Capable of hydrolysing variety of esters
- No physiological function found for enzyme yet
- Synthesized in liver, half life 5-12d
- Can metabolise 70% of 100mg sux <1min
- Synthesis controlled by pair of autosomal recessive genes:
    - normal = Eu
    - abnormal genes = Ea, Ef, Es
        ↳ single amino acid substitutions
- 4 alleles identified at single locus on chromosome 3:
    - normal – 96% of population
    - atypical (dibucaine resistant):
        - heterozygotes no issue unless concurrent illness
        - Homozygous - 1:3000 - paralyse for 2-3hrs
    - silent (absent)
        - Heterozygote - mild prolongation sux
        - Homozygote - prolonged apnoea - 3-4 hrs but upto 24hr
    - fluoride resistant
        - Homozygote very rare - 1:150000, moderatly sensitive to sux
    - others also seen with varying effects
- Quality of P-ChE measured by
    - adding plasma to choline substrate
    - then add dibucaine as well
    - observe using spectrophotometry how well dibucaine inhibits P-ChE
        - Dibucaine =
            - amide LA which inhibits normal P-ChE
            - inhibits abnormal P-ChE less well
    - normal inhibition = 80%
    - homozygous abnormal EaEa inhibition = 20%
      ↳diff variations of genes give diff inhibitions which = dibucaine number
    - dibucaine no ∴ gives measure of quality of P-ChE but not quantity
- Rx is:
    - sedation, ventilation & wait
    - FFP – contains P-ChE

Anticholinesterase Agents

- Ach in synaptic cleft compete with NDNMBs for post-synaptic nictonic receptor:
  - NDNMBs take <1ms to dissociate from receptor
  - Ach is hydrolysed prior to this
    ↳ ∴ ↑time of Ach in cleft impt
- reversal of NDNMBs can be achieved by 3 mechanisms:
  - K blocking drugs:
    - works presynaptically ⇒ prolonged AP ⇒ ↑Ca entering presymaptic membrane ⇒ ↑Ach release
    - very non specific & ∴ not widely used
  - anticholinesterase drugs
  - chelating agents - sugamadex

Cholinesterases

'True' AChE (acetylcholinesterase)

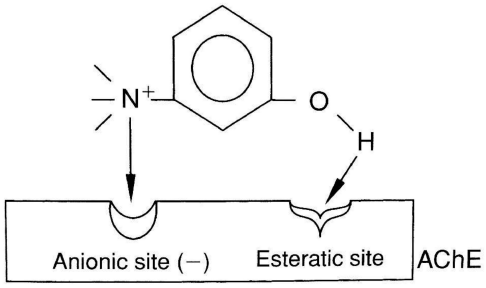
- hydrolses Ach ⇒ choline & acetate
- enzyme bound to postsynaptic membrane
- present in all cholinergic synapses
- also 2 other forms of AchE:
  - brain
  - rbc's – metabolises
    - esmolol
    - remifentanyl – also by non specific tissue esterases
    - 6-mono-acetyl-morphine (MAM) (1st breakdown product of heroin) ⇒ morphine
- active site of enzyme contains 3 amino acids:
  - serine
  - histidine
  } = esteratic site
  - glutamate = anionic site
- Ach bind to AchE:
  - quaternary nitrogen of Ach binds ionically to anionic site
    ↳orientates Ach ⇒ ester linkage to esteratic site

Plasma Cholinesterase

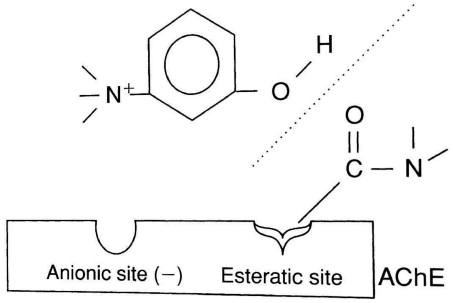
- aka pseudocholinesterase, nonspecific cholinesterase, butyrylcholinesterase or BchE
- physiological role unknown
- subtrates:
  - sux
  - mivacurium
  - ester LA's
- Mild-mod ↓ in activity:
  - pregnancy
  - liver disease
  - renal failure
  - CPB
- markedly inhibited by:
  - organophosphates
  - reversible inhbibitors of Ach ie neostigmine, phyostigmine, edrophonium
- displays pharmacogenitc variation – see sux

Anticholinesterases

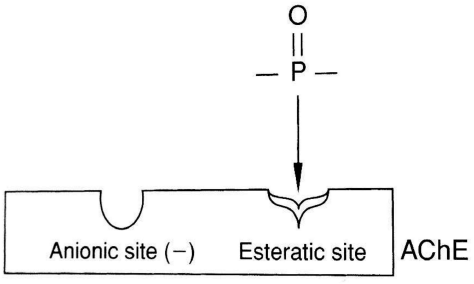
- most clinically important drugs inhibit AchE & P-chE **equally**
- 3 broad categories of drugs:
  - **short acting** - reversible:
    - eg edrophonium



  - **medium acting** - formation of carbamylated enzyme complex
    - (strictly not reversible as gets hydrolysed)
    - mechanism:
      - forms ionic bond at anionic site to align molecule
      - carbamyl then transferred to esteratic site ⇒ forms covalent bond
      - covalent bond is hydrolysed slowly over minutes
        ↳normally: Ach acetylates AchE which can be hydrolysed in milliseconds
    - eg
      - neostigmine, pyridostigmine = quaternary ammonium compounds eg reverse NDNMBs
      - physostigmine = naturally occurring tertiary amine eg atropine poisoning, glaucoma
      - tacrine = tertiary amine eg used in Alzheimers



  - **long acting -** irreversible inactivation
    - covalently binds to esteratic site
    - non-polar ∴ ↑lipid solubility ⇒ ↑ed central effects
    - eg organophosphorous compounds – used in chem. warfare



Edrophonium

Chemical

- only drug in easily reversible group
- phenolic quaternary amine

MOA

- bonds to **both** site on AchE:

- quaternary amine group ⇒ reversible ionic bond with anionic area of AchE
- hydroxyl group ⇒ Hydrogen bond at esteratic site to stabilise complex

↳Ach now unable to reach active site of AchE

- no covalent bond ∴ Ach competes with edrophonium
- erdrophonium also ⇒ ↑Ach release

Pharmacokinetics

- low lipid solubility:
  - poor oral absorption
  - dose not cross BBB or placenta
- faster onset than neostigmine

M

- 65% excreted in urine unchanged
- 35% metab in liver ⇒ bile excretion

Uses

- used to rapidly distinguish between a
  - myasthenic crisis - muscle power improved
  - cholinergic crisis – clinical picture worsened

Adverse Reactions

- slight muscarinic side effects: bradycardia, salivation

Dose

- 2-10mg IV

Neostigmine

Chemical

- = quaternary ammonium compound
- = derivative of physostigmine but has greater stability & equal or greater potency

↳ = lipid soluble tertiary amine which can cross bbb

↳ pyridostigmine = closely related to neostigmine but x4-5 less potent

MOA

- reversible inhibitor of AChE
- covalently bonds to esteratic site & forms a carbamylated enzyme
- complex slowly hydrolysed by AChE over 3-4hours

Pharmacokinetics

- poorly absorbed from GI tract
- doesn't cross bbb
- plasma half life 0.5-1.5 hours
- excretion:
  - faeces >50%
  - urine 55% excreted unchanged in urine
- metab by plasma cholinesterases

↳∴ liver disease has no effect on drug

Uses

- used for reversal of non depolarising competitive NMJ blockers
- Rx myasthenia gravis

Adverse Reactions

- best seen in overdose situation which ⇒ cholinergic crisis ie ↑↑Ach action at synapses:
  - NMJ –
    - ↑twitch tension – AchE inhibition ⇒ single end plate potential lasts long enough to cause short train of AP's ⇒ mm fibre
    - fasiculations,

        - poisoning doses:
            - so much Ach at pos-synaptic membrane that see prolonged depolarisation of NMJ ⇒ depolarised block (akin to sux) ⇒ weakness, paralysis, depressed vent
    - muscarinic, postganglionic AND nictonic ganglia
        ↳ = cholinergic crisis – use **DUMBELS** mnemonic (see later)
        - salivation, tears,
        - ↑Gi &, ↑bowel acivity
        - bronchonconstriction & bronchial secretions
        - brady & hypotension
        - constricted pupils, ↓IOP
        - D&V & urination

        ↳larger doses:
            - initially ⇒ stim parasymp ganglia;
            - later ⇒block ganglia with complex nicotinic results
    - CNS –
        - does not cross BBB (only tertiary amines & organophosphates)
            ↳see initial excitation ⇒ convulsions ⇒ CNS depression ⇒ LOC & resp failure
            ↳mechanisms muscarininc ∴ antagonised by atropine
    - CVS –
        - reflex ganglionic & postganglionic effects of Ach accumulation
            - initial – excitation
            - later – ganglionic blockade through persistent depolarisation ∴ inhibitory
        - ↑parasymp vagal tone ⇒
            - bradycardia
            - ↑refractory period & conduction time SAN/AVN
- ∴ always given with an anticholinergic eg atropine or glycopyrrloate

Cautions/Contraindications

- care in
    - asthma
    - heart disease
    - ↓bp
    - peptic ulceration

Interactions

- ↓effect:
    - steroids
- any drugs with anticholinergic activity will ↓effect of neostigmine & vice versa

Dose

- reversal of NMJ blockade 50-70mcg/kg to max 5mg over 1min
    ↳give after or with atropine 0.6-1.2mg

Practical Aspects for Reversing NDNMBs

- neo much better matched pharmacokinetically with glycopyrrolate :
    - same onset & offset
    - holds true for renal failure:
        - glycol = quaternary amine ∴ water soluble
        - neo – 55% excreted unchanged by kidneys

        ↳ both prolonged elimination in renal failure
- glycol better choice in:
    - IHD – less tachycardia
    - elderly – dosent cross bbb ∴ no central anticholinergic syndrome
    - renal failure
- atropine:

- much cheaper
- can be used in uncomplicated young patients

Comparison of Pharmacokinetics

- very similar between all drugs if norm renal & hepatic function
- ∴ difference in potency, onset due to pharmacodynamics

D

- lipid solubility:
  - quaternary structures = poor lipid solubility (neo/edro/pirido)
  - tertiary amines (physostigmine) & organophosphates (sarin)= ↑lipid soluble ⇒ ↑CNS effects
- volume of distribution:
  - neo = 0.7L/kg
  - edro & pyrido = 1.1

  ↳this is surprisingly large esp compared to NDNMBs

  ↳is due to tissue binding/storage in kidneys & liver

E

- renal clearance:
  - 50% elim of neo
  - 75% elim of edro & pyrido

    ↳∴ renal failure doubles their half lives
- elim T1/2:
  - edro 110m
  - neo 80min
  - pyrido = 110min

M

- liver metabolism:
  - neo 50%
  - 30% edro
  - 25% pyrido

Onset & duration of Action

- =reflection of pharmacodynamics
- speed of onset:
  - edro =
    - 2mins post injection
    - most rapid onset – due to ↑ed action on ↓pre synaptic Ach release
  - neo & pyrido are more predominantly active post synaptically on AchE
    - neo = 5-7mins post IV
    - pyrido = 8mins
- duration of action:
  - neo (0.043mg/kg) & edro (0.5mg/kg) = 60mins
  - pyrido (0.35mg/kg) = 90mins

Pharmacodynamic Comparisons

- organophosphates: demielinisation of periph nerves ⇒ weakness + ↓sensation
- preference of action:
  - NMJ = neostigmine & pyrido
  - autonomic ns = physostigmine + organophosphates
- potentially fatal side effects of toxicity of anticholinesterases:
  - bradycardia
  - ↓bp
  - bronchoconstriction
  - ⇒ fatal

Table 34.1 Commonly used anticholinesterases. (Adapted from Stoelting RK. Pharmacology in anesthetic practice. Philadelphia: JB Lippincott; 1987.)

Dose (mg/kg)	Elimination half-time (min)		Volume of distribution (L/kg)		Clearance (mL/kg/min)		% of renal contribution to total clearance	Speed of onset	Duration (min)	Recommended dose of atropine* (μg/kg)
	Normal	Anephric	Normal	Anephric	Normal	Anephric				
Edrophonium (0.5 mg/kg)	110	206	1.1	0.7	9.6	2.7	66	rapid	60	7
Neostigmine (0.043 mg/kg)	80	183	0.7	0.8	9.0	3.4	54	intermediate	60	15
Pyridostigmine (0.35 mg/kg)	112	379	1.1	1.0	8.6	2.1	76	slow	90	15

* Dose to be co-administered with anticholinesterase during reversal of neuromuscular blockade. (Adapted from Stoelting RK. Pharmacology in Anesthetic Practice. Philadelphia: Copyright © Lippincott Williams and Wilkins; 1987.)

Organophosphorous Compounds

- = highly toxic & mainly used as
  - insecticides eg TEPP
  - nerve gases eg sarin
- highly lipid soluble ⇒ rapidly absorbed across skin

MOA

- esteratic site of AchE is phosphorylated by organophosphorous compounds ⇒ very stable complex which is resistant to hydrolysis or reactivation
  - ↳∴ virtual inhibition of AchE
  - ↳need resynthesis of AchE
- toxic manifestations:
  - nicotininc
  - muscarinic effects
  - ↳∴ autonomic instability ⇒ central excitation progressing to depression, coma, apnoea

Reversal

- eg pralidoxime = reactivator of phosphorylated AchE by promoting hydrolysis
- may also need atropine, anticonvulsants, ventilation

Sugammadex

- = a chelating agent
- modified cyclodextran ie sugar type drug
- 3D looks like a doughnut with hole in middle which stereo-specific for aminosteroids esp rocuronium
- forms a complex with monoquaternary aminosteroid neuromuscular blockers ⇒ ↓active aminosteroid at NMJ ⇒ binding to nicotinic receptors
- rapid effect within 3 mins (compared to t1/2 elim 80mins of neostigmine (although will see clinical effect of neo 5-20mins depending on dose & NDNMB blockade)
- SEs:
  - taste sensations
  - allergic reactions
    - ↳ BUT no anticholinergic side effects
- interacts with some drugs –
  - fluclox ⇒ can displace NDNMB from sugamadex ⇒ ↑in block again. Should avoid <4hrs post sugamadex

    - progesterones (take extra contraceptive precautions)
- excreted renally unmetabolised

By Adam Hollingworth

Toxicity Of Autonomic Nervous System

Parasympathetic NS

Nicotinic vs Muscarinic Cholinergic Toxicity

- common causes include
  - mushrooms
  - organophosphates
  - overdose acetylcholinesterase inhibitors
- symptoms cholinergic toxicity depend on which receptor stimulated
- muscarinic:
  - D iarrhoea
  - U rination
  - M iosis
  - B ronchorrhoea/bronchoconstriction/bradycardia
  - E mesis
  - L acrimation
  - S alivation
- nicotinic: occur more from
  - stim of somatic nervous system eg skeletal mm twitching, weakness/paralysis
  - catecholamines from adrenal medulla

Anticholinergic Toxicity

- anticholoinergic classes:
  - anticholinergics
    - atropine
    - scopolamine
    - glycopyrrolate –
      - pre op to ↓ airway secretions
      - intra op – counteract surg induced vagal reflexes eg brady
  - antihistamines:
    - chlorpheniramine
    - promethazine
    - cyclizine
  - antipsychotics:
    - chlorpromazine
    - olanzapine
    - quetiapine
  - Antispasmodics:
    - Hyoscine
    - Oxybutynin
  - anti-parkinsons
  - TCAs
    - Amitryptilline
  - Mydriatics
    - Cyclopentolate
    - Tropicamide -
  - Plants:
    - Mandrake
    - Deadly nightshade
    - Jimsonweed - strongest

the 5 'anti's'

- Features:

[blind as a bat, mad as a hatter, red as a beet, hot as hell, dry as a bone, the bowel & bladder lose their tone, and the heart runs alone]

- Altered mental state- drowsiness, confusion
- Mydriasis (dilated pupil) & loss of accommodation (cycloplegia)
- Dry & flushed skin
- Urinary retention
- ↓bowel sounds
- fever
- dry mucous membranes
- tremulousness & myoclonic jerk
- HT & tachycardia

- features of poor prognosis (with risk of death):
  - seizures
  - dysrthythmias
  - rhabdomyolysis
- treatment:
  - sedation with benzodiazepines
  - cooling
  - hydration
  - ±physostigmine

Sympathetic Nervous System

Sympathomimetic Toxicity

- causes eg cocaine & amphetamines
- very similar to anticholinergic toxicity but distinguished by:
  - hyperactive bowel sounds
  - **sweating**
- features:
  - psychomotor agitation – hallucinations/deliurium
  - mydriasis
  - hyper-reflexia
  - diaphoresis
  - tachycardia
  - HT
  - Hyperthermia
- Complications:
  - Seizuires
  - Rhabdomyolysis
  - MI
- Rx:
  - Cooling
  - Sedation – benzo's to control seizures
  - Hydration
  - Use IV nitrates to control HT, avoid BB's

By Adam Hollingworth

Local Anaesthesia

Timeline

- cocaine used in ophthalmology in 1884
- procaine 1st synthetic LA in 1905
- dibucaine ⇒ amethocaine 1920s & 30s
- lignocaine 1947
- prilicaine 1959 ⇒ bupivacaine 1963 ⇒ ropivacaine 1980s

- cocaine =
  - ester of benzoic acid
  - found in large amounts in leaves of Coca plants in Peru/Andes (erythroxylon coca)
  - freud 1st used cocaine to wean a colleague from opioid addiction
  - LA in ophthalmology in 1884, used dentistry same year
  - spinal anaesthesia in dogs 1885

Ideal LA

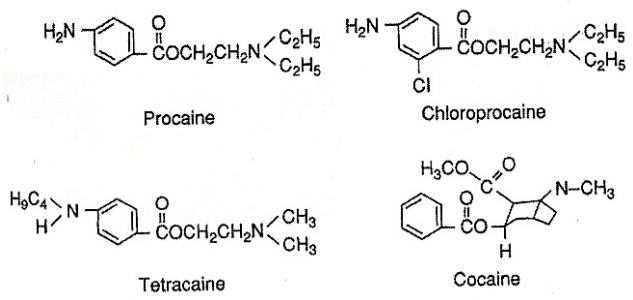
- ideal LA
  - target sensory nerves only
  - rapid reversible
  - non toxic:
    - systemic
    - local – no nerve damage
  - rapid painless onset
  - effective topically & by infiltration
  - duration of action – sufficient to allow surgery but not so long as to require extended period of recovery
  - cheap
  - long shelf life
- 2 commonest used =
  - lignocaine
  - bupivacaine
- rapid evapouration ⇒ cooling can provide similar LA effect
  ↳eg ethyl chloride
- = membrane stabilisers or ion channel modulators

Classification

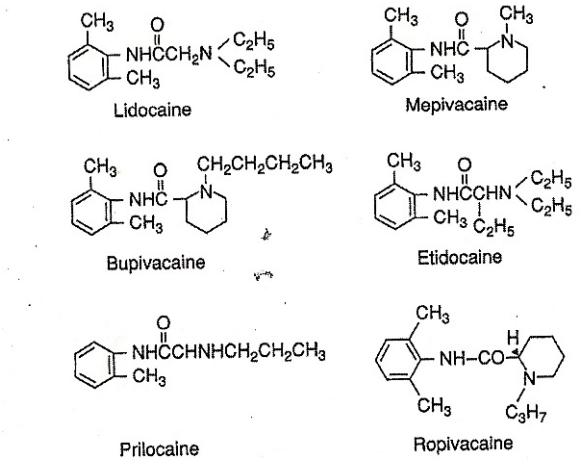
- classified according to linkage between the:
  - lipophilic aromatic ring
  - hydrocarbon chain

  ↳ ∴ either:
    - **esters**: -COO:
      - cocaine
      - procaine, chloroprocaine
      - benzocaine
      - amethocaine (aka tetracaine in USA)
    - **amides**: -NHCO:
      - lignocaine
      - bupivacaine
      - ropivacaine
      - prilocaine
      - etidocaine

- mepivacaine
- dibucaine



esters



amides

Structure Activity Relationships

- include:
  - weak bases
  - amphipatic molecules
  - lipophilic portion
  - hydrophilic portion
  - modification of chemical structure

1. Weak Bases

- LA's are all weak bases:
  - ∴ acidifying environment ⇒ ↑ed ionisation of drug ⇒ ↓penetration of lipid membrane ie nerves
- all IV LA's can exist as either: (R=any radical)
  - uncharged amine form (NR_3)
  - charged quaternary amine form (N^+R_3H)

  ↳move in equilibrium: $H+ + NR3 \leftrightarrow N^+R_3H$
- balance of equlibirum depends on:
  - chemistry of individual LA drug
  - pH of solution
- balance is impt:
  - uncharged form (basic) is
    - unionised

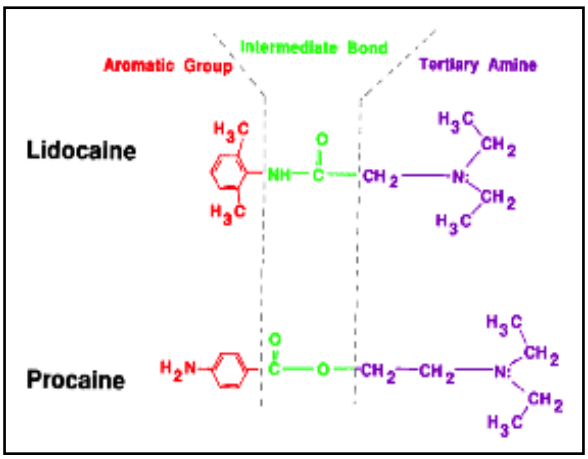
      ↳∴can diffuse across membranes and enter cells
  - charged form (cation) is:
    - ionised

        - active form of the LA which blocks Na channels
    - @pH 7.4 (physiological):
        - sufficient basic/uncharged form to enter cells
        - in cell picks up H+ ⇒ charged form ⇒ active cation LA molecule
    - @ acidic pH eg inflamed/septic tissue:
        - equilibrium R shift to charged cation form ∴ cannot enter cells
            ↳∴ LA less effective

2. Amphipatic Molecules

- generally have
    - aromatic (phenyl gp) at one end:
        - makes this end lipid soluble
    - tertiary amine (nitrogen containing) gp at other end
        - makes this end hydrophilic

    ↳joined by intermediate hydrocarbon chain
- hydrocarbon chain linked to aromatic (lipophilic) end by either:
    - ester
    - amide bond
        ↳this bond impt as defines:
        - site of metabolism
        - propensity for allergic reaction
        - potency
- different solubilities at either end of molecule allows chemical to align & act in nerve cell membranes
    ↳in the phospholipid bilayer



3. Lipophilic Portion (aromatic gp)

- responsible for lipid solubility ∴ for **potency**
    - is most true in vitro
    - in vivo potency as linked to:
        - vasodilator properties
        - tissue distribution

4. Hydrophilic Portion (tertiary amine)

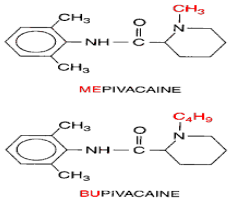
- defines :
    - water solubility
    - affinitiy for receptor – drug can only bind to receptor in ionised state

5. Modification of Chemical Structure

Alkyl Substitution

- can do on either end (aromatic or amine)
- result is
    - ↑lipid solubility ⇒ ↑potency

  - ↑PPB
  - ↑duration of action
- examples:
  - procaine: substitute amine gp on benzene ring for a butyl gp ⇒ amethocaine
    ↳result =
    - ↑lipid solubility ⇒ ↑x10 potency
    - ↓metabolism ⇒ longer duration of action
  - procaine: halogenation ⇒ chloroprocaine
    ↳result = ↑x4 hydrolysis by P-ChE ⇒ ↓duration of action
  - mepivacaine: addition of butyl gp to amine end ⇒ bupivacaine
    ↳result:
    - x35 ↑lipid soluble ⇒ ↑potency
    - ↑duratio of action x4



  - lignocaine:
    - substitute propyl for an ethyl @ amine end
    - add ethyl on αcarbon of hydrocarbon connecting chain
    ↳ ⇒ etidocaine
    ↳result =
    - ↑x50 lipid soluble ⇒ ↑x3 potency
    - ↑duration of action

Ester vs Amide

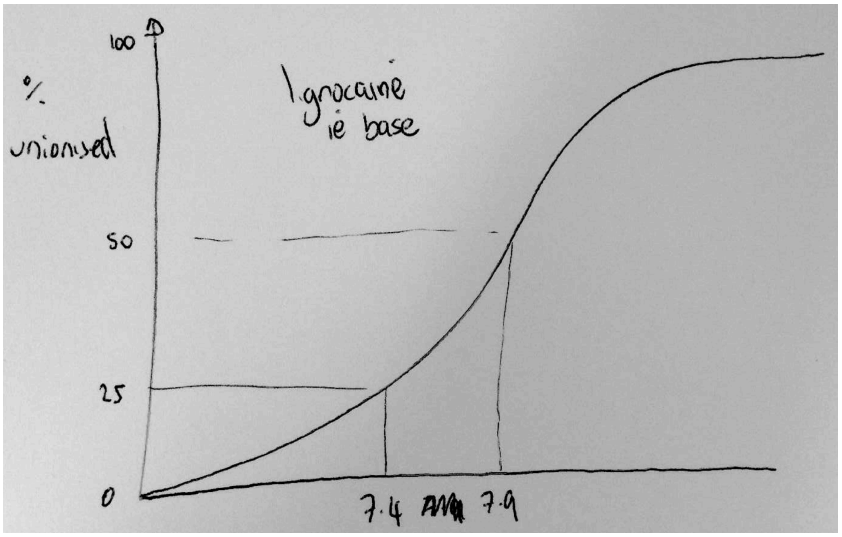
- ester link -COO
  - metab'ed rapidly by P-CHE & other esterases ⇒ metabolites of which one is PABA metabolites
  - PABA metabs responsible for allergic reactions
- amide link -NHCO
  - more stable molecule ⇒ slowly broken down by amidases in liver
  - allergic reactions very uncommon – much more likely to preservatives/additives
    ↳no PABA metabolites

Physicochemical changes

- lipid solubility ~ potency
- plasma + tissue protein binding = mostly effect duration of action:
  - eg procaine 6% = short duration action
  - lignocaine 65% = intermediate
  - bupivacaine 95% = long
- pKa = influences onset of action:
  - LA's = weak bases
  - high drug pKa = more in ionized form ⇒ slower onset as unable to penetrate membrane
  - eg lignocaine pKa = 7.7 = shorter onset of action
    ↳at pH 7.4 = 33% unionised
  - eg bupivacaine pKa 8.1 = even slower onset
    ↳at ph 7.4 = 17% unionised

remember:

- extent of ionisation determined by pH^1 of environment:
  - strength of acid = tendancy to dissociate into H+ & anions
  - dissociation defined by pKa:
    - = pH at which half the chemical is in its ionised form (pH – pKa = 0)
  - degree of unionised depends on
    - whether drug is
      - acid: if pKa < physiological pH (7.4) = <50% unionised
      - base: if pKa < 7.4 = >50% unionised
      ↳ ∴ curves drawn differently – for all LA's:



Isomerism

- chiral drugs = prilocaine, etidocaine, mepivacaine, ropivacaine, bupivacaine
- achiral = lignocaine, amethocaine, procaine

- chiral drugs generally supplied as racemic mixtures except:
  - s-ropivacaine: s-enantiomers display:
    - vasoC ie ↑duration & ↓toxicity
    - equipotent
      ↳although R enantiomer of bupivacaine x3 potent than s-enantiomer
    - ↓ed mm paralysis
  - l-bupivacaine

Summary Physicochemical Properties

	Rel lip solubilty	Rel potency	pKa	Onset	%prot bind	Duration	Comments
Procaine	1	1	8.9	slow	6%	short	ester, vasodilation, allergies
Amethocaine	200	8	8.5	slow	75	long	ester, toxicity
Lignocaine	150	2	7.9	fast	65	med	amide, vasodilator
Prilocaine	50	2	7.9	fast	55	med	amide, metHb
Etidocaine	5000	6	7.7	fast	94	long	amide, ↑motor block
Mepivacaine	50	2	7.6	fast	78	med	amide, ~ lignocaine
Ropivacaine	400	6	8.1	med	94	long	amide, vasoconstrictor, ↓ motor blockade
Bupivacaine	1000	8	8.1	med	95	long	amide

MOA

- cause a reversible conduction blockade of nerve impusles
- enter cell by diffusion through:
  - membrane
    ↳binding site is only accessible via inner (axoplasmic) pore
    ↳LA can only diffuse in unionised form
  - open Na channels - ∴ nerve blockade may be intensified by neurnal activity/excitation
    ↳= frequency dependant or use-dependant blockade
- mechanism:
  - bind to modulatory site in voltage dependant Na channel ⇒ block it from opening (in a transient fashion)
  - small contribution by physical blockade of channel

- Na channels in 1 of 3 states during an AP:
  - resting closed – m gate closed, h gate open
  - activated open – m & h gates open
  - inactivated closed – m gate open, h gate closed
- in resting nerve membrane Na channels are distributed in equilibrium between resting closed & inactivated closed
- LA's bind selectively to inactivated closed ⇒ stabilise them in this state ⇒ Na unable to enter cell
  ↳most likely binds with h gate of channel
  ↳ionic form of LA binds in electrostatic form
- ∴threshold potential not reached ⇒ no depolarisation & no AP
- LA's = membrane stabilisers as resting membrane potential remains normal
- note:
  - resting closed & open gates = unaffected
  - baseline RMP is mainly due to K conductance and K channels not effected
  - threshold potential also unaltered

Activity Inside Axoplasm

- LA (B) is exposed to relatively acidic cell interior (pH 6.8-7) ⇒ partial ionisation (BH+)
- ionised (cationic form) interacts with receptor on inner aspect of channel
- selective conduction blockade is related to:
  - anatomical properties:
    - nerve diameter
    - myelination
    - length nerve fibre
  - tissue pH
  - characteristic frequency of activity (frequency dependant blockade)
    ↳active nerve more sensitive to LA block than resting nerve
    ↳etidocaine blocks motor nerves prior to sensory due to frequency dependant blockade

Minimum Concentration

- = minimum concentration of LA necessary to produce conduction blockade
  ↳analogous to principle of MAC of volatiles
- factors determining MC:
  - diameter of nerve – large nerve needs ↑ed MC
  - ↑tissue pH ⇒ ↓MC (more LA in unionised form ∴ able to move to effect site)
  - ↑frequency of stimulation ⇒ ↓MC
  - ↑potency of LA ~ lipid solubility ⇒ ↓MC
  - length of myelinated nerve fibre exposed to adequate LA prior to blockade
    ↳need at least 2 nodes of Ranvier = ~1cm
  - type of periph nerve = differential conduction blockade:
    - periph nerves comprised of:
      - myelinated A – subtypes α,β,γ,δ
      - myelinated B – (preganglionic sympathetic) fibres
      - unmyelinated C fibres
    - Sensitivity to blockade:
      - myelinated preganglionic B > (small distance between their nodes of Ranvier & only need 3 nodes blocked)
      - C >
      - Aδ >
      - Aγ (proprioception) >
      - Aβ (touch/pressure) >
      - Aα (motor)

      ↳sensitivity does not depend on sensory vs motor

↳differential block results from differences in critical lengths of axons
↳axons must be exposed to LA
↳smaller axons have shorter critical lengths
↳diffuses inward across neurolemmal sheath ⇒ infrafasciicular route
↳small discrete fibres most exposed ∴ Aδ, C fibres blocked (and recover) first

- sequence of anaesthesia:
  - loss pain
  - loss temp sens
  - loss proprioception
  - loss touch/pressure

Dosing Recommendations

Maximum recommended doses of common agents (BNF)

Agent	Maximum recommended doses	Maximum recommended doses with vasoconstrictor
Bupivacaine	2mg/kg	2mg/kg
Levobupivacaine	2mg/kg	2mg/kg
Ropivacaine	3mg/kg	3mg/kg
Lidocaine	3mg/kg	6mg/kg
Prilocaine	6mg/kg	8mg/kg
Cocaine	1.5–3mg/kg	

Speed of Onset & Duration of Action

- classification:
  - drug factors:
    - pKa **esp onset of action**
    - lipid solubility/protein binding **esp duration of action**
    - concentration & volume administered
    - intrinsic vasoconstrictor properties
    - effect of local & distant metabolism
    - effect of additives
  - patient factors
    - site of administration
    - structure & function of nerve
    - pH of tissues

1. pKa

- most LA's weak bases and administered as water soluble salts with HCL (B.HCL)
- after injection:
  - tertiary amine gp liberated by alkaline pH of tissue fluid:

$$B.HCL + HCO_3^- \Leftrightarrow B + H_2CO_3 + Cl^-$$

- in tissues the LA is present in both:
  - ionised (BH+)
  - unionised forms (B)
- proportions of each is determined by drugs pKa & ambient pH
- pKa explained by Henderson-Hasselbach equation:

Lidocaine: $pK_a = 7.9$
At pH 7.4

$$pH = pKa + \log\left\{\frac{[B]}{[BH^+]}\right\}$$

$$7.4 = 7.9 + \log\left\{\frac{[B]}{[BH^+]}\right\}$$

$$-0.5 = \log\left\{\frac{[B]}{[BH^+]}\right\}$$

$$0.3 = \left\{\frac{[B]}{[BH^+]}\right\}$$

so 75% ionized and 25% unionized.

At pH of 7.1

$$7.1 = 7.9 + \log\left\{\frac{[B]}{[BH^+]}\right\}$$

$$0.16 = \left\{\frac{[B]}{[BH^+]}\right\}$$

so 86% ionized and 14% unionized (i.e. less available to penetrate nerves).

- only unionised form of drug can cross cell membrane ∴ re-ionised and becomes active
- drugs with larger unionised portion ∴ quicker onset of action eg lignocaine 33% vs bupivacaine 17%

2. Lipid Solubility/Protein Binding

- ↑ed lipid solubility ⇒
  - ↑avid binding to target tissue ⇒ ↓ diffuse away from target site ⇒ ↑duration of action
    - eg bupivacaine 1000 vs 150 lignocaine lipid solubility
  - ↑potency:
    - ∴ smaller doses needed
    - Ficks Law of diffusion: ↓ed concentration gradient ∴ slower onset compared to less potent agent

3. Concentration & volume administered

- ↑ed concentration & ↑volume ⇒ ↑ed gradient of diffusion ⇒ ↑speed of onset
  ↳again Ficks law of diffusion

4. Intrinsic VasoConstrictor/Dilator Properties

- s-enantiomers of bupivacaine & ropivacaine = highr intrinsice vasoconstrictor properties ⇒ ↓ed systemic uptake of drug ⇒ ↑duration of action
  ↳other amines = intrinsic vasodilators
- adrenaline used as lignocaine co-agent for same reasons
  ↳has no added benefit to longer acting LA agents

5. Effect of local & distant metabolism

- ester LA's – broken down @ site of action by non-specific plasma esterases ⇒ short duration of action
- amide LA's – diffuse away, then metab in liver ⇒ longer duration

6. Effect of Additives

- vasopressors (adrenaline) may ↑duration of action of short acting agents (but limited benfit in longer acting agents)

a. Site of Administration

- diffusion distance to target site – effect speed of onset:
  - eg spinal LA = quicker onset than epidural
- ↑vascularity of site ⇒ ↑systemic uptake ⇒ ↓duration of action

b. Structure & function of Nerve

- order of sensitivity (see prev) - B effected first followed by Aδ then C

c. pH of tissues

- as described prev – more acidic tissue ⇒ ↑amount of drug in ionised form ∴ unable to move to effect site quickly ⇒ ↓ed speed of onset

↳a function of pKa

LA Pharmacokinetics

Absorption

- absorption into systemic circulation from site of injection (∴ peak plasma conc) depends on:
  - site of injection:
    - impt factors here are (Ficks Law of diffusion):
      - vascularity
      - surface area
    - in order of most systemic uptake > least:
      - IV (inadvertent) > tracheal > intercostal > caudal > paracervical > epidural > brachial plexus > spinal > sciatic/femoral > subcut
  - dosage used:
    - Ficks law of diffusion – linear relationships
  - pharmacological characteristics of drug:
    - inherent vasoC/vasoD of LA:
      - constrictors = cocaine, S enantiomers eg ropiv & bupiv
      - dilators = procaine > prilocaine > lignocaine > mepivacaine > bupivacaine (racemic) > ropivacaine (racemic)
    - addition of vasoconstrictors:
      - eg adrenaline or phenylephrine –
      - useful in less lipid soluble ie adrenaline but not in highly lipid soluble ie bupiv
  - use of vasoC's with LA

Distribution

- Vd determined by:
  - physicochemical properties of drug:
    - PPB ⇒ duration of action
    - lipid solubiliuty ⇒ potency
    - degree of ionisation/pKa ⇒ speed of onset
  - pt factors:
    - regional blood flow
    - acid-base status
- PPB:
  - plays role in:
    - pharmacokinetics ie Vd & excretion
    - pharmacodynamics ie duration
  - degree of binding:
    - ↓esters : ↑amides
  - LA's binds to greater % of α-1-acid glycoprotein (AAG)
    ↳although due to albumin's greater quantity = actually binds more
  - AAG also an acute phase protein
  - order of binding:
    - bupiv 96% > ropiv 94%>mepiv 78% > lingo 65% > prilocaine 55%
  - binding is reversible & weak ∴ does not restrict uptake by organs
  - ↑in AAG ⇒ ↓free fraction:
    - MI
    - renal failure
    - post op
    - infancy
  - ↓in AAG =
    - pregnancy

        - neonates
        - severe liver disease
    - PPB also influences placental transfer ∴ ↓amide transfer
- generally Vd > total body water:
    - lignocaine 0.7-1.5 L/kg, 70% bound to AAG
    - bupivacaine = 0.6-1.5 L/kg, 95% bound to AAG
- following rapid IV injection ⇒ rapid decline in serum conc:
        - drug distributed from plasma into
            - vessel rich gp (brain, heart, kidneys)
            - 1st pass pulmon uptake
        - then redistribution to mms & fat

        ↳lipid solubility (&∴potency) impt factor in redistribution
- lung extraction:
    - lungs = capable of extracting certain amides from circulation
                ↳?also metabolises drugs
    - can extract lingo, bupiv, prilocaine
    - acts as buffer to protect against systemic toxicity
    - ∴ following IV inj pulmon extraction will limit conc which reaches systemic circulation
    - eg bupivacaine:
        - 1st pass lung extraction = dose dependant & rapidly saturated
        - propranolol limits lung extraction & ↓s hepatic clearance
- placental transfer:
    - esters – due to rapid local metabolism not transferred in sig amounts
    - amides - depends on PPB
        - umbilical vein:maternal arterial conc:
            - bupiv = 0.32
            - lignocaine = 0.73
                ↳ie lignocaine t/fed more
    - if fetal acidosis present – is a risk of ion trapping ⇒ accumulation in fetus

Metabolism

Amides

- clearance of amides depends on metabolism ie 1-5% excreted renally unchanged
- amides have variable rates of metabolism by liver microsomal enzymes:
    - fast – prilocaine = most actively metabolised
    - intermediate(~6ml/kg/min) = lignocaine, mepivacaine, ropivacaine
    - slow = bupivacaine + etidocaine
- $Cl_{Hep} \sim Q_{Hep}$:
    - due to high intrinsic clearance, ie high hepatic extraction ratio
    - ∴ metb not largely affected unless severe hepatic failure
    - ∴∴factors ↓ing Q_{Hep} have greatest effect on ↓ing metabolism ∴ ↓ Cl_{Tot} :
        - ↓MAP or ↓CO eg esp with GA
        - drugs:
            - halothane
            - BBs esp propranolol
            - SNP

            (isoflurane ⇒ ↑liver flow)
        - type of surgery – upper abdo surgery ⇒ ↓flow by 20%
        - ventilation: IPPV + PEEP
- compared to esters: amides metab ∴slower ⇒ ↑risk of toxicity

Esters

- hydrolysis by cholinesterases:
    - mostly in plasma

- much less occurs in liver
  ↳except cocaine which mostly occurs in liver
- varying rates:
  - fastest = chloroprocaine
  - intermediate = procaine
  - slowest = amethocaine
- resulting metabolites are inactive – para-amino-benzoate (PABA)
  ↳PABA metabolites may be antigen responsible for allergic reactions:
- systemic toxicity is inversely proportional to rate of hydrolysis
  ↳∴ amethocaine most likely accumulate & toxic
- CSF contains no cholinesterase ∴ subarachnoid amethocaine ⇒ persistent anaesthesia until drug systemically absorbed
- Pl-ChE activity is decreased in:
  - liver disease
  - uraeamia
  - pregnancy
  - drugs
  - atypical P-ChE – see sux apnoea

Summary Factors Affecting LA Metabolism

1) Liver disease:
   - Esters: ↓ Cl secondary to ↓ pl-ChE
   - Amides: ↓ Cl secondary to either ↓ Q_{hep} (more important) or liver disease.
2) Cardiovascular disease:
   - CCF: ↑ s-lignocaine due to ↓ Vd and ↓ Cl (↓Q_{hep} and liver congestion causes hepatocellular dysfunction)
3) Renal disease:
   - Esters: unaffected (except cocaine to some degree)
   - Amides: metabolites may accumulate
4) Pulmonary disease:
   - Shunting may ↑ available drug to the systemic circulation (bypass 1st-pass)

Renal Elimination

- poor water solubility of parent drugs ⇒ limits renal route for elimination
  ↳except cocaine which excreted 10-20% unchanged in urine
- water soluble metabolites from esters (eg PABA) = easily excreted in urine

Specific Drugs Pharmacokinetics

Lignocaine (& mepivacaine)

- rapid onset action 5-10mins
- Peak blood level usually occur 10-25min post injection
  ↳when toxicity most likely to occur
- pKa 7.9 ∴ 25% unionised
- 65% PPB
- VD 1L/kg
- high extraction ratio: $Cl_{hep} \sim Q_{hep}$
- OBA <30%
- metab in liver:
  - oxidation dealkylation: lignocaine ⇒ mono-ethyl-glycine xylidide (MEGX)
  - hydrolysis: MEGX ⇒ xylidide
- MEGX =

  - 80% activity (anti-arrhythmic properties)
  - prolonoged t1/2
- xylidide =
  - 10% activity
  - 75% renally excreted
- $Cl_{Tot} \sim Cl_{Hep}$ = 10ml/kg/min
- excretion via kidneys - <10% unchanged
- $T1/2_{dist}$ 8min, $t1/2_{elim}$ 100min min
- intermediate duration

Bupivacaine

- pKa 8.1 ∴ 15% unionised
- PPB 94%
- VD 0.9L/kg
- highly lipid soluble
- liver metab:
  - N-dealkylation, aromatic hydroxylation & amide hydrolysis: bupivacaine ⇒ N-des-buthyl-bupivacaine
- Cl = 3ml/kg/min
- 16% excreted unchanged in urine
- T1/2elim = 160min
- medium onset
- long duration

Ropivacaine

- pKa 8.1 ∴ 15% unionised
- PPB 95% (AAG)
- VD 0.4L/Kg
- less lipid soluble than bupivacaine

↳∴ compared to bupiv slightly shorter duration of action and slightly less potent

↳∴ need higher dose to get same block!!

- liver metb by C-P450 to
  - 4-hydroxy-ropivacaine
  - 3-hydroxy-ropivacaine

↳both contain some but minimal LA activity

- Cl_{tot} = ~ 11 ml/kg/min,
- $t1/2_{terminal}$ = 60-170 min ie shorter than bupiv due to higher clearance

↳advantage in toxicity

- long duration

Prilocaine

- fastest & most active metabolised
- liver: metabolised ⇒ O-toluidine
- O-toluidine = oxidising compound capable of oxidising Hb (Fe^{++}) ⇒ Hb (Fe^{+++})

↳= Methaemoglobin

- if total dose >600mg ⇒ 3-5g/dl MetHb
- clinical cyanosis seen ~1.5g/dl MetHb
- Rx of MetHb:
  - methylene-blue – short lived effect as methylene-blue cleared faster than conversion of MetHb ⇒ Hb
  - ascorbic acid
- ∴dose dependant MetHb formation limits prilocaine use – except for Bier's blocks

Dibucaine

- slowest metab of lot

Procaine
- hydrolysed to PABA ⇒ urine

Chloroprocaine
- ↑ed rate of hydrolysis x3-4 over procaine
  ↳due to addition of Cl to benzene ring
- inactive metabolites
- T1/2 elim = 1-5mins even in pregnancy

Cocaine
- metab by mostly liver ChEs (some plasma) ⇒ water soluble metabolites ⇒ urine
- absorption across mucus membranes = slow – as vasoC
- t1/2elim = 60-90mins
- metabolites in urine for 24-36hrs

Comparisons
- short acting: (30-60mins)
  - procaine:
    - least toxic LA
    - low lipid solubility ∴ slow onset
    - potency 0.5
- intermediate acting (30mins- 4hrs)
  - lignocaine:
    - potency 1
    - more cardiotoxic than prilocaine
  - prilocaine:
    - products of liver metab may ⇒ methaemoglobinuria
  - EMLA (lignocaine/prilocaine)
    - local irritation
    - toxic if swallowed
    - <6months risk of metharmoglobinaemia
- long acting (3-10hrs):
  - bupivacaine:
    - potency 4
    - ↑cardiotoxic than lignocaine
    - slow onset
    - less motor blockade
  - amethocaine (tetracaine):
    - topical LA
    - potency 5
    - slow onset

Reversal
- recovery of sens can be accelerated with phentolamine:
  - α receptor antagonist
  - infiltrate into same site as LA ⇒ VD ⇒ ↑clearance of lignocaine
  ↳good in dental surg

Local Anaesthetics in Paediatrics
Dosing
- neonates:
  - initial doses:
    - ↓by 50% from adult dose
    - should be given slowly in increments

- maintenance infusion:
  - ↓50% from older children/adults
  - limit to 36hrs;
  - consider ↓ing infusion rate by 33% after 24hrs
    ↳ evidence of accumulation even with low infusions

- >6yrs:
  - initial doses = Rx as adults
  - maintenance & cumulative dosing is ↓ed to prevent accumulation

Table 1 Local anaesthetic doses in neonates and infants

Drug	Age (months)	Initial dose (mg kg^{-1})	Maintenance dose (mg kg^{-1} h^{-1})	Maximum dose per 4 h (mg kg^{-1})	Duration (h)
Levo-/bupivacaine	0–6	0.5–1.0	0.2–0.25	1.0	36
	>6	1–2	0.25–0.5	2.0	
Ropivacaine	0–6	0.5–1.5	0.2	0.8	36
	>6	1–3	0.4	1.6	

Pharmacodynamics

- <6yr old is at ↑ed risk of amide LA toxicity:
  - no early warning signs ie 1st sign of toxcitiy may be a seizure/apnoea/arrhythmia
  - risk of toxicity ↑ed:
    - hypoxia
    - hypothermia
    - acidosis ⇒ ion trapping within tissue
    - hypercarbia
  - toxicity relates to absolute & rate of rise of plasma conc

Pharmacokinetics

- causes of ↑ed risk in kids:
  - ↑ed % cerebral blood flow
  - under-developed bbb
  - ↓ed PPB
  - ↓hepatic clearance ⇒ continuous infusions mean accumulation >6hrs & toxicity 36-48hrs
  - undiagnosed R-L cardiac shunts – lose 1st pass clearance from lungs

Specific Commonly Used LA's

Lignocaine

Chemical

- weak base
- amide

Presentation

- varied forms:
  - clear solutions as HCl salt – 1%, 2%, 10% (with or without adrenalin 1:200,000)
  - pink coloured solution 4%
  - spray 10% (0.1ml/spray or 10mg/spray)
  - gel: 2%
  - combinations:
    - cophenylcaine (5% lignocaine, 0.5% phenylephrine)
    - EMLA

MOA

- amide –type LA
- blockade of Na channel ⇒ prevents initiation & propogation of nerve impulses
  ↳also stabilises all potentially excitable membranes incl heart

Pharmacokinetics
- see prev

Pharmacodynamics
- same as rest
- vasodilator (> bupivacaine)

Uses
- LA
- Rx or prevent ventricular arrhythmias

Adverse Reactions
- CC:CD 7:1
- less cardiotoxic than bupivacaine
- antiarrhythmic in low concentrations
- allergy rare

Cautions/Contraindications
- ↓dose: children, elderly, CVS, Neuro, hepat-renal disease
- contraindicated if:
  - infection at site injection
  - severe shock
  - hypotension
  - SVTs

Interactions
- other anti-arrhythmics/phenytoin/alcohol ⇒ ↑CVS effects of lignocaine
- ↓clearance of lignocaine:
  - β-blockers
  - cimetidine
  - erythromycin

Dose
- lowest effective dose
- Max safe dose 3mg/kg(adults & child) (7mg/kg with adrenaline)
  Thus 70kg man = 210mg. 1% contains 10mg/ml thus 20mls contains 200mg
  2% contains 20mg/ml thus 10mls contains 200mg
- anti-arrhythmic dose: not more 300mg/1hr

Eutectic Mixture of Local Anaesthetic (EMLA)
- eutectic = when 2 compunds are mixed to produce a substance that behaves with a single set of characteristics

Chemical
- EMLA 5% =
  - 2.5 lignocaine
  - 2.5% prilocaine
  - in white oil:water emulsion
- mixture has lower melting point being an oil at room temp
  ↳individual components would be crystalline at room temp

Presentation
- emulsion tubes containing 5g or 30g
- needs 60mins to take effect

Caution
- caution in pts
  - congenital or idiopathic metHb
  - <12months who may have been given metHb inducing drugs
  - pts taking metHb inducing drugs:
    - phenytoin
    - sulphonamides

  - taking class 1 anti-arrhythmics – additive & synergistic effects
- do not apply to mucous membranes

Ropivacaine

Chemical

- amide – sub gp = bupivacaine & mepivacaine
- has a propyl gp on the piperidine nitrogen
  ↳bupivacaine has a butyl gp here instead

Presentation

- prepared as s-enantiomer
- available as 0.2%, 0.75%, 1%
- prepared as Hcl salt ⇒ gives it water solubility & stability

Pharmacokinetics

see prev

Pharmacodynamics

- vasoConstrictor effects
- marketed as ↑ed motor sparing compared to bupivacaine eg walking epidurals in obstetrics
  ↳most likely reflects lower lipid solubility ~ potency ⇒ ↓penetration large Aß motor fibres

Adverse Reactions

- same as other amides

Dose

- infiltration: max 3mg/kg
- epidural: 200mg (20ml of 1% solution)

Bupivacaine

Chemical

- amide
- butyl gp in piperidine nitrogen

Presentation

- racemic mixture of R –S- bupivacaine
- 0.25% or 0.5% +/- adrenaline 1:200,000
- heavy bupivacaine contains 80mg/ml glucose ⇒ gracity 1.026
- levobupivacaine: (-s enantiomer)
  - 2 major useful properties in humans:
    - higher dose to block cardiac K channels ⇒ myocardial depression
    - higher dose to cause CNS toxicity

Pharmacokinetics

- see prev

Pharmacodynamics

- vasodilator effects (less than lignocaine)

Adverse Reactions

- as others but selective cardiac toxicity (CC:CD 4:1)

Dose

- infiltration: 2.5mg/kg +/- adrenaline
- epidural – 100mg 20mls 0.5%

Amethocaine

- =ester LA for topical anaesthesia
- preparations:
  - 0.5% or 1% drops in lens surgery
    ↳burning sensation on initial instillation
  - 4% cream –
    - similar use to EMLA but faster onset in 30mins
- duration of action 4-6hrs

- produces some local vasoD & erythema which can help in venous cannulation

Local Anaesthetic Toxicity

- classification:
  - systemic toxicity:
    - CNS
    - CVS:
      - direct effects on myocardium
      - perpih vascular effects
  - local tissue toxicity
  - allergic reactions
  - misc:
    - membrane stabilising: NMJ, anutonomic ganglia
    - metHb
- order of toxicity (less ⇒ more):
  - procaine ⇒ prilocaine ⇒ lignocaine ⇒ bupivacaine ⇒ amethocaine ⇒ cocaine

Systemic Toxicity

- signs of systemic toxicity
  - Mild:
    - Perioral tingling
    - Metallic taste
    - Tinnitus
    - Visual disturbance
    - Slurred speech
  - Moderate:
    - Altered consciousness
    - Seizures
    - Coma
  - Fatal:
    - Cardiovascular collapse
    - Resp arrest
- toxicity ~ lipid solubility:
  - amides: prilocaine < lignocaine < bupivacaine (most toxic)
- serum concentration = balance on plasma circulation:
  - uptake – absorption factors:
    - inadvertent IV admimistration (commonest)
    - dose (volume x conc)
    - surface area/vascularity
      - (intercostal > epidural > brachial plexus > peripheral s/c)
    - presence of vasoC
    - physiochemical properties of drug (lipid solubility, pKA, PPB, vasoC/vasoD)
  - removal:
    - redistribution
    - clearance:
      - pulmon uptake
      - metabolism
      - renal excretion
- S-enantiomers generally less toxic than racemic mixtures – esp CVS toxicity
- LA toxicity = additive (not synergistic) ie cumulative dosing
  ↳can be additive across types ie esters & amides
- systemic toxicity more likely with amides (slow hepatic metabolism)

CNS Toxicity

- generally more sensitive than CVS
- signs & symptoms based on serum concentrations of **lignocaine**:
  - ~**2 ug/ml**: numbness of tongue + circumoral areas (=vascular, ie direct effect)
  - **2-4 ug/ml** (crosses the BBB): restlessness, vertigo, tinnitus, difficulty focusing
  - **~ 5 ug/ml**: slurred speech, muscle twitching (face/extremities) ⇒ early signs of impending seizures…
  - **~ 8 ug/ml**: Drowsiness (amides cause drowsiness before seizures)
  - >**10 ug/ml:** Seizures ⇒ ⇒ CNS depression / coma ⇒ hypotension + **apnoea**

  ↳Death is usually due to respiratory depression
- other drug levels ⇒ severe CNS toxicity:
  - lignocaine, mepivacaine, prilocaine = 5-10ug/ml
  - bupivacaine, etidocaine, ropivacaine = >1.5ug/ml (5 for seziures)
- active metabolites may exert late additive effects towards toxicity after eg epidural dosing

  ↳ eg MEGX
- other factors effect seizure threshold for LA's:
  - ↑5-HT ⇒ ↓seizure threshold & prolongs seizure
  - ↑PaCo2 ⇒ ↓seizure threshold - ?2nd to ↑Qbrain ⇒ ↑drug to brain

    ↳opposite to normal ie ↓PaCO2 normally ⇒ ↓seziure threshold (∴ hypervent pt for ECT to improve seizure)
  - ↑K ⇒ ↓seizure threshold – depolarises nervous membranes
  - some anti-arrhythmics (mexiletene) ⇒ ↓lignocaine seizure threshold
- specific Rx:
  - ABC
  - consider hyperventilation:
    - ↓Qbrain
    - but will also ↓removal of drug from brain
  - benzo's –
    - careful with diazepam as is also highly PPB and may displace bupivacaine ⇒ ↑free drug
  - thiopentone 1-3mg/kg slow IV
  - intralipid

CVS

- CVS is more resistant to LA toxicity (except bupivacaine)
- signs & symptoms based on serum concentrations of **lignocaine**:
  - <5ug/ml – only ↓rate of ph-4 spont depolarisation ie ↓automaticity of pacemaker cells
  - 5-10ug/ml – hypotension/ ↓↓MAP:
    - perpih vasoD ⇒ ↓SVR
    - direct myocardial depression ⇒ ↓SV ⇒ ↓CO
  - >10ug/ml:
    - block cardiac Na-channels ⇒ conduction blocks (↑PR interval, ↑QRS)
    - block Ca & K channels
- bupivacaine exhibits selective cardio-toxicty:
  - bupiv:lignocaine 16:1
  - levobupivacaie (s-enantiomer) = less toxic
  - mechanism:
    - bupiv ⇒ ↓ed max rate of depolarisation of AP in phase 0 (Vmax)
    - bupiv dissociates from Na channels slower than ligno & ropiv 2nd to ↑lipid solubility

    ↳∴ persistent depression of Vmax
  - symptoms:
    - severe hypotension
    - arrhythmias – can be very refractory

    - +/-AV block
  - factors causing ↑toxicity:
    - pregnancy & neonates - ↓AAG ⇒ ↑free fraction
    - ↑PaCo2
    - ↓PaO2
    - ↓pH
    - ↑HR - ↑ed frequency dependant blockade
      ↳ conversely low degree of frequency dependant blockade enhances anti-arrhythmmic effect of lignocaine (lingo dissociates faster from Na channel)
  - specific Rx:
    - ABCs
    - bretylium – one of few indications for use, 20mg/kg IV
    - intralipid
    - avoid ↑PaCO2, ↓PO2, tachycardia

Generic Treatment of Systemic Toxicty

- Stop injection
- ABC
- Mild symptoms - consider midaz or small doses of propofol to ↑seizure threshold
  - ↳ NB hypoventilation & acidosis will worsen toxicity
- Moderate to severe toxicity:
  - Conventional therapies to Rx hypotension/tachy/bradycardia
  - Early use of 20% intralipid:
    - 1.5ml/kg bolus over 1min
    - Start infusion 15ml/kg/hr
    - @5mins: if CVS still unstable
      - repeat bolus (can do total of 3 boluses)
      - Double infusion rate
  - Continue CPR - arrythmias may be very refractory to treatment
- Methaemoglobinaemia Prilocaine toxicity
  - Specific to prilocaine
  - Hb oxidated to metHb by o-toluidine
  - O-toluidine formed by metabolism of prilocaine in liver
    - ↳ in high doses >600mg
  - MetHb has ↓O2 carrying capacity ⟹ cyanosis
  - ∴ avoid prilocaine in pregnancy and anaemia
- Rx: methylene blue 1mg/kg IV

Safety Ratios for CVS & CNS Toxicity

- = CC:CD
- = blood levels causing cardiovascular collapse (CC) & convulsive dose (CD)
- lignocaine = 7:1 (ie causes convulsions at much lower dose than CC)
- ropivacaine 4:1
- bupivacaine = 3:1 (ie more likely than ligno to cause CC)

Cocaine Toxicity

- has specific actions:
  - standard LA effects – CNS, CVS
  - inhibit pre-synaptic uptake of NA & dopamine
- toxicity:
  - CVS:
    - heart – tachy, HTN, coronary vasospasm ⇒ -ve effect on cardiac O2 balance
      ↳∴ ischaemia/arrhythmias
      ↳ risk of VF/AMI/arrest

        - cerebral – stroke
        - uterus - ↓flow ⇒ fetal distress
    - CNS: seizures, hyperpyrexia (contributes to seizures)
    - drug interactions – esp with MAOIs, sympathomomimetics, halothane

Allergic Reactions

- to either drug or additive
- reactions to LA are rare (esp amides)
- type 1 or anaphylactoid
- 'allergic' symptoms much more likely to be emotional responses to needle
- true allergic reactions more likely against
    - esters (PABA metabolites)
        ↳although commonly used in food preservatives
        Na-meta-bi-sulfate common preservative
    - preservatives/additves
- cross sensitivity
    - seen between esters – due to common PABA metabolite
    - not seen amide – ester

↳2nd choice LA should be preservative free

Local Tissue Toxicity

- common = burning/pain on injection – due to acidic nature of solution (HCl)
- all LA's can potentially cause local tissue/nerve toxicity
    ↳should always avoid direct injection into nerve

Intrathecal Neurotoxicity

- transient neurological symptoms (TNS)
    - esp if lignocaine injected intrathecally (can occur with all LA's)
        ↳incidence x7-0 > bupivacaine
    - = pain/paraesthesia in buttocks/legs
    - symptoms 6-36hrs post recovery from single shot
    - usually only annoying but may need opioids
    - usually self terminating 1-7days
- cauda equine syndrome (CES):
    - rare complication
    - assoc with 5% lignocaine in continuous spinal anaesthesia
    - = diffuse injury of lumbrosacral plexus:
        - sensory anaesthesia
        - bowel/bladder incontinence
        - paralplegia
- anterior spinal artery syndrome (ASAS):
    - =lower limb paresis with variable sensory deficit
    - thought due to spasm/thrombosis of ASA
    - no proven causality but ?hypotension or adrenaline added to LA's
    - RF's = age & PVD

- reactions:
    - specific to drug eg prilocaine = metHb ⇒ cyanosis
    - allergies eg bronchospasm & anaphylaxis (more common with esters)
    - systemic effects of LA:
        - numb tongue
        - CNS stim: tremor, visual disturbance, convulsions
        - CNS depression: relax smooth mm & skel mm; CVS/resp depression, ↓bp

LA Additives

- include:
  - preservatives
  - vasoconstrictors
  - anti-oxidants
  - baricity modifiers
  - alkalinisers
  - dextran
  - other drugs eg clonidine, opioids

Preservatives

- preservatives include:
  - sodium metabisulphite
  - methyl parahydroxybenzoate

    ↳should not be used for intrathecal injection
- also may contain fungicide

VasoConstrictors

- added to slow rate of absorption from site of injection ⇒
  - prolong duration
  - ↓risk of toxicity
- vasoC's have greater effect on
  - LA with intrinsic vasodilatory properities ie lignocaine, procaine, prilocaine
  - poorly lipid soluble ∴ short acting LA's

    ↳∴ no change in max safe dose or duration of action in bupivacaine/ropivacaine
- examples:
  - adrenaline 1:200 000 = 5ug/ml

    ↳added to lignocaine ⇒ ↑duration 50% & ↓systemic absorption by 33%
  - phenylephrine eg 5mg/ml with lignocaine 5% = co-phenylcaine
  - felypressin or ornipressin = vasopressin analogues
- adrenaline added to lignocaine + bupivacaine in spinals ⇒ ↑duration of sensory anaesthesia in LLs (not abdomen
- adrenaline no effect on rate of onset
- use adrenaline in caution in epidurals in:
  - PET
  - HTN pts
  - IHD pts
  - halothane volatile to be used – risk of arrhythmias

Baricity modifiers

- added to influence spread of block by gravity when given intrathecally
- hyperbaric =
  - dextrose added ~80mg/ml
  - specific gravity 1.026
- hypobaric = distilled water added

Alkalinisers

- Adding $NaHCO_3$ to LA ⇒
  - ↑ed unionized fraction ⇒ ↑speed of onset
  - ↓pain on injection
  - eg 2mls 8.45% $NaHCO_3$ to 20mls LA can speed onset of block for emergency C section

Carbonation

- also speeds onset
- CO_2 ⇒ diffuses into tissues ⇒ ↓pH inside membrane ⇒ ↑ionisation of LA ⇒ trapping active drug at effect site

Dextran

- LMW dextran addition ⇒ prolong duration of action
- mechanism = ?↓absorption rate

Others

- clonidine = epidurals & caudals ⇒ prolong duration & improve quality of analgesia
- opioids = eg fentanyl, morphine, diamorphine, sufentanyl
- adrenaline = ↓s systemic uptake
- neostigmine & ketamine – analgesic adjuvants

LA in Neuraxial Use

	Subarachnoid block (spinal)	Epidural
Mech action:	- act on spinal cord and nerve roots (preganglionic autonomic B fibers blocked 1st, then afferent C + A_δ)	- Similar as for SAB, but must 1st diffuse through dura mater - Also: Leaks out through intervertebral foramina ⇒ multiple paravertebral blocks.
Block differentiation:	- Sympathetic block ~ 2 segments Above sensory level - motor block ~ 2 segments below below sensory block	- no sympathetic differentiation - motor block up to 4 segments below sensory block
Miscellaneous:	- **Dose** (in mg) NB for block height - Block spread also influenced by extremes of height, weight (morbid obese + pregnant ⇒ ↓ dose 25%), position, baricity of soluion, angulation of needle - TNS more with lignocaine	- Dose also NB for spread, but volume too (eg 20ml 1% larger spread than 10ml 2%). Other = age/height/weight, position(slight) Site: even spread with mid thoracic epidurals up and down, vs > cranial spread with lumbar - Addition of adrenaline ↓ systemic abs by ~ 30%. Important with lignocaine, as 400mg epidurally gives peak s-[ ]'s of 3-4ug/ml.

- epidural:
  - injection into extradural space between dura & lig flavum
  - space filled with loose adipose & lymph & blood vessels
  - injection C7-T10
  - injection stays local to level
  - post op urinary retention common 2nd to block of parasymp nerves
- spinal anaesthesis
  - injection into CSF in subarach space
  - below spinal cord level ie >L2
  - onset action 1-2mins
  - duration 1-3hrs
  - specific gravity of LA & position of pt is important to prevent LA rising though spinal cord
  - SEs:
    - include hypotension; ↓CO; resp depression 2nd to depression symp pathways & medullary centes
    - Rx with sympatomimetics eg ephedrine & metaraminol

Other Drugs with LA Properties

- ie membrane stabilising properties
- eg:
  - anticonvulsants – phenytoin, carbamazepine
  - atropine + hyoscine
  - antiarrhythmics – procainamide, quinidine, disopyramide
  - adrenaline

  - antihistamines – H1 antagonists eg cyclizine
  - analgesics – pethidine
  - barbituates – phenobarbitone
  - B-Blockers – propranolol
  - phenothiazines – chlorpromazine
- ∴ all above can potentially interact/additive effect with LA's

CNS Neurotransmitters

- over 40 diff types of CNS neurones which use neurotransmitters
  ↳classified based on neurotransmitter
- examples:
  - amino acids:
    - excitatory:
      - glutamate
      - aspartate
    - inhibitory:
      - γ-aminobutyric acid (GABA)
      - glycine
  - monoamines: NA, adrenaline, Dopamine, serotonin (5HT), histamine
  - ACh
  - neuroactive peptides:
    - opiods eg enkephalines & endorphins
    - gastrointestinal peptides eg substance P, Cholecystokinin (CCK)
    - hypothalamic releasing factors eg TRH, somatostatin
  - other hormones & peptides eg:
    - oxytocin
    - calcitonin
    - bradykinin
    - neuropeptide Y

ACh

- in PNS present at:
  - ANS:
    - all ganglia
    - PNS effector organs
    - SNS –
      - apocrine sweat glands
      - adrenal medulla (is the ganglia)
      - skeletal mm capillary beds
  - somatic ns:
    - NMJ
- CNS – diff conc in diff area's
  - high areas of conc:
    - reticular formation
    - basal ganglia
    - ant spinal roots
- in CNS ACh =
  - excitatory
  - involved in cognition, memory, conciousness, & motor control
- levels low in Huntington's & Alzheimer's

Monoamines

- Dopamine –
  - D1-D5 receptors
  - involved in:
    - motor control
    - behaviour
    - reward systems
    - endocrine control
  - high conc in:

        - basal ganglia
- NA:
    - excitatory
    - found in: hypothalamus & medullary centres
    - involved in:
        - central autonomic control
        - arousal
        - mood & reward systems
- serotonin (5HT):
    - extensive innervation of all parts of CNS
    - high conc in
        - midbrain – cortex
        - raphe nuclei of brainstem
    - big variety of receptors
        ↳7 types
    - may be excitatory or inhibitory
    - involved in:
        - cognition
        - behaviour
        - sleep-wake cycles
        - mood
        - vomit
        - pain – esp migraines
- ↑level of catecholamines & serotonin ⇒ CNS stimulation

Amino Acid Transmitters

- inhibitory amino acids:
    - GABA
    - glycine:
        - permissive effect on NMDA receptors (required for agonist glutamate to work)
        - transmitter at inhibitory interneurons esp brainstem + spinal cord
        - function to ↑Cl conductance
- GABA:
    - = major inhibitor in brain ie 20% all CBS synapses
    - also found in retina, presynaptic inhibition
    - different receptors:
        - $GABA_A$ – ligand gated Cl channel
            - agonist: benzo's
            - antagonist: flumazenil
        - $GABA_B$ – GPCR ⇒ ↓cAMP & ↑K conductance
            - agonist: baclofen
    - prevalent in:
        - spinal cord interneurons
        - cerebellum
        - hippocampus

        } impt inhibitory transmitter eg to prevent seizures
    - involved in:
        - motor control
        - spasticity
        - sleep/wakefulness
- excitatory amino acids (EAA)=
    - L-glutamate – **major** excitatory transmitter
        - mediates exitotoxicity ⇒ neuronal death in brain inj & stroke
        - eg MSG ⇒ excitatory ⇒ flushing & nausea

- aspartate = transmitter in cortical pyramidal cells & spiny stellate cells in visual cortex
  ↳present in all regions

Autoreceptors

- eg similar to presynaptic α2 receptors in sympathetic ns ⇒ negative feedback control of self
- in CNS:
  - NA transmission effected by:
    - ↓ release: agonist of muscarinic, opiod & DA receptors
    - ↑release: agonists β2 adrenergic, ACh on N receptors, ATII receptors
  - DA presynaptic autoreceptors which inhibit DA synthesis & release
    ↳∴ ↓firing of dopaminergic neurons
    ↳?involved in on/off phenomenon of L dopa in Parkinsons

Neurotransmitter Imbalances in Diseases

- simplistic view: monoamines balance ACh especially on
  - mood
  - motor control
  - thought processes
- depression:
  - ACh>NA & 5HT
  - ∴ SSRIs, TCAs, MAOIs all ↑levels of monoamines
- parkinson's:
  - Ach>DA
  - ∴ drugs either ↑DA levels or block ACh
- schizophrenia: DA>ACh
- Mania: Glutamate, NA, DA> ACh
- Dementia: all monoamines> ACh

General Anaesthesia

- GA drug = produces reversible state of unciousness with absence of pain sensation over entire body
- drugs need rapid onset of action and to be reversible
- usually
  - induced by injection of anaesthetic agent eg propofol or thiopentone
  - maintained by inhalational of a gas (nitrous oxide) mixed with volatile liquid eg halothane/sevoflurane

Stages of Anaesthesia

- 4 stages:
  - 1-2 = induction
    ↳stage 2 dangerous ∴ rapid induction to stage 3, with maintenance there
  - 3 = surgical anaesthesia
  - 4 = medullary paralysis

Stage 1 Analgesia

- beings with onset of anaesthetic administration
- lasts until LOC
- order of effects:
  - smell & pain ↓ed first
  - auditory or visual hallucinations
  - speech difficult
  - hearing last sense lost

Stage 2 Excitement

- varies greatly individuals
- depends on
  - amount & type of premeds
  - anaesthetic agent
  - levelof external stimuli
- most reflexs still present & exaggerated esp noise
- swallowing risk abolished ⇒ risk aspiration
- signs:
  - increase in:
    - autonomic activity
    - mm tone
    - eye movement
    - dilation of pupils
  - irreg breathing – uneven inhalation of anaesthetic
  - vomiting

Stage 3 Surg Anaesthesia

- surgery generally done in plane 2 – upper plane 3
- subdivided into 4 planes:
  - plane 1:
    - resp incr shallow & rapid until paralysis & requires assisted ventilation
  - plane 2:
    - loss of reflexs in cephalocaudal direction
    - conjunctival reflex lost
    - pupil constrict ⇒ reaction to light lost ⇒ dilate
    - gag & laryngeal reflexs lost
  - plane 3:
    - ↓mm tone – need flaccid abdo wall for surgery
    - ↓body temp: skin cold, wet & pale
  - plane 4: ↓ing bp & weaker pulse

Stage 4 – Medullary Paralysis

- toxic stage
- impending overdose, resp arrest & vasomotor collapse
- artificial resp required to reverse this stage

Mechanisms of Action of GA's

- characteristics of a GA:
  - loss of conscious awareness
  - loss of response to noxious stimuli
  - reversibilty
- assumed no one anaesthetic receptor
- any GA has narrow band of conc at which LOC

Targets for GA Actions

- many theories – no completely proven mechanism
- CNS anatomical sites of action of GA drugs:
  - brain:
    - primary target = sensory pathways in thalamus & cortex ⇒ potentiation of sleep & LOC
    - hippocampus/limbic system ⇒ amnesia of GA
  - spinal cord:
    - multiple molecular targets in spinal cord ⇒ immobility

  ↳ halogenated volatiles have greater influence on spinal cord compared to IV agents

Outdated Theories Of GA MOA

Unified Lipid Theory

- 19th Century: Overton & Meyer described linear relationship of potency of anaesthetic effect and lipid solubility of GA drug

  ↳ie very lipid soluble = very potent
- this held true for multiple agents with v diff structure ∴ theory that non specific mechanism of GA must be true
- cell membrane & lipophilc area in drug structure thought to be interaction

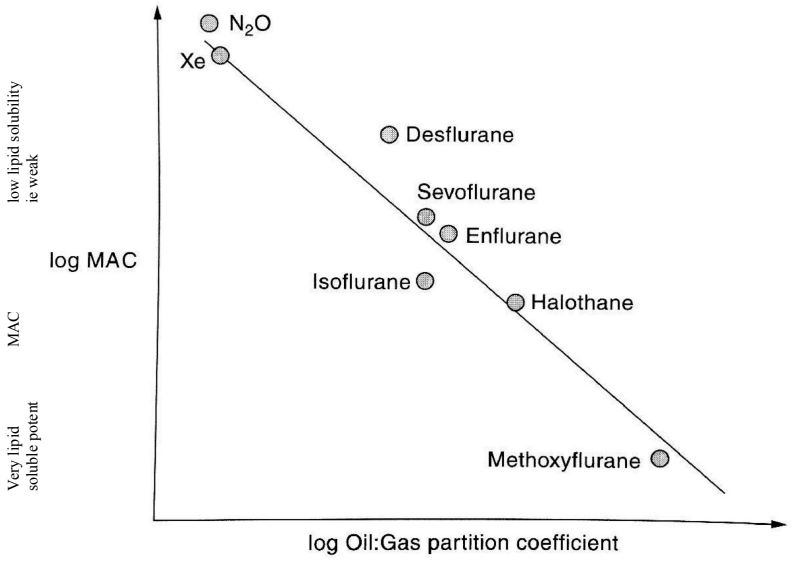


Figure 8.1. Straight line relationship between MAC and an index of lipid solubility logarithmic scales).

- problems with this theory:
  - ketamine = extreme outlier (in terms of linear relationship)
  - stereoisomers R-etomidate & S-etomidate have identical lipid solubility but only R-etomidate has GA properties

Critical Volume Theory

- several potential lipophilic site in cell membrane:
  - lipid bilayer
  - annular lipids surrounding ionic channel
- theory that:
  - agents could penetrate bilayer
  - alter molecular arrangement of phospholipids
  - ⇒ expansion of membrane
  - ⇒ disruption of function of membrane spanning ionic channels
- calculations = volume of anaesthetic agent required to expand membrane ⇒ ∴ critical volume hypothesis
- to disprove this theory:
  - ↑1deg C temp ⇒ same ↑thickness of membrane seen with volatiles but no GA

Perturbation Theory

- GA agents act at specific sites
- composition of phospholipids in immediate vicinity of ion channel is diff from general lipid bilayer
- GA agent act on annular lipids ⇒ disruption of specific ion channels

Modern Protein-Receptor Theories

- based on protein-receptor interactions
- correlation between potency & lipid solubility reflects lipophilic nature of protein based binding sites
- ligand gated ion channels are most sensitive to GA agents
  ↳ voltage gated channels much less so
- effects occur at excitatory & inhibitory channels & their receptors:
  - excitatory neurotransmitters:
    - neuronal nicotinic ACh
    - NMDA
    - (5HT)
    - (glutamate)
  - inhibitory neurotransmitters:
    - $GABA_A$
    - glycine

Table 8.1. General anaesthetic effects at central receptors.

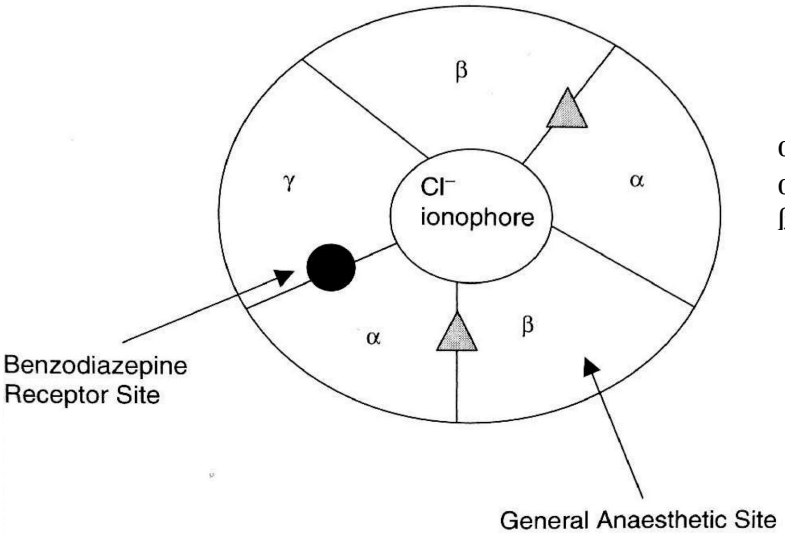
	Inhibitory Neurotransmitters		Excitatory Neurotransmitters	
	$GABA_A$	Glycine	NMDA	Neuronal nACh
propofol	++++	++	0	–
thiopental	+++++	++	0	–
R-etomidate	+++++	0	0	0
S-etomidate	0	0	0	0
Ketamine	0	0	–	0
Isoflurane	++++	+++	0	–
Nitrous Oxide	0	0	–	0
Xenon	0	0	–	0

+: enhances effect of neurotransmitter; –: reduces effect of neurotransmitter; 0: no effect on neurotransmitter. nACh: central nicotinic acetylcholine receptor.

$GABA_A$ Receptor

- = pentameric family of ligand gated ion channel receptors
  ↳nicotinic Ach receptor also same kind
- 30 types of GABAA receptor each with diff subunit composition:
  - ß2 & ß3 subunits – most sensitive to etomidate

  - ß1 – less so
- subunits:
  - α x2
  - ß x2
  - γ



αγ = Benzo site
αß = GABA site (endogenous)
ß = barbiturate site

Figure 8.2. The $GABA_A$ receptor.
The $GABA_A$ Receptor Complex, from above. The grey triangles show the two agonist sites for gamma amino butyric acid (GABA). Diazepam, temazepam and midazolam are agonists and flumazenil is an antagonist at the benzodiazepine site. Propofol, etomidate, barbiturates and halogenated volatile agents are agonists at the general anaesthetic site. Both sites produce positive allosteric modulation.

- eg etomidate action at GA site:
  - pure R-etoimdate = active
  - pure S-etomidate = clinically inactive ie shows x30 less activiy
- certain GA agents at $GABA_A$ ⇒ ↑ed channel opening time ⇒ ↑Cl entry to cell ⇒ ↑hyperpolarisation of cell ↳etomidate, barbituates, propofol, volatiles (see table)

$GABA_B$ Receptor

- metabotropic receptor ie GPCR ⇒ ↑ed K conductance
- made of subunits

Glycine Receptor

- present in brain & spinal cord
- inhibitory
- assoc with Cl channel similar to $GABA_A$
- volatiles specifically very active here & all potentiate –ve effects of this receptor

NMDA Receptor

- neurosignalling as ↓ed by inhbiting excitatory pathways (predominantly glutamate mediated)
- = cation channel, but permits passage of calcium
- located in neurons predominantly post synaptically
  ↳ but also though to be presynaptic
- NMDA receptor involved in long term signal potentiation associated with learning and memory
- receptor function:
  - glycine:
    - binds to receptor
    - essential for receptor normal function
  - agonist = **glutamate** which binds (in presence of glycine) ⇒ opening of channel
  - Mg modulates channel:
    - at normal membrane will block channel
    - partial depolarisation of surrounding membrane will nullify any Mg effect

- other blockers (non-competitive) eg ketamine + phencyclidine – bind to other sites within channel

- ∴ another target for GA agents
- this mechanism is generally less sensitive than $GABA_A$ mechanism
  ↳eg GA agents such as barbituates less potent at this receptor compared to $GABA_A$

Other possible Targets

- K channels – 2 pore domain channels
  - opening of these mediates effects of some volatile GAs
- glycine receptrs
- cyclic nucleotide-gated cation channels
- presynaptic Na channels

Glutamate

- = main excitatory transmitter in brain & spinal cord
  ↳ 75% of all excitatory action
- acts on 2 types of receptors:
  - metabotropic – G protein linked ⇒
    - ↑intracellular IP3 + DAG or
    - ↓cAMP
  - ionotropic – ligand gated ion channels
    - 3 types of receptor:
      - Kainate
      - AMPA

      ↳both =
        - simple ion channels which ↑Na influx & ↑K efflux
        - found in glia & neurons
      - NMDA – see prev

By Adam Hollingworth

Intravenous Induction Anaesthetics

- = agent which will induce loss of consciousness in 1 arm-brain circulation time
- groups of agents:
  - barbituates introduced in 1930's:
    - hexobarbitone – 1st
    - thiopental
    - methohexitone
  - non-barbituates –
    - propofo
    - ketamine
    - etomidate
  - midazolam – actually a benzo but has benefits & common adjunct
- ideal IV anaesthetics agent:
  - rapid onset ie mainly unionised at physiological pH
  - high lipid solubility
  - rapid recovery with no accumulation during prolonged infusion
  - analgesia at sub anaesthetic concentrations
  - minimal CVS & resp depression
  - no emetic effects
  - no pain on injection
  - no excitation or emergenc phenomena
  - no interaction with other agents
  - safe following inadvertent arterial injection
  - no toxic effects
  - no histamine release
  - no hypersensitivity reactions
  - water soluble formulation
  - long shelf life at room temp
  - amnesic effects
  - ↓amount of inhalational agent required
  - no risk of expolsion
- disadvantages of current IV anaesthetics:
  - minimal mm relaxation & analgesic properties
  - subject to liver & renal excretion
  - common hypersensitivity reactions
  - tissue reactions if extravasation
  - hypotension/laryngospasm & resp failure a risk

Pharmacokinetics

- high lipid solubility ⇒ high potency & rapid onset
- short duration of action as drug quickly redistributed into fat deposits
- 2 compartment distribution of drug:
  - obese people have shorter effect of single IV dose
- saturation of fat ⇒ prolonged action of drug as drug slow release back into circulation

Table 8.3. Pharmacokinetics of some intravenous anaesthetics.

	Dose ($mg.kg^{-1}$)	Volume of distribution ($l.kg^{-1}$)	Clearance ($ml.kg^{-1}.min^{-1}$)	Elimination half-life (h)	Protein binding (%)	Metabolites
Thiopental	3–7	2.5	3.5	6–15	80	active
Methohexitone	1.0–1.5	2.0	11	3–5	60	minimal activity
Propofol	1–2	4.0	30–60	5–12	98	inactive
Ketamine	1–2	3.0	17	2	25	active
Etomidate	0.3	3.0	10–20	1–4	75	inactive

Pharmaceutics

- 2 problems:
  - need high lipid solubility ⇒ to cross bbb
  - water soluble to be formulated as a solution for safe IV injection
- ∴ formulated as oil in water emulsions (milk)
- propofol in soya oil/egg lecithin/glycerol emulsion

Table 8.4. Pharmacological properties of some intravenous anaesthetics.

	Thiopental	Methohexitone	Propofol	Ketamine	Etomidate
BP	↓	↓	↓↓	↑	→
CO	↓	↓	↓↓	↑	→
HR	↑	↑	↓→	↑	→
SVR	↑↓	↑↓	↓↓	→	→
RR	↓	↓	↓	↑	↓
ICP	↓	↓	↓	↑	→
IOP	↓	↓	↓	↑	→
Pain on injection	no	yes	yes	no	yes
Nausea and vomiting	no	no	? reduced	yes	yes

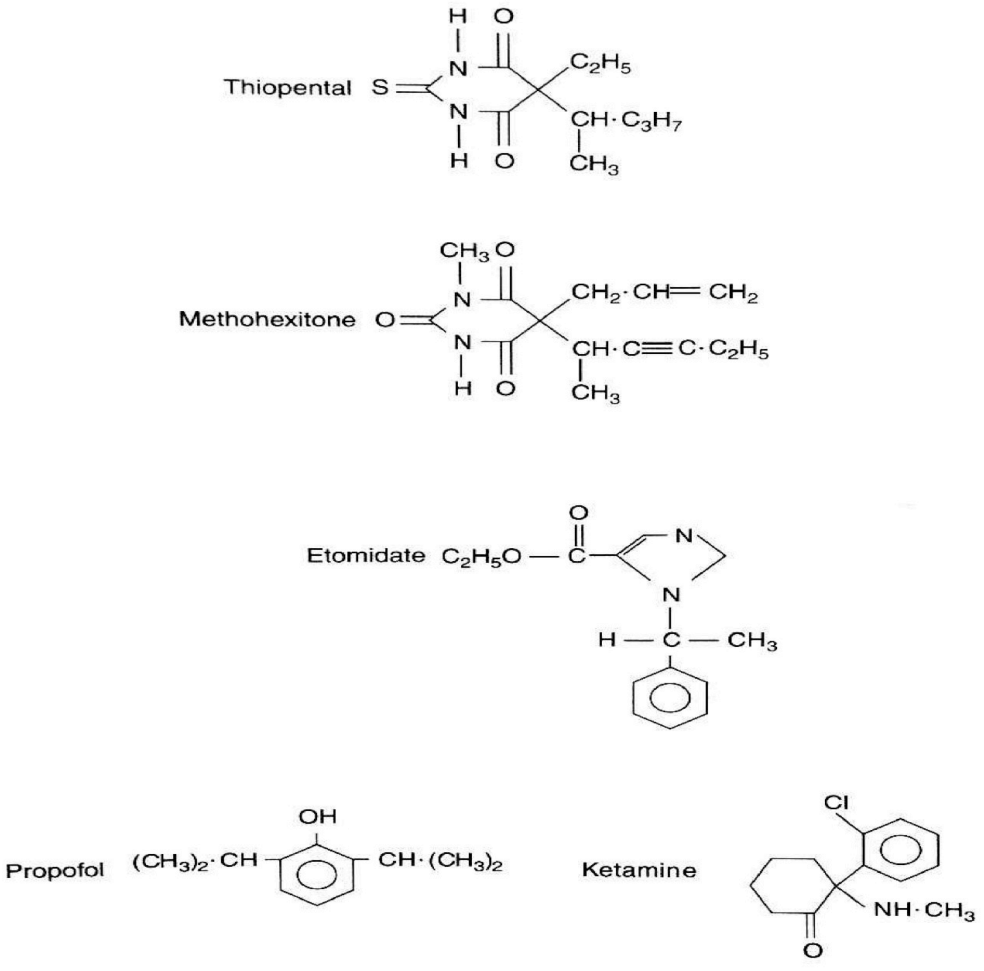


Figure 8.6. Chemical structure of some intravenous anaesthetics.

Barbituates

- urea + malonic acid condensed to form barbituric acid
- barbituric acid ⇒ oxybarbiturates
- oxybarbituates: oxygen is replaced by sulphur at C2 ⇒ thiobarbituates ⇒ ↑↑lipid solubility

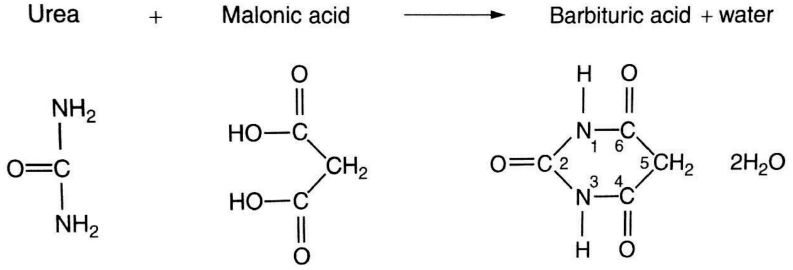


Figure 8.3. Formation of barbituric acid.

- barbituates:
  - not readily soluble in water at neutral pH
  - solubility depends on transformation form keto to enol form
    - ↳= tautomerism
    - ↳occurs most easily in alkaline solutions
- thiobarbituates:
  - very lipid soluble
  - highly protein bound
  - completely metabolised in liver
- oxybarbituates:
  - less lipid soluble
  - less protein bound
  - some excreted unchanged in urine

Table 8.2. Lipid solubility and protein binding of a few barbiturates.

	Type	Lipid solubility	Protein binding (%)
Thiopental	Thio	+++++	80
Pentobarbitone	Oxy	+++	40
Phenobarbitone	Oxy	+	10

Thiopentone

- CNS depressant produces hypnosis & anaesthesia without analgesia
- combine with mm relaxant & analgesia

Chemical

- =sulphur analogue (on C2) of the oxybarbituate pentobarbitone

Presentation

- formulated as a sodium salt
- presented as pale yellow powder
- vial contains unique additives to improve solubility of reconstituted solution:
  - sodium carbonate (Na2Co3 6%by weight):
    - reacts with water ⇒ strong alkaline solution (pH11)
      - ↳favours water soluble enol form

$$Na_2Co_3 + H_20 \Rightarrow NaHCO_3 + Na^+ + OH^-$$

  - nitrogen – instead of air:
    - CO2 in air would react with water ⇒ bicarbonate & H ions ⇒ less alkaline solution

- reconstituted to 2.5% solution which stable for days due to bacteriostatic alkaline pH

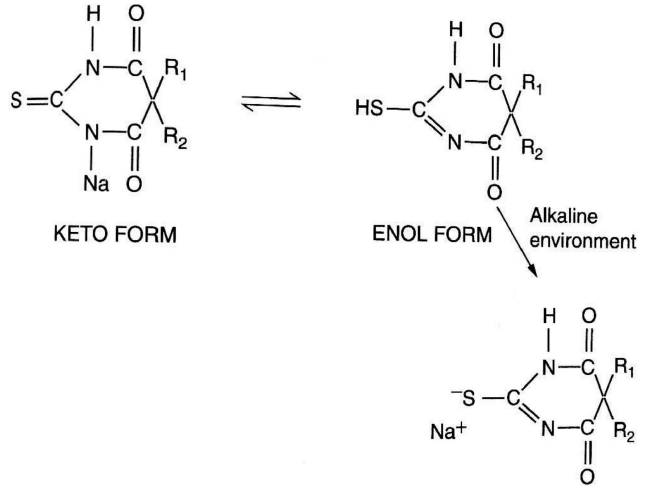


Figure 8.4. Keto-enol transformation of barbiturates – tautomerism. Alkaline solutions favour the water-soluble enol form.

MOA

- suppression of RAS

Pharmacokinetics

D

- pKa 7.6 ⇒ 60% unionised at pH 7.4
- 80% drug PPB

↳∴ unbound drug = 20% & of that 60% unionised = 12% overall unbound & unionised active drug

- despite small 12% still has rapid onset due to
  - high lipid solubility
  - large proportion of CO to brain
- critically ill pts demonstrate even faster onset due to:
  - acidotic ⇒ ↑free drug
  - ↓PPB

  ↳∴ much large proportion active free drug ∴ need less induction agent
- other drugs which have high PPB can interact ⇒ ↑fraction free thiopentone

  ↳eg NSAIDs

M

- rapid emergence from single bolus dose due to redistribution – not metabolism
- tri exponential decline in serum concentration seen by redistribution to:
  - well perfused regions – brain, liver
  - muscle
  - skin

  ↳then metabolism
- metabolism:
  - hepatic oxidation ⇒
    - mostly active metabolites eg pentobarbitone
    - some inactive
- metabolic pathway displays zero-order kinetics ie easily saturated

E

Uses

- IV induction agent: single dose ⇒ rapid GA with 5-10min duration
- status epilepticus: anticonvulsant properties – continuous infusion can ⇒ isoelectric EEG

  ↳ie maximum reduction of cerebral O2 requirements

↳considered good induction drug in trauma: ?↓ICP, anti-seizure properties, ↓cerebral O2 requirements

Adverse Reactions

- CVS:
  - dose dependant ↓SVR, ↓SV ⇒ ↓CO
    ↳may provoke compensatory tachycardia
  - effects more common in pts which:
    - hypovolaemic
    - acidotic
    - ↓ed PPB
- resp:
  - dose dependant resp depression
  - +/- degree of laryngospasm & bronchospasm
- CNS:
  - ↓cerebral O2 consumption
  - ↓cerebral blood flow ⇒ ↓cerebral blood volume
  - ↓CSF pressure
  - @ very low dose = antanalgesic
  - prolonged fatigue & headache
- renal: ↓UO caused by:
  - ↑ed ADH release 2nd to CNS depression
  - ↓ed CO
- severe anaphylactic reactions – 1:20,000
- porphyria (via ↑DAVA synthase) –
  - can precipitate acute porphyric crisis ∴ absolutely contraindicated in porphyria pts
  - other at risk drugs:
    - other barbituates
    - etomidate
    - enflurane, halothane
    - cocaine, lidocaine, prilocaine
    - clonidine
    - metoclopramide
    - hyoscine
    - diclofenac
    - ranitidine
- other:
  - emergence delirium – excitability, confusion, hallucinations
  - during recovery - shivering & trembling

Intra-Arterial Injection

- 2.5% pH 10.5 thiopentol injected into arterial blood pH7.4 ⇒
  - tautomeric equilibrium moves (from enol) to keto form
  - ⇒ ↓water solubility ⇒ precipitation of thiopental crystals
  - crystals wedge in small end vessels ⇒ ischaemia & pain
- Rx immediately:
  - arterial injection of papaverine (opium alkaloid antispasmodic) or procaine
  - analgesia
  - sympathetic block of limb
  - anticoagulation
- when injected intra-vein: no precipitation due to continual dilution by more venous blood
- extra-vasation – very painful & may cause serious tissue necrosis due to alkaline nature

Methohexitone

- = methylated oxybarbiturate

- generally no longer available

Uses

- 1% solution 1-2mg/kg for induction
- used when excitatory phenomena were of little concern eg ECT

Effects

- similar pharmacological profile to thiopental:
  - rapid onset & offset
  - similar effects on CVS & hepatic systems
  - porphyric crisis

Differences from Thiopental

- could cause an excitatory phase prior to LOC:
  - muscle twitching
  - ↑tone
  - hiccupping
  - seizures – esp if prev Hx of epilepsy
- recovery faster due to ↑ed hepatic clearance
- less damaging if injected arterially or extravasation due to lower concentrations
- greater incidence of hypersensitivity reactions (although less severe)
- mostly inactive metabolites (hydroxyl-methohexitone)

Non Barbituates

Propofol

Chemical

- =phenolic derivative (2,6 di-iso-propyl-phenol)
- highly lipid soluble

Presentation

- 1% or 2% lipid water emulsion due to poor solubility in water
  ↳contains soya bean oil & purified egg phosphatide
- weak organic acid

MOA

- rapidly acting non barbiturate hypnotic
- formulated in an emulsion for IV use
- no analgesic properties
- MOA not known- ?CNS depression via GABA receptors

Pharmacokinetics

D

- pKa = 11 ⇒ almost entirely unionised at pH 7.4
- 98% bound to albumin
- Vd = 7 L/kg
  ↳ largest of all induction agents
- rapid onset of action – 40seconds
- duration of effect 3-5mins:
  - due to redistribution out of plasma into well perfused tissues
  - initial distribution phase faster than thiopentone

M

- majority liver metab +/- some extrahepatic metabolism
- split in metabolism:
  - 40% conjugated to glucuronide (direct)
  - 60% ⇒ quinol (intermediary step) then ⇒ glucoronide & sulphate

  ↳all metabolites inactive

E

- inactive metabolites all excreted in urine

- clearance exceeds hepatic blood flow suggesting some extra-hepatic metabolism
- T1/2 elim = 5-12 hrs
  ↳although figures quoted 24-60hrs due to slow release of propofol from fat
- context sensitive half life ↑s with prolong infusion

Uses

- induction & maintenance of GA
- sedation of ICU patients
- PSA

Adverse Reactions

- CVS effects:
  - ↓SVR ⇒ ↓bp (major effect)
  - ↓myocardial contractility & ↓sympathetic activity
  - reflex tachycardia is rare & in fact usually assoc with bradycardia esp if opiates co-administered
- resp:
  - depression ⇒ apnoea (common)
    - 1mg/kg = 10-20% apnoeic
    - 2-3mg/kg = 30-40% apneoic
  - depresses cough reflex & inhibits laryngospasm reflexs
- CNS:
  - excitatory effects - in 10%:
    - manifestation of subcortical excitatory-inhibitory centre imbalance
      ↳ie not cortical seizure activity
    - observed movements are dystonia with
      - chreiform elements
      - opisthotonos (= hyperextension & spasticity)
- GI:
  - may exhibit some anti-emetic properties
  - ?antagnoism of D2 receptor
- Pain – injection into small vein possible
  ↳can use small vessel or inject with lignocaine
- metabolic syndrome –
  - risk highest with prolonged infusion esp in children <16yrs
    - ?contraindicated <16yrs for ICU sedation
    - signs:
      - lipaemic serum: fat overload with hyperlipidaemia, fatty infiltration major organs
      - progressive metabolic acidosis
      - refractory bradycardia
- allergies:
  - egg allergies - unlikely:
    - pts allergic to egg are normally allergic to egg protein or albumin
    - egg component of propfol = lecithin (=a phosphatide)
  - soya bean allergy – unlikely:
    - again usually allergic to protein
    - all protein from soya bean oil has been removed
- Arterial injection – no issues except delayed onset
- other:
  - urine & hair may turn green

Cautions/Contraindications

- pain & thrombophlebitis on injection
- potential for abuse
- <16 ICU sedation

Interactions
- sedative effects of other CNS depressants ↑ed
- no other sig interactions

Dose
- IV dose 1-3mg/kg (4-5mg/kg in paeds)
- TCI plasma conc to maintain anaesthesia 4-8ug/ml
- PSA 0.5-2mg/kg

Ketamine
(also covered in analgesia section)
- has certain benefits over other GA/analgesic agents:
    - bronchodilator
    - minimal cardiovascular depression
    - minimal resp depression
    - amnesia

Chemical
- = phencyclidine derivative

Presentation
- presented either:
    - racemic mixture
    - single S- enantiomer – x2-3 more potent than R-enantiomer
- soluble in water forming an acidic solution – pH 3.5-5.5
- 3 concentrations available:
    - 10mg/ml
    - 50mg/ml
    - 100mg/ml

MOA
- non competitive NMDA receptor antagonist:
    - receptor opens in response to glutamate
    - ketamine blocks channel ⇒ analgesic effects
- at high doses: also binds to opiod μ (mu) & σ (sigma) receptors
- also effects on other receptors:
    - potent D2 partial agonist
    - dopamine reuptake inhibitor
    - NA reuptake inhibitor
    - muscarinic agonist
- produces dissociative anaesthesia
    ↳MOA of these hypnotic effects under debate

Pharmacokinetics
D
- plasma conc falls in bi-exponential fashion:
    - initial: distribution across lipid membranes
    - slower phase – hepatic metabolism
- least protein bound (PPB 25%)

M
- metab by P450 in liver:
    - demethylated ⇒ nor-ketamine (active) ⇒ gluronide metabolites (inactive)
    - nor-ketamine = 30% potency of ketamine
- frequent dosing ⇒ tolerance due to induction of hepatic enzymes

E
- conjugated metabolites excreted in urine

Uses
- GA – induction & maintenance
- analgesia

Side Effects
- CVS:
  - racemic mixture:
    - indirect SNS stimulation ⇒ ↑ed circulating adrenaline & NA
      ↳∴ see ↑HR, ↑CO, ↑bp ⇒ ↑myocardial O2 requirements
    - mild direct myocardial depression –
      - R enantiomer to higher degree than S
      - R enantiomer also blocks ATP sensitive K channels (S- does not)
        ↳impt in preconditioning to ↑risk myocardial ischaemia

    ↳overall indirect SNS over-shadows mild direct depression
  - no evidence of ↑ed risk of arrhythmias
- resp:
  - ↑RR
  - preserved laryngeal reflexes – although laryngospasm has been seen
  - ↑mm tone around jaw
    ↳ although patent airway usually maintained
  - bronchodilation
- CNS:
  - dissociative anaesthesia:
    - EEG shows dissociation between thalamocortical & limbic systems
    - α rhythm is replaced by θ (theta) and δ (delta)
  - intense analgesia & amnesia
  - anaesthesia takes > 1 arm-brain circulation time = about 90 secs post injection
  - emergence phenomena:
    - vivid, unpleasant dreams, hallucinations, delirium are possible
    - use benzo's
    - S ketamine – produces less intense emergence phenomena but does not alter frequency
    - less common in young & elderly and those with quite recovery area
  - ↑cerebral O2 consumption ⇒ ↑cerebral blood flow ⇒ ↑ICP
- MSK:
  - muscle jerking & movement of limbs
- GI:
  - hypersalivation – can use anticholinergic premed if required
  - PONV – more common than with propofol or thiopentone
- ↑intraocular pressure

Cautions/Contraindications
- caution in:
  - CVS disease- although tends to maintain or ↑CO
- crosses placenta:

Interactions
- additive effect with other sedatives incl benxo's, barbituates, opiates, alcohol

Dose
- induction dose:
  - IV = 1-2mg/kg
  - IM = 5-10mg/kg
- analgesia dose:
  - IV = 0.2-0.5mg/kg
- paeds dose for minor procedure:

- IM: 2-2.5mg/kg
- IV: 0.5mg-1mg/kg

Etomidate

Chemical

- =imidazole derivative and an ester
- withdrawn in parts of North America & Australia

Presentation

- prepared as 0.2% solution at pH 4.1
- contains 25% v/v propylene glycol ⇒ improve stability & ↓irritant properties on injection
- lipid formulation also available

Pharmacokinetics

D

- 75% bound to albumin
- actions terminated by rapid redistribution into tissues

M

- non-specific hepatic esterases (+/- P-ChE): hydrolyse etomidate ⇒ ethyl alcohol + carboxylic acid metabolite

E

- renal excretion

Adverse Reactions

- CVS:
  - least CVS disturbance of all IV induction agents
  - mild ↓SVR
  - unchanged myocardial O2 supply, contractility, bp
- hypersensitivity reactions:
  - least common of IV induction agents
  - histamine release is rare
- metabolic:
  - supresses adrenocortical function by inhibition of enzymes:
    - 11ß-hydroxylase
    - 17α-hydroxylase

    ↳ ⇒ ↓ed cortisol & aldosterone synthesis
  - clear assoc with ↑mortality in septic ICU pts and IV infusion
  - But single doses in otherwise well people probably of little significance
- other:
  - pain on injection in 25%
  - 20% epileptic activity on EEG
  - antiplatelet effects
  - PONV
  - porphyric crisis

Dose

- IV induction @ 0.3mg/kg

By Adam Hollingworth

Inhalational Anaesthetics

- gases or volatile liquids
- currently in use:
  - gases: nitrous oxide (N2O)
  - volatiles: isoflurane, halothane, sevoflurane, desflurane, enflurane
- not used but useful = xenon
- using inhalational agents have following chars:
  - complete anaesthesia ∴ abolish superficial & deep reflexs
  - controllable anaesthesia – depth can be varied quickly
  - lung function critical to administration & excretion
  - may not have analgesic action
  - rapid recovery with removal of drug
  - allergic reactions uncommon

Minimum Alveolar Concentration

- = measure of potency
- = minimum alveolar concentration at steady state that prevents reaction to a standard surgical stimulus (skin incision) in 50% of subjects at 1 atmosphere
- key measure of MAC is the partial pressure of the agent – hence why 1 atmosphere very impt
- is a noticed inverse correlation between lipid solubility and dose (MAC) (as prev discussed)

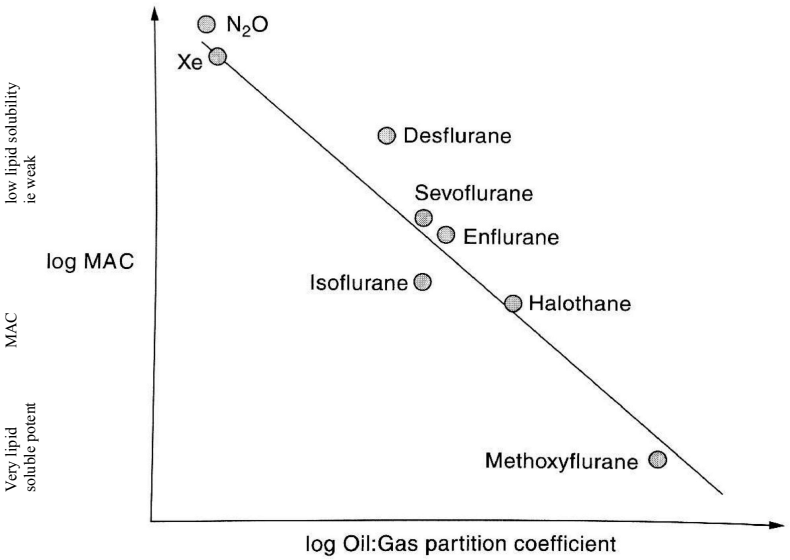


Figure 8.1. Straight line relationship between MAC and an index of lipid solubility logarithmic scales).

- physiological factors which affect MAC:

Table 8.5. Factors altering MAC.

Factors increasing MAC	Factors decreasing MAC
Infancy	During the neonatal period
	Increasing age
	Pregnancy
	Hypotension
Hyperthermia	Hypothermia
Hyperthyroidism	Hypothyroidism
Catecholamines and sympathomimetics	α_2-agonists
	Sedatives
Chronic opioid use	Acute opioid use
Chronic alcohol intake	Acute alcohol intake
Acute amphetamine intake	Chronic amphetamine intake
Hypernatraemia	Lithium

Ideal Inhaled Anaesthetic Agent

- physical:
  - stable to light & heat
  - inert when in contact with metal, rubber, soda lime
  - preservative free
  - not flammable or explosive
  - pleasant odour
  - atmospherically friendly
  - cheap
- biochemical:
  - high oil:gas partition coefficient ⇒ ∴ low MAC
  - low blood:gas partition coefficient
  - not metabolised
  - non-toxic
  - only affects CNS
  - not epileptogenic
  - some analgesic properties

Pharmacokinetics of Inhaled Anaesthetic Agents

- P_A = partial pressure of inhaled in alveoli
- P_a = partial pressure in arterial blood
- P_B= partial pressure in brain
- at steady state: $P_A = P_a = P_B$
  - ↳ ∴ P_A gives an indirect measure of P_B
- BUT for most inhaled agents steady state is rarely achieved due to lack of time:

< FRC><vessel rich><muscle><fat>

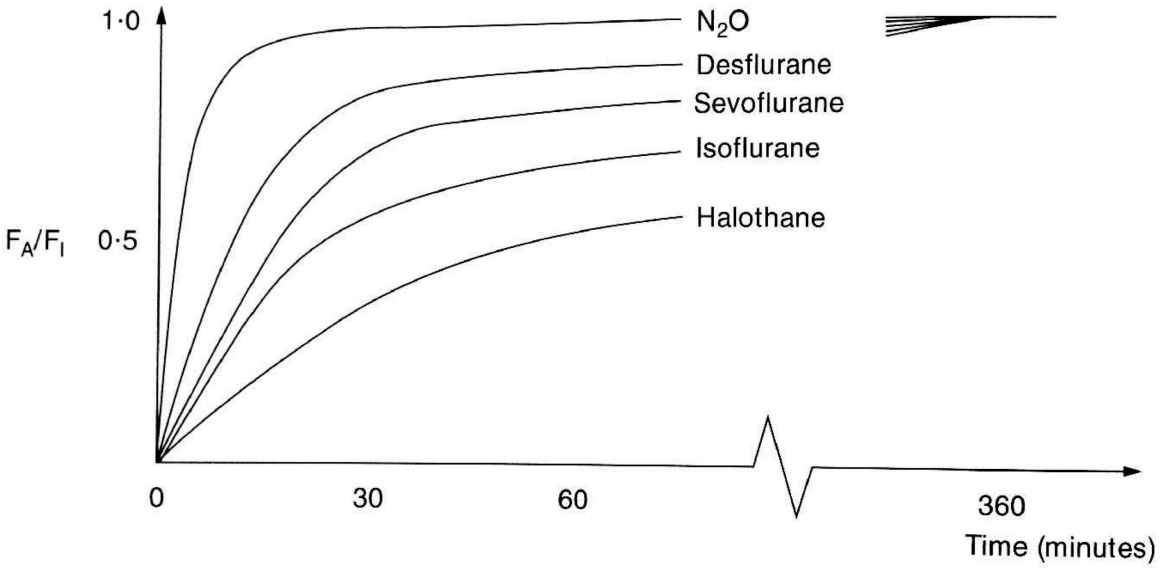


Figure 8.7. Different agents approach a F_A/F_I ratio of 1 at different rates. Agents with a low blood:gas partition coefficient reach equilibrium more rapidly. (F_A/F_I represents the ratio of alveolar concentration to inspired concentration.)

Factors Effecting Onset

- include:
  - MAC
  - alveolar ventilation
  - inspired concentration
  - cardiac output
  - blood:gas partition coefficient
  - concentration & second gas effect
  - V/Q mismatch
  - Anaesthetic circuit/soda lime
  - metabolism

1. MAC

- oil-gas partition coefficient = lipid solubility
- high lipid solubility ⇒ ↑potency
- ↑lipid solubility/potency = ↓MAC – as above an inverse relationship exists
- high lipid solubility delays recovery & onset:
  - agent forms depot in fat tissues = 2 compartment pharmacokinetic model
  - take hrs to be cleared – hangover effect

2. Alveolar Ventilation

(bigger effect on soluble agents than insoluble agents)

- ↑V_A ⇒ faster rise in P_A ⇒ quicker ↑P_B ⇒ quicker onset anaesthesia
- ↑size of FRC ⇒ effective dilution of inspired concentration ⇒ slower onset anaesthesia
  ↳and vice versa

3. Inspired Concentration

- high inspired conc ⇒ ↑rapid rise in P_A ⇒ rapid onset
- concentration is easily titratable by vaporiser control

4. Cardiac Output

(bigger effect on soluble agents than insoluble agents)

- high cardiac output ⇒ rapid flow of pulmonary blood ⇒ maintenance of conc gradient between alveolus and blood ⇒ ↑diffusion of agent out of alveolus ⇒ slower rising of P_A
  ↳and vice versa

- this problem overcome by modern inhaled agents which are less soluble in blood
  ↳ ∴ CO less impt

5. Blood Gas Partition Coefficient

- = ratio of the amount of anaesthetic in blood and gas when the 2 phases are of equal volume & pressure in equilibrium at 37 deg.
  - high solubility = high blood:gas p. coefficient
- high blood-gas partition coefficient ≈ longer time for equilibrium of gas to tissues
  - if agent is highly soluble ⇒ agent washed away from alveolar ⇒ longer time for alveolar partial pressure of agent to build in blood ∴ tissues might be receiving a lot of anaesthetic **but** it would be at a low partial pressure
    ↳ie it is the pp of anaesthetic in blood (& ∴ brain) which causes anaesthesia – **not** the content/conc
- low blood-gas partition coefficient ≈ faster equilibration of agent ∴ quick onset and offset time
- need to consider blood-gas & oil:gas partition coefficients together:
  - sevoflurane = ∴ an optimal agent
    - low blood & tissue solubility with high lipid solubility (potency)
  - NO = rapid but weak (low blood solubility but less lipid solubility).
    - Cannot produce anaesthesia alone except in hyperbaric conditions
  - ether = slow but potent (high blood solubility but very lipid soluble)

6. Concentration & Second Gas Effect

- covered under N2O

7. Metabolism

- most inhaled agents are eliminated without metabolism
- hepatic cytochrome P450 metabolises the C- (halogen) bond to release halogen ions (F-, Cl-, Br-)
  - the halogen ions have potential to cause hepatic or renal damage
  - diff bonds have diff stability ∴ metabolised by diff amounts:
    - stable & min metabolism = C-F bond
    - ↑ed metabolism:
      - C-Cl
      - C-Br
      - C-I

Table 8.6. Metabolism of inhaled anaesthetic agents.

Agent	Percentage metabolized	Metabolites
N_2O	<0.01	(N_2)
Halothane	20	Trifluoroacetic acid, Cl^-, Br^-
Sevoflurane	3.5	Inorganic and organic fluorides
		Compound A in the presence of soda lime and heat
		(Compound B, C, D and E)
Enflurane	2	Inorganic and organic fluorides
Isoflurane	0.2	Trifluroacetic acid and F^-
Desflurane	0.02	Trifluroacetic acid

8. V/Q Mismatch

- effects ability of agent to move from blood to alveolar gas to the anaesthetic circuit

Factors Effecting Offset

- anaesthetic factors:
  - length of surgery
  - circuit size
  - FGF
- volatile factors:
  - agent
  - solubility & biotransformation
  - blood fat:solubility
- patient factors:
  - alveolar ventilation
  - FRC size

< 1 > < 2 > < 3 >

- 1 =
  - circuit
  - FRC
  - V1
- 2 =
  - V2
  - V3
- 3 =
  - elimination phase

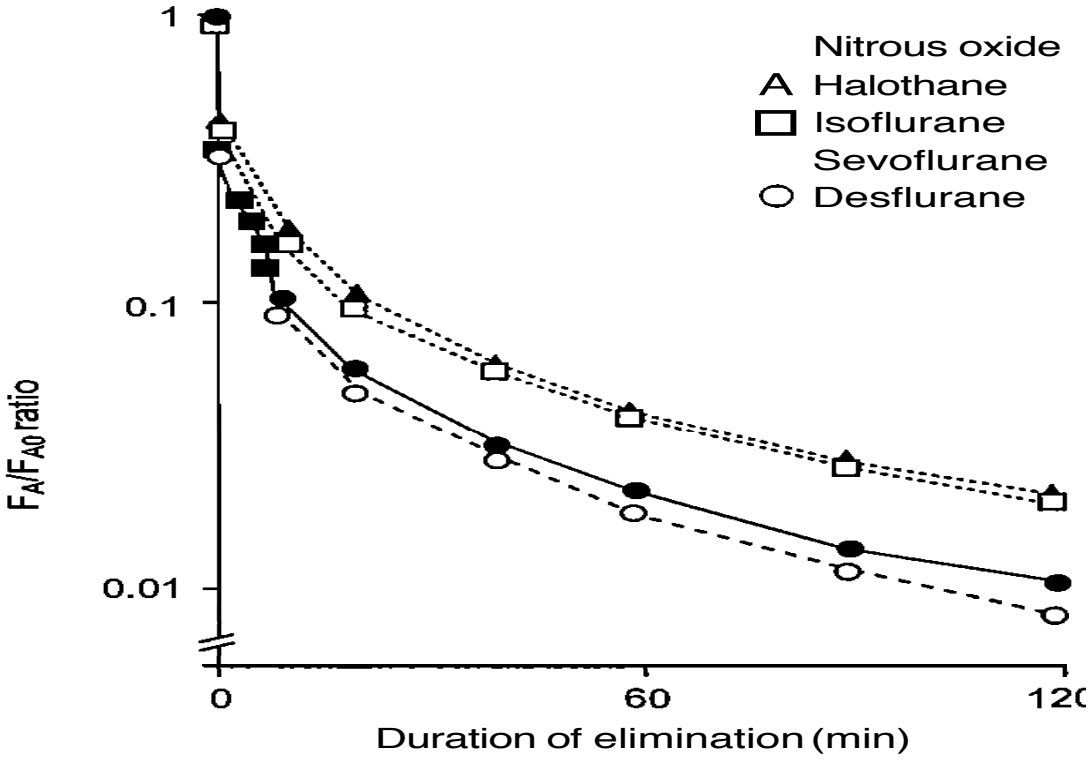


Fig. 5. Elimination of sevoflurane and other inhalational thetics over 120 minutes. F_A/F_{A0} is the ratio of end-tidal tration (F_A) to the F_A immediately before the begir elimination (F_{A0}) [from Yasuda et al.,[55] with permission

Adverse Effects & toxicity of GA

- common SEs:
  - post op convulsions
  - headache
  - N&V = 1:4
  - kidney/liver toxicity
  - hepatotoxicity – esp with chloroform & halothane
  - malignant hyperthermia
  - mm relaxation – including uterine

Drug Interactions

- anticoags eg hep/warf: stopped 6/24hrs prior to surg

- CNS depressants eg alcohol, antiHs, antianxiety, opiods, sedatives:
  - all ↑ CVS, resp & CNS depressant effects of GA
  - reduce GA dose as required
- antiayyhythmics: may ↑CVS depression & hypotension from GA
- Ca & β blockers: ↑CVS depression & ↑arrhythmias. ↓GA
- chronic steroids: adrenal suppression ⇒ ↓bp during surg due to lack stress response. ↑steroids
- inhibitors of CYP3A4 eg azole antifungals, protease inhibitors, macrolides:
  - inhibit metab of midazolam ⇒ ↓midaz dose
- drgs which affect bp or HR: interact with ketamine which ↑s bp & HR
- NMBs – all potentiate NMB's

Special Considerations

- young:
  - halothane & NO commonly used as incidence of hepatitis low in kids
  - neonates more sensitive to non-depolarising mm relaxing agents
- old:
  - ↑ed and longer drug effect
- preg & childbirth:
  - lipid solubility means drugs will cross placenta
  - careful monitoring of drugs
  - avoid GA if possible
  - epidural with lignocaine & fentanyl
- obesity:
  - obtaining desired depth anaesthesia & mm relaxation may be difficult
  - highly fat soluble anaesthetics should be avoided
- smoke: post op complications x6 more common
- high alcohol:
  - liver/stomach/pancreas problems
  - ↑liver enzymes ⇒ ↑drug doses required
  - alcohol withdrawal post GA

Premedication

- no longer essential as less use of ester & chloroform
- some uses still:
  - ↓anxiety ⇒ ↓GA doses needed eg opiates, benzos
  - ↓secretions eg salivary, gastric, bronchial eg anticholinergics atropine
  - ↓post op vomiting eg phenothiazines ie prochlorperzine, promthezine
  - prophylactic analgesia & sedation eg opiates, benzoes, phenothiazones

Premedication in Children

- agents used:
  - ketamine
  - midazolam
  - clonidine

  ↳ see specific section for detailed pharmacology

Midazolam

- traditional most used agent
- arguably gold standard but possible side effects:
  - paradoxical reactions –
    - <1%
    - = restless & agitated child
    - more common with IV dose
    - MOA not understood
- effects:

    - ↓anxiety
    - ↑cooperation
    - ↓negative behaviours
- advs:
    - rapid & reliable onset
    - min resp depression
    - anterograde amnesia
    - ↓emergence delirium
- dose:
    - oral/rectal: 0.5mg/kg (max 15mg)
    - IV 0.1mg/kg (max)
    - intranasal/sublingual 0.3mg/kg
- onset within 20mins

Clonidine

- = recent addition
- dose:
    - orally 5mcg/kg
    - intranasal 2mcg/kg
- well tolerated with predictable effect
- onset 45mins
- effect:
    - sedative & anxiolytic
    - analgesic properties
    - anaesthetic sparing properties
- use – especially if chronic pain

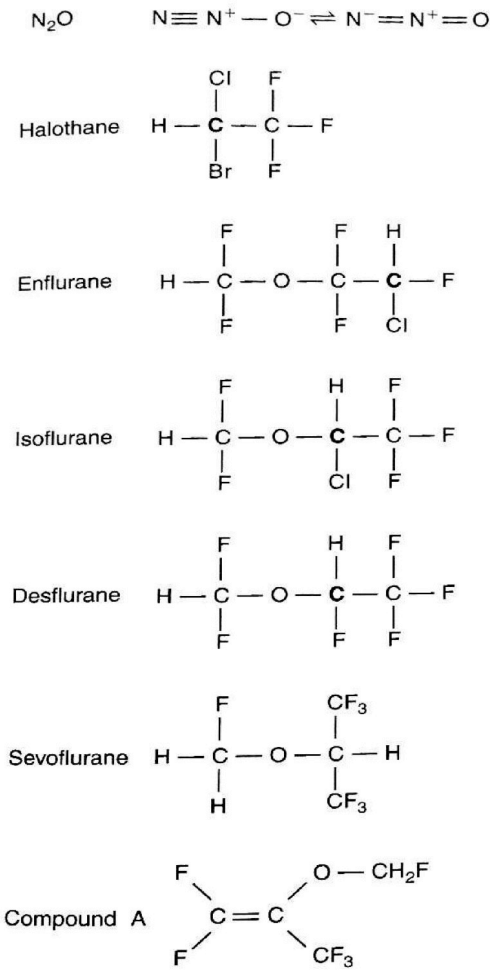
Ketamine

- dose:
    - oral 0.5mg/kg
    - IM 3mg/kg
    - IV 1 mg/kg
- advs:
    - sedation with no ↓resp drive
- disadv:
    - emergence delirium
    - prolonged recovery
    - salivation – use atropine 10-20mcg/kg orally
- generally used as second line after midaz/clonidine in older children with eg developmental delay who needs IM dose

Fentanyl

- oral transmucosal fentanyl 15-20mcg/kg
- onset of 15-20mins
- risk of ↓RR & N&V limit use

Individual Agents



= halogenated hydrocarbon

= halogenated methyl ether

= halogenated ethyl methyl ether

= fluorinated ethyl methyl ether

= polyflurinated isopropyl methyl ether

Figure 8.10. Structure of some inhaled anaesthetics and centre.

Table 8.7. Physiochemical properties of inhaled anaesthetics.

	Halothane	Isoflurane	Enflurane	Desflurane	Sevoflurane	N_2O	Xenon
MW	197.0	184.5	184.5	168.0	200.1	44.0	131.0
BP (°C)	50.2	48.5	56.5	23.5	58.5	−88.0	−108
SVP at 20°C (kPa)	32.3	33.2	23.3	89.2	22.7	5200	
MAC (%)	0.75	1.17	1.68	6.60	1.80	105	71.0
Blood:gas partition coefficient	2.40	1.40	1.80	0.42	0.70	0.47	0.14
Oil:gas partition coefficient	224	98	98	29	80	1.4	1.9
Odour	non-irritant, sweet	irritant	non-irritant	pungent	non-irritant	odourless	odourless

Table 8.8. Cardiovascular effects of inhaled anaesthetics.

	Halothane	Isoflurane	Enflurane	Desflurane	Sevoflurane
Contractility	↓↓↓	↓	↓↓	minimal	↓
Heart rate	↓↓	↑↑	↑	↑ (↑↑ > 1.5 MAC)	nil
Systemic vascular resistance	↓	↓↓	↓	↓↓	↓
Blood pressure	↓↓	↓↓	↓↓	↓↓	↓
Coronary steal syndrome	no	possibly	no	no	no
Splanchnic blood flow	↓	unchanged	↓	unchanged	unchanged
Sensitization to catecholamines	↑↑↑	nil	↑	nil	nil

Table 8.9. Respiratory effects of inhaled anaesthetics.

	Halothane	Isoflurane	Enflurane	Desflurane	Sevoflurane
Respiratory Rate	↑	↑↑	↑↑	↑↑	↑↑
Tidal volume	↓	↓↓	↓↓↓	↓↓	↓
$PaCO_2$	unchanged	↑↑	↑↑↑	↑↑	↑

Table 8.10. Other effects of inhaled anaesthetics.

	Halothane	Isoflurane	Enflurane	Desflurane	Sevoflurane
Cerebral blood flow	↑↑↑	↑ (nil if < 1 MAC)	↑	↑	↑
Cerebral O_2 requirement	↓	↓	↓	↓	↓
EEG	burst suppression	burst suppression	epileptiform activity (3 Hz spike and wave)	burst suppression	burst suppression
Effect on uterus	some relaxation	some relaxation	some relaxation	some relaxation	some relaxation
Potentiation of muscle relaxation	some	significant	significant	significant	significant
Analgesia	none	some	some	some	some

	MAC in oxygen/air[1] (%)			MAC in 67% N_2O (%)			BP (°C)	SVP (kPa)	Oil: gas part. coeff.	Blood: gas part. coeff.	MW	Bio trans. (%)
	1yr	40yr	80yr	1yr	40yr	80yr						
Halothane	0.95	0.75	0.58	0.47	0.27	0.10	50.2	32.5	224	2.3	197.4	25
Enflurane	2.08	1.63	1.27	1.03	0.58	0.22	56.5	22.9	96	1.91	184.5	3
Isoflurane	1.49	1.17	0.91	0.74	0.42	0.17	48.5	31.9	91	1.4	184.5	0.2
Sevoflurane	2.29	1.80	1.40	1.13	0.65	0.25	58.5	21.3	53	0.59	200	2.5
Desflurane	8.3	6.6	5.1	4.2	2.4	0.93	23.5	88.5	18.7	0.42	168	Minimal
Nitrous Oxide	133	104	81	NA	NA	NA	-88	5080	1.4	0.47	44	0
Xenon	92	72	57	NA	NA	NA	-107.1	5800	20	0.14	131.3	0

Characteristics that influence the choice of an agent

Agent	Useful	Problems
Halothane	Cheap Low pungency makes induction tolerable Bronchodilation	Cardiac depression Arrhythmias 'Halothane hepatiis' *
Isoflurane	Rapid onset and elimination Cardiac stability Little increase in ICP, marked reduction in $CMRO_2$	Pungent Tachycardia ± Coronary steal *
Enflurane	Few major problems	Seizure promotion Respiratory depression Product of metabolism toxic to renal tubules
Sevoflurane	Pleasant, rapid induction	Apnoea, laryngospasm more common than with halothane Compound A production Expensive
Desflurane	Very rapid elimination	Pungent Sympathetic stimulation at induction because of the above Requires special type of vaporiser Expensive

* Although hepatitis and coronary steal are *classically* associated with halothane and isoflurane, the problems are described with all inhalational agents.

Nitrous Oxide

- simple inorganic molecule N20
  ↳NB not NO (nitric oxide)
- used alongside volatile agents & in combo with O2 eg entonox (50:50)
- low solubility, low potency ∴ used at high concentrations
- has favourable physical properties (except high MAC)
- use is now limited due to concerns about interfering with DNA synthesis

Chemical

- manufactured by heating ammonium nitrate to 250 degC

$$NH_4NO_3 \Rightarrow N_2O + 2H_2O$$

- unless temp carefully controlled may see contaminents in gas:
  - NH3
  - N2
  - NO
  - NO2
  - HNO3
- contaminents are actively removed by passage through scrubbers, water, caustic soda
- non irritant with no odour

Storage

- N2O is stored as a liquid in French blue cylinders:
  - C = 450 litres
  - G = 9000 litres
- gauge pressure = 51 bar at 20degC
  ↳but unless all N2O is in gaseous phase gauge bears no relation to remaining content
- filling ratio = mass of N2O in cylinder/mass of water that cylinder could hold:

  - temperate regions = 0.75
  - tropical regions = 0.67 – reduced to avoid explosions as only stored as gas ∴ less efficient
- critical temp = 36.5
- critical pressure = 72bar

MOA

- 2 main actions:
  - analgesic action similar to opiods ?mediated by opiod receptors
  - anxiolytic action: ⇒ enhanced GABA mediated CNS depression

Pharmacokinetics

- inhaled & absorb by lungs
- very low potency
- low solubility in blood & tissues ∴ rapid onset and offset
- 100% excreted unchanged via lungs

Uses

- powerful analgesic
- useful anxiolytic
- weak anaesthetic

↳∴ other combined with other volatile anaethestics to enhance effects in major surgery

- eg entonox 50:50 O2:N20

Adverse Reactions

- respiratory:
  - small ↓ tidal volume
  - small ↑RR

  ↳∴ minute volume & PaCO2 unchanged
  - diffusion hypoxia – see later
- CVS:
  - mild direct myocardial depressant
  - mild indirect central SNS stim

  ↳∴ 2 effects counteract each other unless eg pt with heart failure who unable to ↑their sympathetic drive ⇒ depressant effects predominate
  - does not sensitise heart to catecholamines
- CNS:
  - ↑cerebral blood flow ∴ caution in pts with ↑ed ICP
-
  - risk of hypoxia:
    - at termination of gas administration rapid movement of N2O from circ into lungs
      ↳may dilute O2 in lungs = diffusion hypoxia
      ↳to avoid 3-5mins 100% O2 cover this period
  - post op nausea & vomit++
- gas filled spaces:
  - N2O causes rapid expansion of air filled spaces
  - mechanism same as diffusion hypoxia just using different membrane of diffusion
  - will effect: Pneumothorax, vascular air embolis, intestinal lumen expansion in obstruction/perf
- DNA damage:
  - N2O inhbits methionine synthetase:
    - directly
    - indirectly –
      - oxidises cobalt ion in vitamin B12
      - altered vit B12 inhibits methionine synthetase

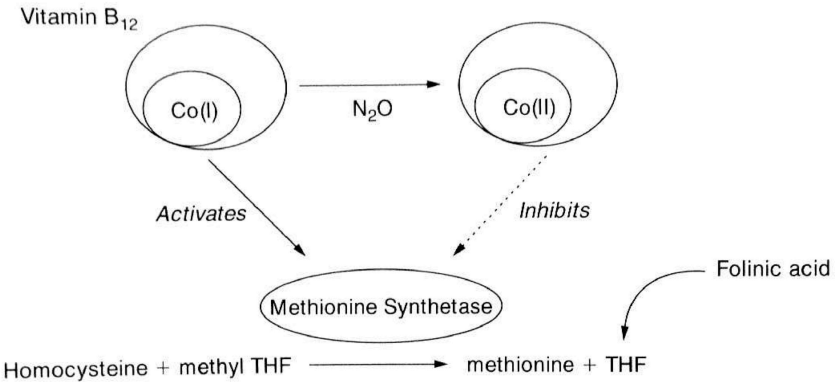


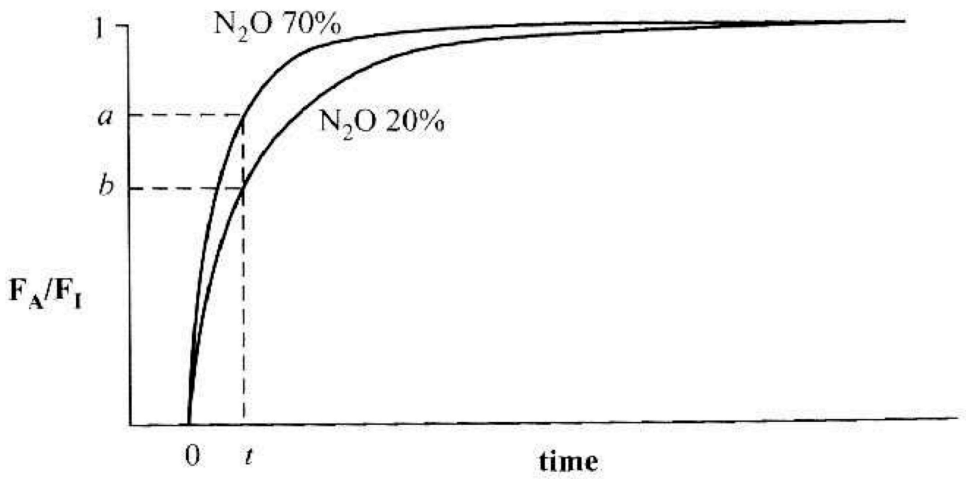
Figure 8.9. N_2O inhibits methionine synthetase by oxidizing cobalt (Co(I)). THF, tetrahydrofolate.

- methionine synthetase involved in synthesis of:
  - methioninethymidine
  - tetrahydrofolate (THF)
  - DNA
- length of exposure varies effect:
  - only few hours ⇒ megaloblastic bone marrow changes
  - days ⇒ agranulocytosis
- recovery effected by:
  - synthesis of new methionine synthase
  - addition of folinic acid supplementation
- environmental problem:
  - N2O concentrations >50ppm pose risk to healthcare staff and chronic exposure
    ↳unlikely in operating room with properly scavenged environment
    ↳seen in some dental surgeries
  - symptoms similar to subacute combined degeneration as seen with low B12 levels

- pregnancy:
  - teratogenic in rats but reversed with folinic acid
  - never demonstrated in humans but N2O not used in 1st trimester

Concentration effect

- = observed phenomenon of disproportionate rate of rise of alveolar fraction compared with inspired fraction when high high concentrations of N2O are inspired
- see a slower rate of rise with lower N2O concentrations inspired
- displayed on graph:



- effect only applies to N2O as is only agent used at sufficiently high conc
- various models (all with problems) used to explain phenomenon
- driving force:

- large gradient which high conc of N2O create
- assume >50% inspired conc:
  - large amounts of N2O absorbed into pulmon capillaries from alveoli mixture
    ↳ occurs despite low blood:gas coefficient (=0.47)
  - ∴ in order for alveolar volume to remain constant: gas from conducting ariways sucked into alveoli ⇒ delivering more N2O to alveoli for exchange
    ↳ sucking of gas from conducting airways = augmented alveolar ventilation
  - ⇒ higher conc of N2O in alveolar mix than would expect
- this model doesn't account for effects of other gases eg N2 leaving body

Second Gas Effect

- =direct result of concentration effect
- describes effect on a second gas used alongside N20 eg oxygen or volatile agent
- rapid uptake of N2O & augmented alveolar ventilation ⇒ ↑ed concentration of the 2nd agent in the alveoli ⇒ ↓ed induction time

Diffusion Hypoxia

- occurs at the end of anaesthesia when N2O/O2 is replaced by air (N2/O2)
- = the reverse of the second gas effect/concentration effect
- process =
  - large volume of N2O returning to alveolar gas mix due to reverse of concentration gradients
  - N2O exceeds volume of N2 entering pulmon capillaries
  - ⇒ dilution of all alveolar gases by N2O

Cautions/Contraindications

- safe in pregnancy
- altered mental state
- recent scuba
- v cold conditions (<-6deg)
  ↳gases may seperate
- Severe pulmonary disease may alter elimination of NO

Interactions

- nil

Dose

- GA:
  - induction 70:30 N20:O2
  - maintenance 30:70 N20:O2
- obstetrics: entonox 50:50
- dental procedures 25:75% mixture

Entonox

- = 50:50 mixture of N2O & O2
- 2 gases effectively dissolve into each other
- they behave in way not predicted by their individual properties
  ↳= Poynting effect ie dissolution of gaseous O2 when bubbled thru liquid N2O, with vaporization of the liquid to form a gaseous 50% mixture of O2/N2O
- used for analgesia during labour & other painful procedures
- stored in French blue cylinders with white & blue checked shoulders:
  - cylinder sizes : G = 3,200; J = 6,400
  - 137 bar pressure
- pseudo-critical temp;
  - @117 bar = -7degC
  - below this temp will separate into constituent parts
  - pressures outside 117 ↓likelihood of separation of gases
  - pipeline pressure of 4.1 bar ⇒ pseudocritical temp = -30degC

- if using a cylinder in which gases have separated:
  - O2 will be delivered first
  - when O2 exhaused ⇒ ↑ing potency of mixture until 100% N2O
  ↳ ∴ should always mix cyclinder before use

Isoflurane

Chemical

- =halogenated ethyl methyl ether
- is a structural isomer of enflurane
- widely used to maintain anaesthesia

Pharmacokinetics

- 0.2% metabolised
- no products linked to toxicity

Pharmacodynamics

- toxicity:
  - presence of a –CHF2 group in its structure
    ↳also found in enflurane & desflurane
  - this may react with dry soda lime ⇒ carbon monoxide
  - this reported in circle systems where dry gas circulating over a weekend then use of isoflurane ⇒ release of carbon monoxide

Adverse Reactions

- resp:
  - causes depression of ventilation:
    - ↓minute volume
    - ↑PaCO2
    - ↑RR

    ↳order most to last: enflurane > isoflurane > halothane
  - upper airway irritability ∴ rarely used for induction:
    - pungent smell
    - coughing
    - breath holding
  - bronchodilation
- CVS:
  - main effect = ↓SVR:
    ↳ see reflex tachycardia – suggests barorecptor reflex intact
  - small ↓contractility ⇒ ↓mild CO
  - possible coronary steal – although new evidence suggests unlikely:
    - = normally responsive coronary arterioles are dilated
    - diseased vessels and ischaemic areas are unresponsive to dilatatory effects of agent
    - ∴ blood diverted away from ischaemic areas ⇒ ↑ing ischaemia
  - may be protective against ischaemia - effects of ATP sensitive K channels
- CNS:
  - produces best balance of ↓ed cerebral O2 requirements & minimal ↑in cerebral blood flow
    ↳compared to all volatiles
  - at concentrations up to 1MAC cerebral autoregulation is preserved
  - antiseizure – opposite to enflurane

Sevoflurane

Chemical

- =polyfluorinated isopropyl methyl ether
- achiral –
  ↳ all other volatiles have chiral centre

Presentation

- during storage where concentration of added water < 100ppm is susceptible to attack by Lewis Acids
  - attack at ether and/or halogen bonds
  - release highly toxic hydrofluoric acid (HF)
- Lewis acids = any substance that can accept an electron pair
  ↳includes many metal oxides but also H+
  ↳glass = source of Lewis acids
- HF capable of corroding glass ⇒ exposure of sevo to further Lewis acids
- ∴ sevoflurane
  - (wet) formation is:
    - formulated with 300ppm water acting as a Lewis acid inhibitor
    - stored in polyethylene napthalate bottles (not glass)
  - (dry) formulation:
    - 13-ppm water
    - aluminium bottle lined with an epoxy-phenolic resin lacquer

Manufacture

- one pot method:
  - all ingrediants are added to produce sevoflurane
  - water added to 300ppm
- chloro-fluoro method:
  - basic molecular architecture is manufactured but with chorine attached
  - chlorine then substituted out for fluorine

Pharmacokinetics

- favourable combination of:
  - low blood:gas partition coefficient (0.57)
  - pleasant odour
  - low MAC (1.8)

M

- 2.5% biotransformation
- hepatic metabolism P450 (2E1)
- occurs to greater extent than all other commonly used volatile agents except halothane
- metabolites produced:
  - hexa-fluoro-iso-pro-panol
  - inorganic F-
- inorganic F-:
  - seen to cause renal toxicity when high levels of if (>50umol/l) were created as a metabolite of meth-oxy-flurane (now an unsued volatile)
  - but not seen to be toxic when a metabolite of sevo even at those same high levels
    ↳ possible as sevo only metabolised in liver, whereas methoxyflurane was also metabolised in kidneys

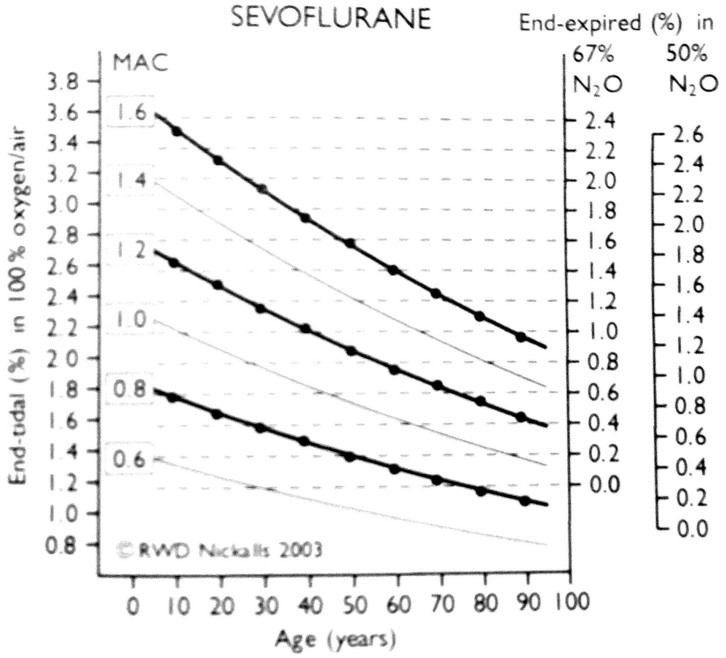
Toxicity

- when sevo used with carbon dioxide absorbants different compounds are created: A, B, C, D, E
- only compound A, B made in sufficient amounts to be analysed
- formation is favoured:
  - soda lime is wet
  - use of absorbants made of potassium hydroxide (rather than sodium hydroxide)
- compound creation:
  - releases heat
  - consumes sevoflurane
- compound A:
  - production:
    - directly related to

        - sevo concentrations
        - absorbant temp
    - inversely related to fresh gas flow rate (FGF)
- lethal concentration in
    - 50% rats = 300-400ppm after 3hrs exposure
    - suggested in humans = 150-200ppm
        - recent work suggest flow 0.25l/min for 5 hrs = compound A peak 20ppm & norm renal function
        - nevertheless manufacture recommends sevo not used in FGF <1L/min and for no longer than 2 MAC hours
            ↳?? for anaesthetic >2hrs FGF should be at least 2L/min

Mechanism of Action

- resp:
    - predictable dose dependant ↓minute volume ⇒ ↑PaCO2
    - pleasant odour ∴ good for induction
- CVS:
    - ↓SVR
    - unchanged HR (baroreflex abolished)
    ↳ ∴ ⇒ ↓bp
    - contractility unaffected
    - heart not sensitised to catecholamines
    - ↓coronary circulation resistance
- CNS:
    - ↓cerebral vasc resistance
    - compared to halothane: children may exhibit higher incidence of post op agitation/delerium



Halothane

Chemical

- = halogenated hydrocardon
- chars:
    - unstable when exposed to light
    - corrodes certain metals
    - dissolves into rubber
    - may leach out into breathing circuts after vaporizer is turned off

Presentation

- stored with 0.01% thymol to prevent liberation of free bromine

Pharmacokinetics

M

- metabolism can be ocidative or reductive:
  - oxidative – under norm conditions 25% via hepatic P450:
    - metabolites =
      - trifluoro-acetic acids
      - Br-
      - Cl-
  - reductive – predominate when liver becomes hypoxic
    - reductive metabolites including F-
    - metabolites are toxic but thought not to be cause of halothane hepatitis

Adverse Reactions

- resp:
  - ↓Vt ⇒ ↓MV
  - blunted response to hypoxia & hypercarbia esp with MAC >1
  - ↓bronchiolar tone ∴ usueful in asthmatics
  - useful for induction – sweet non-irritant odour
- CVS:
  - ↑vagal tone ⇒↓SAN & AVN activity ∴ bradycardia
    ↳ use node blocking drugs with caution eg CCB, BB's
  - direct myocardial depressant ⇒ ↓CO
  - sensitises heart to catecholamines ⇒ ↑chance arrhythmias (more than other agents)
    ↳ low dose of adrenaline with LA (<100mcg/10mins)
  - ↓SVR ⇒ ↑cutaneous blood flow
    ↳↓flow to liver/kidney 2nd to ↓CO
- CNS:
  - ↑cerebral blood flow – more than any other agent ⇒ significant ↑ICP >0.6MAC
  - cerebral O2 requirements ↓ed

Toxicity

- hepatic damage in 2 diff forms:
  - reversible form =
    - often subclinical
    - ↑transaminases
    - probably due to hepatic hypoxia
  - fulminant hepatic necrosis (halothane hepatitis)
    - trifluoro-acetyl chloride (TFA's) (oxidative metabolite) – principle mediator:
      - may behave as a hapten
      - binds covalently with hepatic proteins
      - induces antibody formation
    - diagnosis of exclusion
    - Risk:
      - adults = 1:2,500 to 35,000
      - children = 1:80,000 to 200,000
    - RFs:
      - multiple exposures
      - obesity
      - middle age
      - female
    - mortality = 50-75%

- in theory all other volatiles could cause similar reactions but they are significantly less metabolised ∴ much less risk
- enflurane only other drugs with case reports of similar

Cautions

- avoid if
  - administered in last 3 months
  - Hx of prev reaction
  - pre-exisitnig liver disease

Enflurane

Chemical

- halogenated methyl ether
- structural isomer of isoflurane
- ↓ing use due to newer agents with better profiles

Pharmacokinetics

M

- 3% metabolised by P450
- F- ions are produced but rarely in significant level (>40umol/L) to produce reversible nephropathy

Adverse Reactions

- resp:
  - ↓ventilation ⇒ ↓MV ⇒ ↑PaCO2
    ↳ more than any other agent
  - blunt response to ↓O2 & ↑PaCO2
- CVS:
  - ↑HR vs
  - ↓contractility + (slight) ↓SVR ⇒ ↓CO ⇒ ↓bp
  - no sensitisation to catecholamines
- CNS:
  - high MAC & hypocarbia ⇒ 3Hz spike wand EEG waveform consistent with seizure
    ↳∴ generally avoided in epileptics
  - ↑CBF & ↑ICP – less than halothane but more than isoflurane
  - ↑CSF production, ↓CSF absorption ⇒ ↑ICP

Toxicity

- as prev – can see hepatitis akin to halothane but v uncommon

Desflurane

Chemical

- = fluorinated ethyl methyl ether
- slow to be introduced due to difficulties in preparation & administration
- boiling point of 23.5C ∴ extremely volatile and dangerous to administer conventional vaporiser
- administered instead via Tec 6 vaporiser = heats des to 39C at 2 atmospheres
- low blood:gas partition coefficient ensures rapif onset & offset
- low potency means need high concentrations – MAC 6.6%

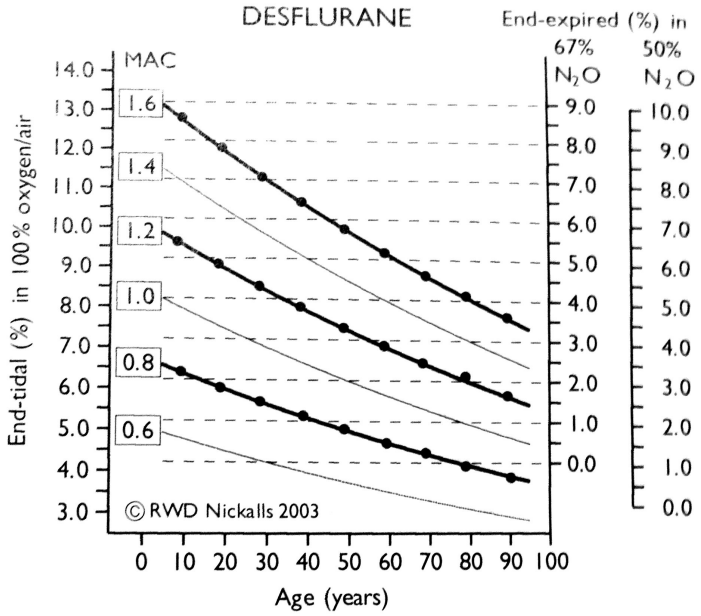
Pharmacokinetics

- only 0.02% is metabolised ∴ minimal toxicty

Adverse Reactions

- resp:
  - similar effects to other agents – slightly less than isoflurane & enflurane
  - pungent odour that causes coughing & breath holding ∴ not suitable for induction
- CVS:
  - similar to isoflurane

- can cause CVS stimulation ie ↑HR, ↑bp – esp >1 MAC
  ↳ caution if Hx IHD
- does not sensitise to catecholamines
- vasc resistance to cerebral & coronary circ is ↓ed



Xenon

Chemical

- = inert odourless gas
- no occupational or environmental hazards
- makes up 0.0000087% of atmosphere
- MAC = 71% & very low blood gas partition coefficient (0.14)
  ↳ ∴ onset & offset = quickest of all agents
- produced by fractional distillation of air at x2000 cost of producing N2O

Pharmacokinetics

- not metabolised – eliminated via lungs

Adverse Reactions

- resp:
  - MV remains constant:
    - ↓RR
    - ↑Vt
  - compared to N2O; xenon has:
    - x3 density
    - x1.5 viscocity

    ↳ but clinical sig of ↑ed airway resistance is unlikely even at high concentrations
  - does not display diffusion hypoxia – even though used at high concs
- CVS:
  - no effect on contractility
  - small ↓ in HR
- CNS:
  - ↑ed cerebral blood flow – not recommended for neurosurg
  - may be used to enhance CT images of brain
  - 133Xenon – used to measure cerebral blood flow
- analgesia – has significant analgesic properties via NMDA receptor

Non Anaesthetic Medical Gases

Oxygen

see respiratory.pages under physiology section

Helium

- = inert gas ∴ does not support combustion
- presented as:
  - heliox
    - 79% He, 21% O2
    - brown cylinders with white shoulders
  - 100% helium – brown cylinders at 137bar
- has a lower density (∴ lower specific gravity) than O2 and air:
  - helium = 0.178
  - heliox = 0.337
  - oxygen 1.091
  - air = 1
- ∴ during turbulent flow the velocity will be higher with Heliox than air/O2
  ↳good to ↓WOB in eg upper airway obstruction 2nd to tumour
- also used by divers – avoids nitrogen narcosis
- lower density ⇒ squeaky voice

Carbon Dioxide

- CO2 = colourless gas with pungent odour at high concentrations
- stored as a liquid at 51bar at 20degC in grey cylinders
- physiochemical properties:
  - boiling point -78.5C
  - critical temp 31degC
  - critical pressure 73.8bar
- uses:
  - insufflating gas during laproscopic procedures
  - stim resp following GA's
  - cryotherapy
- effects:
  - CVS:
    - SNS stim ⇒ ↑HR, ↑bp, ↑CO
    - dilates coronary arteries
    - ↑ed chance of arrhythmias
  - resp:
    - resp centre & periph chemoreceptors ⇒ ↑MV & bronchodilation
    - PaCo2 >10Kpa ⇒ resp depression
  - CNS –
    - ↑cerebral blood flow & ↑ICP

Carbon Dioxide Absorbents

- used to prevent rebreathing in circle system
- 2 systems:
  - sodium hydroxide = sodalime
  - potassium hydroxide = baralyme (now withdraen)
- 3 steps in chemical reaction

$H2O + CO_2 \Rightarrow H_2CO_3$

$H_2CO_3 \Rightarrow 2NaOH \Rightarrow Na_2CO_3 + 2H_2O$

$Na_2CO_3 + Ca(OH)_2 \Rightarrow CaCO_3 + 2NaOH$

- CaCO3 = insoluble precipitate

Malignant Hyperthermia (MH)

- = state of hypermetabolism due to calcium imbalance in skeletal muscle in response to certain triggering agents in a genetically susceptible person

Aetiology

- = pharmacogenetic disease of skeletal mm
- Induced by exposure to:
  - Volatile agents-
    - halothane most potent,
    - N2O seems safe
  - Depolarising mm relxant ie sux
    ↳NDNMBs = safe
- Inherited autosomal dominant condition with incomplete penetration
- Caused by loss normal Ca homeostasis within excitation-contraction coupling process on exposure to trigger
- Any defect along complex process can trigger MH
- Most likely site:
  - Junction between T tubules
  - Voltage sensor of dihydropyridine receptor (DHPR) & Ryanodine receptor (RYR)
    - = efflux Ca channel in sarcoplasmic reticulum
    - effectively channel gets stuck open allowing Ca efflux
- 70% families RYR1 gene linkage on chromosome 19
- genes for muscular dystrophy also lie close to MH gene
  ↳eg Duchene MD has similar clinical picture to MH if given six

Epidemiology

- Rare 1:10,000. All races
- Mortality fallen from 70-80% to 2-3% due to awareness & dantrolene
- Young adults; males>females
- Previous uneventful anaesthetic does not prevent occurance

Signs & Symptoms

- Varied presenation:
  - Floird & life threatening vs insidious onset
  - Acutely vs 2-3d postop with massive myoglobinuria & rhabdomyolysis
- Signs:
  - Early:
    - ↑metabolism:
      - Tachy/Arrhythmia
      - ↑ed CO2 production = most important early sign
      - Met acidosis
    - Muscle signs:
      - Masseter muscle spasm (MMS) after sux
        - = spasm impeding intubation persisting for around 2mins
        - 30% pts with MMS alone & otherwise normal anaesthetic ⟹ MH susceptible
        - If present:

        - Abandon surgery - possible OR
        - TIVA - volatile free surgery
        - Consider A line
    - Investigations:
        - Initial and 24hr CK
        - First void urinary myoglobinuria
    - Consider neurological opinion
- Intermediate:
    - Pt feels hot/sweaty
    - Cyanosis
    - Dark blood in wound
    - Arrhythmias - ↑K
- Late:
    - Fever!!! ↑temp 2deg/hr
    - Generalized rigidity
    - DIC ⇒ prolonged bleeding
    - Unstable haemodynamics
    - Renal failure ⇒ high CK, myoglobinuria ⇒ oliguria
    - Myoglobinuria ⟹ renal failure
    - Death

Labs

- Electrolyte abnormalities eg ↑K
- ABG:
    - Met acidosis
    - Mixed picture if SV and compensating

Differential

- Rebreathing
- Sepsis
- Awareness
- Neuroleptic malignant syndrome
- Ectasy
- Thyroid storm

Treatment

- ABC. Stop volatiles
- Hyperventilate - 100% O2 to flush volatiles from system
- Declare problem to team and get help
- Use fresh breathing circuit machine if able
- Dantrolene – use early
- Stop surgery or use TIVA
- Reduce core temp:
    - Ice to groin & axilla
    - Cold fluid into
        - bladder via catheter
        - Veins
        - Stomach via NG tube
- ABG - correct acidosis & potassium
    ↳ beware bicarb as will produce more CO2
- Fluid + diuretics +/- urinary alkalinsation ⇒ flush kidneys to ↓occlusion from myoglobinuria/CK
- Call for surg team help to conclude operation as quickly as possible
- ICU care postop

Dantrolene

- 2-3mg/kg up to 10mg/kg
- indications:
  - Rx & prophylaxis of MH
  - neuroleptic malignant syndrome
  - chronic spascity spasticity
  - ecstacy intoxication
- vials as an orange powder containing (also comes in capsule):
  - dantrolene 20mg
  - mannitol 3g
  - sodium hydroxide
- each vial needs to be reconstituted with 60mls water ⇒ solution pH 9.5
- side effects:
  - highly irritant if extravasated
  - may produce resp failure 2nd to skeletal mm weakness
  - diuresis – manitol
  - chronic use ⇒ hepatitis & pleural effusion
- mechanism action:
  - uncouples excitation contraction process by binding to RyR ⇒ preventing Ca release from SAR
    ↳∴ does not effect cardiac or smooth mm
  - no effect on mm AP
  - little effect on duration of NDNMBs
- PKs:
  - variable oral bioavailability
  - 85% bound to albumin
  - duration of action = 6hrs
  - metab in liver
  - excreted in urine

PreOp Testing

- muscle biopsy testing with 2% halothane & caffeine
- results:
  - susceptible (MHS) = positive to both halothane & caffeine
  - equivocal (MHE) = +ve to one only
  - non-susceptible (MHN) = -ve to both

Peri-MH Treatment

- Invasive monitorring
- Clotting screen & CK
- Urine samples
- Monitor renal function ⟹ diuretics and IVF

Post Episode Care

- Ref to MH investigation unit for mm biopsy & testing
- Warn pt & family
- Pt & family should be offered screening

Anaesthesia for known MH

- MH safe technique - TIVA with no sux may be safe - but balance risks
- All LA's are safe
- Dantrolene should not be given prophylactically
- Standard monitoring
- Baseline temp recorded 2hr preop & temp monitored for 4 hrs post op
- Use vapour free machine
  ↳ if unable: remove soda lime, vapourisers and purge for 30mins with O2

Anaesthesia for suspected FHx

- Establish goof Fhx and d/w MH centre for contact tracing & diagnoses:
    - to test:- mm biopsy & invitro testing with caffeine & halothane
- If case urgent then proceed with MH safe technique

AntiPsychotics

Classification

- high – low potency:
  - low potency = chlorpromazine 100mg
    - features:
      - sedating
      - hypotensive
      - anticholinergic effects

      ↳but fewer extrapyramidal SEs
  - high potency = haloperidol 2mg
    - less sedating/↓bp/anticholinergic

    ↳but ↑ed extrapyramidal
- typical – atypical:
  - typical = 1st generation:
    - phenothiazines eg chlorpromazine, prochlorperazine
    - thioxanthines
    - haloperiodol
  - atypical = 2nd gen:
    - clozapine, olanzapine, risperidone
    - ↓extrapyramidal effects
    - ↑metabolic effects ie DM, obesity

Therapeutic Actions

- effective against +ve symptoms of schizophrenia ie↓
  - hallucinations
  - delusions
  - inititative
  - emotion
  - aggression
  - though disorder
- can prevent relapses
- drowsy but rousable with no confusion
- antagonise dopamine receptor – esp D2:
  - mediate inhibitory effects of DA in CNS
  - action:
    - slow thinking & antiemetic
    - extrapyramidal effects
    - hyperprolactaemia ⇒ gynaecomastia & milk secretion
- takes weeks for onset of action even though biochem actions immediate

  ↳?cos transient ↑Dopaminergic activity

Adverse Reactions

- phenothiazines also block receptors:
  - Ach ⇒ anticholinergic effects & movement disorders
  - NA α receptors ⇒ hypotension
  - histamine ⇒Gi effects
  - 5HT ⇒ sedation & GI effects
- ∴ wide ranging
- chlorpromazine = strong sedative; haloperidol less daytime sedation

Extrapyramidal Effects

- = marked motor stim mediated by extrapyramidal pathways:
  - akathisia

        - = motor restlessness – urgent need to move/rock/tap foot
        - female>male
        - within few wks of therapy
        - use lower dose of drug or antiparkinson drug eg benztropine
    - dystonia:
        - acute reaction with mm spasms
            - hands/neck/face/tongue
            - hyperextension of neck/trunk/arching
            - oculogyric crisis – fixed upward gaze
            - laryngeal spasm – fatal
        - usually within 1 wk of drug
        - males>females
        - Rx: IV procyclidine (antimuscarinic used in Parkinsons
    - drug induced Parkinsons:
        - add anti-parkinson drug eg benztropine
        - switch to atypical
    - tardive dyskinesia:
        - oral or facial dyskinesias eg abnormal involuntary mm movements – lip smacking
            ↳+/- limb movements
        - older women>young
        - may be irreversible ⇒ watch for early signs and stop agent asap

Neuroleptic Malignant Syndrome

- 0.5-1% on typical antipsychotics
- pyrexia, mm rigidity, LOC, impaired ANS homeostasis
- Rx:
    - withdraw drugs
    - bromocriptine – DA agonist
    - dantrolene – mm relaxant

Metabolic

- all groups cause:
    - weight gain
    - DM – esp clozapine, olanzapine
    - dyslipidaemia

Other

- chlorpromazine –
    - skin reactions & photosensitivity
    - cholestatic jaundice
    - agranulocytosis
    - leucopaenia
    - haemolytic anaemia
- several ⇒ prolonged QT

Atypical Antipsychotics

Clozapine

- differs from other neuroleptics – less affinity for D2:
    - D1, D2, D4 antagonist
    - 5HT2 antagnonist
    - α1 adrenoceptor antagonist
    - H1 antagonist
- ↓D2 ⇒ less extrapyramidal SEs
- best for –ve symptoms of schizophrenia
- SEs:

  - agranulocytosis
  - seizures
  - cardiomyopathies
  - severe constipation

  ↳∴ reserved for for Rx resistant schizophrenia
- need weekly FBC (WCC) for first 18wks

Others

Olanzapine, Risperidone

- block:
  - predominant D4 block
  - also:
    - D2
    - 5HT2
- advantages over clozapine:
  - less sedating
  - ↓anticholinergic SEs
  - no agranulocytosis

  ↳disadvantages - ↑risk of stroke in elderly
- interact with other CNS depressants, anti HTs, dopamine agonists & antidepressants
- olanzapine use IM in
  - acute manic episodes
  - agitation
  - behavioural symptoms in dementia

Quetiapine

- blocker of
  - 5HT1a & 5HT2;
  - D1 & D2
  - α1 & α 2
- low potency & short half life

Typical Antipsychotics – Phenothiazines

- phenothiazines subclassified based on structure:
  - propylamine = chlorpromazine
  - piperidine = thioridazine
  - piperazine = prochlorperazine

	Chlorpromazine	Thioridazine	Prochlorperazine
Sedation	+++	++	+
Anticholinergic effects	++	+++	+
Extrapyramidal effects	++	+	+++

Chlorpromazine

MOA

- therapeutic antagonism at D2
- but as above also see widespread antagonism (largactil):
  - D2
  - muscarinic
  - noradrenergic α1 & α2
  - H1
  - 5-HT

- also has:
  - membrane stabilising properties
  - prevents NA uptake into nerves (uptake1)

Pharmacokinetics

- lipid soluble ∴ good oral absorb & CNS concentrations
- heptic 1st pass metab ∴bioavailability 10-80%
- peak plasma level
  - oral 1-4hrs
  - IM injection 15-30min
- peak clinical action 6wks-6months
- duration action 6-24hrs
- liver metab to inactive metabolites & excreted by kidney

Uses

- schizophrenia & other psychoses – isolates RAS from afferent connections ⇒ sedation & ↓motor activity (neurolepsy)
- intractable hiccups
- short term Rx anxiety/agitation/disturbed behaviour
- control vomit & pain in terminal care
- pONV prophylaxis

Adverse Reactions

- see earlier
- IM & s/c are painful & risk of mm necrosis

Cautions/Contraindications

- caution in
  - breast Ca
  - CVS disease
  - liver disease
  - ↑thyroid
  - parkinsons
  - epilepsy
- contra:
  - phaeochromocytoma
  - profound CNS depression
  - alcohol abuse
  - preg women
  - during lactation
  - bright sunlight

Interactions

- lithium ⇒ ↓conc of drug
- propanolol ⇒ ↑ conc of drug

Dose

- start low, titrate up
- stop therapy – reduced dose slowly over 2-3/52 otherwise rebound dyskinesia/N&V/tremors
- max adult daily dose 600-800mg

Thioridazine

- used in schizophrenia & other psychoses
- favoured in elderly as ↓ed sedation & EP side effects

Prochlorperazine

- used in:
  - PONV
  - vertigo

    - psychoses
- has highest incidence of EP side effects – esp young adults & children
- has ↓ed sedation
- extensive 1st pass metab ⇒ low OBA

Haloperidol

- selective CNS effect
- competitively blocks D2 receptors in mesolimbic system
- sig degree of extrapyrimadal effects but has less effect on NA receptors
- used:
    - antiemetic
    - severe behavioural problems in children
    - mania
    - tourettes

Serotonin & 5-HT Drugs

Serotonin

(see physiology section neurophysiology for distribution, synthesis, degredation detail)

Classification of Serotonin Receptors

(copied from physiology)

- 7 types of 5-HT receptor with many specific functions:
  - 5-HT1 (**Gi**) = GPCR to adenyl cyclase ⟹ ↓cAMP
    - found in:
      - CNS - mostly inhibitory
      - blood vessels - mostly vasoD except cerebral vasoconstrictor $5HT_{1D}$
    - 5HT1a = role in mood, behaviour ie sleep, feeding, anxiety, thermoreg
    - 5HT1b = presynaptic inhibition & behaviour
    - $5HT_{1D}$: agonist = sumatriptan, partial agonist = ergotamine
  - 5-HT2 (**Gq**) = GPCR to PLC ⟹ ↑IP3 & DAG ⟹ ↑Ca
    - more in periphery than CNS
    - 5-HT2a =
      - most impt
      - found in:
        - platelets & smooth mm (GIT, bronchi, uterus)
          ↳ impt in thrombosis & asthma
        - CNS - agonist = LSD
    - 5-HT2b = contraction gastric fundus
    - 5-HT2c = choriod plexus CSF production
  - 5-HT3 (**ion channel**) = direct ion channel:
    - found in:
      - periph nerves (mostly) - strong excitatory effect on nociceptive input & enteric/autonomic neurons
      - CNS - emesis & anxiety
    - antagonists = ondansetron
  - 5-HT4 (**Gs**) = GPCR to adenyl cyclase ⟹ ↑cAMP
    - found in:
      - periph nervous system (GIT) - main physiological role ⟹ ↑motility
      - CNS - neuronal excitiation
    - agonist = metoclopramide ie ↑motility & ↑gastric emptying
  - 5-HT5-7 (**Gs**) = GPCR to adenyl cyclase ⟹ ↑cAMP
    - mainly in brain - linked to anxiety

Classification of Action Based on Organ

Smooth Muscle

- GIT = 5-HT2a, 5-HT4
  - ↑motility & contraction
  - peristaltic reflex
  - vagal stimulation ⇒ 5-HT release from chromaffin cells
- blood vessels:
  - 5-HT2a: large arts & veins ⇒ vasoC (direct)
  - 5-HT1: smaller arts & veins ⇒ vasoD
    - several mechanisms:
      - direct action
      - inhibiting NA release from symp nerve terminals

        - NO formation acting on endothelial cells
    - microcirculation ⇒ ↑cap permeability via
        - direct action
        - ↑cap hydrostatic pressure (arteriolar dilation & venular constriction
- bronchi = 5-HT2a
    - bronchoconstriction – minor in human unless eg carcinoid syndrome
- uterus = 5-HT2a
    - constriction – minor in human

Neuronal Tissue

- PNS = mainly 5-HT3
    - stim nociceptive sensory nerve endings
    - given systemically ⇒ afferent fibres from heart/lung ⇒ autonomic reflexs
- enteric NS
- CNS = 1a, 3, 2a
    - can exhite or inhibit neurons
    - postulated role in mood, apetite, sleep, migraine, halucinations, pain perception, N&V

Platelets

- = 5-HT2a
- 5-HT released from dense bodies after plt adhesion (within 30secs)
- causes further aggregation ⇒ further 5-HT release
- response depends on state of endothelium:
    - intact ⇒ vasoD ie blood flow maintained
    - damaged ⇒ vasoC ie ↓flow

Drugs Acting on Receptors

- Agonists:
    - buspirone = 1a partial agonist - mood disorders
    - sumatriptan = 1d agoinst – migraine
    - metoclopramide = 4 (and other receptors eg dopamine) – N&V/prokinetic
    - LSD = 2a (CNS) – psychoactive effects
- antagonist:
    - ketanserin = 2a (also α-blocker) ⇒ ↓bp, ↓vasospasm
    - LSD = 2a (periphery)
    - ondansetron = 3 – antiemetic but also anxiolytic

Serotonin Syndrome

- excessive stim of diff receptors:
    - 1a
    - 2a
    - 3
    - 4
- char by:
    - cog impariement
        - confusion
        - agitation
        - hypomania
        - seizure
    - GI - diarrhoea
    - autonomic
        - pyrexia
        - sweating
        - tachy

        - ↑ or ↓ bp
        - dilate & unreactive pupil
    - neuromuscular dysfunction
        - **myoclonus**
        - **hypereflexia**
        - mm rigidity
        - tremor
        - hyperactivity
        - shiver
        - nystagmus
        - opisthotonus (bridging spasm of body)
        - trismus
- most cases at therapeutic SSRI levels
- commonly precipitated by SSRI & MAOI taken together
- other drugs which ↑5HT transmission:
    - migraine drugs
    - opiod analgesics
    - CNS stimulants
    - many illicit drugs
    - St Johns Wort
- Rx with:
    - benzodiazepines
    - cyproheptadine = serotonin blocker
    - propanlolol = blocks 5HT1 & 5HT2

AntiDepressants

Affective Disorders

- bipolar affective disorders = manic –depressive psychosis
  ↳must be 1 or more manic or hypomanic episodes
- unipolar depressive disorder:
  - single episode
  - recurrent episodes
- atypical affective disorders
- depression assoc with other psychiatric syndromes eg schizophrenia, personality disorders
- criteria for depression:
  - mood changes – anhedonyia, low mood. Often worse in morning
  - psych symptoms – hopelessness, low self esteem, suicide
  - physiological – EMW, ↓libido, loss of energy, anorexia
  - thought alterations - ↓concentration, confusion, delusions
- criteria for mania:
  - wild mood swings
  - excessive energy
  - high pressure of speech
  - excessive spending
  - lacks need for sleep

Monoamine Theory

- ?cause of depression
- imbalance of centrally acting monoamine neurotransmitters
  - depression ≈ ↓NA or 5HT
  - mania ≈ ↑DA or NA

Delayed onset of Drug Action

- due to:
  - long half lives
  - MOA – alteration of neurotransmission
  - –ve feedback on presynaptic 5-HT_{1A} receptors
- trend towards improvement 2-3wks, full effect 6-8 wks
  ↳in interim may see inhibition rather than facilitation of monoamine transmission
- cont therapy for 6/12 after symptoms improved

Drug Interactions

- TCA/SSRI/MAOIs:
  - other serotonergic drugs ⇒ ↑risk serotonin syndrome
  - other CNS depressants ⇒ ↑CNS depression
- TCA/SSRI:
  - drugs which ↓seizure threshold ⇒ ↓↓seizure threshold

SSRIs

Fluoxetine

MOA

- more selective inhibition of reuptake of 5HT
  ↳ but non selective to 5HT3 receptors
  ↳ very little affinity for NA/DA/Ach/H receptors
- ∴ less CVS SEs & less lethal in OD
- do not interact with tyramine containing foods (MAOI)

Pharmacokinetics

- most SSRIs have half life 24hrs

- fluoxetine :
  - quick absorb – plasma peak 6-8hrs
  - highly tissue protein bound
  - high volume of distribution
  - non-linear kinetics as inhibits its own metabolism
  - liver metabolism
  - has an active metabolite (norfluoxetine) with half life 16days
    ↳∴weeks to achieve steady state or achieve full elimination of drug when stopping

Uses

- Rx of
  - depression
  - anxiety disorders eg OCD, panic disorder
  - bulimia nervosa
  - premenstrual syndrome

Adverse Reactions

- serotonin syndrome:
  - excessive stimulation of 5-HT_{2A}
  - features:
    - mental changes – confusion, delirium, hypomania
    - GI tract – diarrhoea
    - muscular – hyperrelfexia, incoordination, tremor
    - autonomic – sweat, fever, shivering
  - ↑risk if MAOIs combined with SSRIs
  - potentially fatal
- minors:
  - anorexia
  - weight loss
  - headaches
  - dizzy
  - seizures - rare

Cautions/Contraindications

- warn on delayed onset of action
- withdrawl reactions after cessation
- crosses placenta but is saftest gp in preg
- not recommended during lactation
  ↳although others better

Interactions

- inhibits CYP450 enzymes ⇒ ↑levels of:
  - antiepileptics
  - antipsychotics
  - benzos
  - TCAs
  - st Johns wort
- with antiplatelets – additive ↑risk bleeding
- drugs affecting glucose ⇒ SSRIs cause ↑glucose level
- TCAs & tramadol – all ↓ seizure threshold
- protein binding interactions with warf

Dose

- start 20mg; increase after wks to max 80mg
- caution in elderly – 1/3 or half doses

TCAs

- chemical structures have **3 rings**

- all drugs same mechanism & similar efficacies
- imipramine typical
- nortriptyline less likely to cause sedation/hypotension/anticholinergic effects

MOA

- inhibit reuptake of NA & 5HT into presynaptic adrenergic neuron ⇒ ↑neurotransmitter within cleft
- also blocks neurotransmitter receptors:
  - fast Na channels ⇒ ↓ionotropy, QT prolongation, arrhythmia
  - Ach (muscarinic) ⇒ anticholinergic SEs
  - H1 ⇒ sedation
  - D receptor blocker
  - α1 ⇒ hypotension
- ∴ have many symptathetic & sig anticholinergic effects

Pharmacokinetics

- rapidly absorbed
- extensive liver metab – some metabolites antidepressant
- long delay in onset
- plasma levels vary widely independent of dose or therapeutic response

Uses

- major depression – now 2nd line to SSRIa
- adjunct in:
  - pain management
  - prophylaxis of migraine
  - noctural enuresis & urge incontinence
  - 3rd line Rx for ADHD

Adverse Reactions

- toxicity features:
  - dilated pupils
  - extrapyramidal signs
  - CNS excitement/depression
  - arrhythmias
  - seizures
  - death – from CVS affects
- SEs:
  - lethargy
  - weakness
  - impaired cognition
- lower seizure threshold ⇒ ↑risk of seizure

Cautions/Contraindications

- elderly – use 1/3 or half doses
- caution in:
  - psychoses
  - epilepsy
  - prostatic hypertrophy
  - urine retention
  - any organ dysfunction
- preg & lactation caution

Interactions

- widespread drug interactions with all drugs that affect ACh & H1 & α adrenoceptors
- anticholinergic effects – additive effect ↑effects eg delirium
- drugs which prolong QT interval - ↑risk of arrhythmias

TCA Poisioning

- Life threatening symptoms may occur ingestions >10mg/kg
- Most deaths occur in initial hrs before pt reached hosp
- Cardio-toxicity 2nd to Na channel blockade
- See hypotension (opposite to anticholinergic) – due to alpha blocking effect TCAs
- ECG changes
  - Most common is Sinus tachy

  ↳as poisoning worsens:
  - ↑PR & ↑QRS duration
  - P wave may be superimposed on preceeding T

    ↳looks like VT but is actually sinus with prolonged conduction

  ↳in v severe poisioning:
  - Vent arrhythmias & brady's
- Avoid flumazenil – may precipitate seizures
- Rx:
  - Supportive
  - ± Gastric lavage ±activated charcoal
  - IV sodium bicarbonate – Rx QRS widening
  - monitor U&E
  - diazepam as re'd

MAOIs

- inhibit the monoamine oxidase enzymes in mitochondria of nerve cells
- MAO responsible for metabolising NA after release ⇒ build up of NA available for release from nerve terminal
- avoid tyramine containing foods/drinks: eg alcohol, cheese, over-ripe veg & fruit
  - MAO-B inactivates ingested tyramine ⇒ ↑↑sympathomimetic action ⇒ ↑bp

Interactions

- certain very important interactions exist:
  - pethidine ⇒ agitation, HTN, seizures, hyperthermia
  - TAD's ⇒ delirium, seziures, HTN, hyperthermia
  - Indirectly acting adrenoceptor drugs ⇒ HTN, seizures, headache, tachycardia, hyperthermia, stroke
  - tyramine ⇒ hypertensive crisis (cheese reaction)
- less impt interactions:
  - morphine – enhanced depressive effects of morphine
  - volatiles ⇒ enhanced effect of volatiles ie ↓MAC
  - phenothiazines ⇒ enhanced effects
- no effects:
  - direct acting adrenoceptors
  - benzo's
  - NDNMBs
  - LA's

Newer Antidepressants

Mianserin

- enhances postsynaptic $5HT_{1A}$ receptors
- does not block reuptake of monoamines
- also blocks α1 & H1 receptors but less ACh actions that TCAs
- need to monitor neutrophils – risk of neutropaenia

Mirtazepine

- enhances NA activity& 5HT activity at 5HT1A
  ↳fewer periph & central adverse effects
- but it does have selective blockade of:
  - H1
  - α2
  - $5HT_{2A}$ & $5HT_{2C}$, $5HT_3$
- safer in OD, fewer anticholinergic effects
- Does not cause D&V, insomnia, or sexual dysfunction
- SEs include ↑apetite & carbo cravings ⇒ weight gain

Venlafaxine

- SNRI
- metabolite = desvenlafaxine
- more selective in preventing 5HT & NA re-uptake
- SEs incl autonomic, CNS & sexual dysfunction
- in theory less drug SEs

St Johns Wort

- MOA:
  - block reuptake of monoamine neurotransmitters
  - bind to GABA receptors
  - ↑regulate 5HT receptors
  - inhibit MAO & COMT enzymes
- more effective than placebo; less effective than TCAs
- SEs are rare but:
  - serotonin syndrome
  - drug interactions esp with other 5HT drugs
- = a potent inducer of hepatic metab enzymes ⇒ ↓drug levels of eg warf, dig, theophylline, antiretrovirals, OCP

Mania

- acute episodes Rx olanzapine & quetiapine
- prevention of mania:
  - lithium
  - antiepileptics eg valproate, lamotrigine, carbamazepine

Lithium

MOA

- still not been established
- theory:
  - Na levels [in] ↑200% in mania
  - lithium & Na actively transported across cell membranes
  - lithium cannot be pumped out as effectively as Na
  - lithium impairs Na action in physiological processes ie inhibits or slows
    - GPCRs
    - adenylate cyclase activity
    - phosphoinositol cycling
    - phosphokinase activities
  - overall effect:
    - inhibit transmitter release esp DA
    - ↑turnover of NA & 5HT in brain
    - ↓post-synaptic receptor sensitivity

    ↳∴ overactive catecholamine system in manie corrected

- little effect if not suffering from mania

Pharmacokinetics

- rapidly absorbed
- reaches peak plasma conc 1-3hrs
- if acute OD – take >12hrs for features to develop as slow entry into tissues
- long half life – adult 24hrs, teenager 18hrs, elderly 36hrs
  ↳steady state 5-7 days
- no metabolism ⇒ excreted unchanged from kidneys
  ↳partly reabsorbed from prox tubule with Na

Drug Monitoring

- narrow therapeutic range
- conc >1.5 ⇒ severe toxicity although correlates poorly clinically
- ∴ plasma levels monitored reg
- 12hr post does trough level
- targets:
  - bipolar acute 0.8-1.2mmol/L
  - maintenance 0.6-0.8mmol/L
- clinical response 1-3wks
- levels monitor weekly in dose adjustment then 1-3monthly
- levels may be elevated by:
  - renal failure
  - D&V
  - fluid/salt loss incl dehydration, diuretics
  - low salt diets
  - excessive sweating of any cause eg exercise
  - NSAIDs, or ACEIs
- levels may ↓by:
  - high salt
  - high intake NaBic
  - pregnancy

Uses

- prevention of bipolar disorder
- adjunct in
  - schizophrenia
  - Rx resistant depression

Adverse Reactions

- minor SEs:
  - ↑thirst & ↑Peeing
  - fine tremor of hands
  - weight gain
  - diarrhoea
  - long term ⇒ acne, psoriasis, hypothyroid, renal damage
- diabetes insipidus:
  - lithium blocks ADH action on distal tubule ⇒ polyuria

Cautions/Contraindications

- caution in:
  - DM
  - ↓thyroid
  - psoriasis
  - pregnancy
- contra:
  - dehydrated

  - renal impairement
  - lactating – make baby flaccid

Interactions

- antithyroid/iodides: ↑hypothyroid effects of lithium
- NSAIDs: ↓excretion of lithium
- phenothiazines, fluoxetine, haloperidol: altered lithium levels
- diuretics esp thiazides : ↓lithium excretion

Dose

- norm & controlled release form
- acute mania 250-500mg tds upto max 2g/day according to levels& tolerance
- maintenance: 1-2g daily in divided doses
- elderly 1/3-half dose

Lithium Toxicty

- early signs of toxicity:
  - coarse tremors
  - confusion
  - vomiting
  - slurred speech ⇒ drowsiness
- severe toxicity:
  - blurred vision
  - seizures
  - ataxia
  - arrhythmias
  - ↓K
  - ↑urine
- if prolonged toxicity ⇒ permanent brain damage
- charcoal has no effect for Rx
- toxicity Rx:
  - gastric lavage
  - forced diuresis & dialysis

Migraines

- = syndrome of unstable cerebral blood vessels mediated by 5HT
- early phase:
  - prodromal = VC stage
  - platelet 5HT levels drop due to release ⇒ ↑5HT plasma levels ⇒ VC
- later phase:
  - ↓serum 5HT levels ⇒ reflex VD ⇒ severe unilat pulsating pain
  - calcitonin gene related peptide (CGRP, bradykinin, substance P also implicated

Treatment

Analgesics & Antiemetics

- try early in attack moving up ladder
- opioids should be avoided ⇒ exacerbate GIT symptoms of attack
- antiemetics ie metoclopramide added - ↓s vomit & ↑s speed of absorption of antimigraine drug

Ergot Alkaloids

- powerful VC
- many adverse reactions ∴ uncommon use
- see next section

Prevention

- avoid triggers
- if more than one severe attack/month trial agents
- diff strategies:
  - TCAs – amitryptilline
  - βblockers – some action at 5HT receptors
  - anticonvulsants
  - Ca channel blockers
  - antiserotonin/histamine/muscarinic agent eg pizotifen ⇒ SEs drowsy & weight gain

  ↳try 1 agent at a time 1-3month courses

Sumatriptan

MOA

- selectively constricts cranial vessels by agonist actions on 5HT receptors
- structural analogues of 5HT for $5HT_{1D}$ receptors
- relief of headache 50-75% migraines 2-4hrs
- best if given early

Pharmacokinetics

- oral admin:
  - rapid but incomplete absorb
  - high 1st pass metab ⇒ low bioavailability
- s/c admin:
  - peak plasma conc in 30mins
  - much higher bioavailabily ∴ dose smaller
- intranasal option – quicker onset of action than orally

Uses

- Rx
  - acute migraine attack
  - clustr headaches

Adverse Reactions

- minor:
  - dizzy, fatigue
  - CP
  - N&V

- major (rare);
    - arrhythmias, stroke, seizures, MI

Cautions/Contraindications

- use as monotherapy & avoid other antimigraines preps
- caution in elderly & preg
- do not take within 24hrs of ergotamine preps
- contra in:
    - IHD
    - HTN
    - Hx of stroke

Interactions

- interact with other drugs that ↑5HT ie MAOIs, SSRIs

Dose

- oral 50-100mg asap after attack
- s/c dose 6mg, rpt after 1hr to max 12mg/day
- intranasal 10-20mg into 1 nostril up to 40mg/d

Ergot Alkaloids

- complex & diverse actions
- structure based on a complex aromatic acid = lysergic acid
- divided into 2 gps according to side chain:
    - amine side chain:
        - LSD
        - ergometrine
    - amino acid side chain:
        - ergotamine
        - bromocriptine
- actions:
    - smooth mm: stimulation – some selective for vessels, other for uterus
    - amino acid gp affect adrenergic & 5-HT receptors in various ways:
        - ergotamine =
            - α1 partial agonist
            - α2 antagonist

            ↳ ∴ vasoC & blocks vasoconstrictor action of adrenaline
        - bromocryptine = CNS dopamine agonist

Drug	5-HT	α	dopamine	Uterine contr	Main uses
Ergotamine	HT_1 ant/PA	PA		++	migraine
Bromocryptine			agonist/PA		Parkinsons
Ergometrine	HT_1 ant / PA	weak Ag	weak Antag	+++	PPH, carcinoid

By Adam Hollingworth

Seziures

Classification of Seizures

- partial:
  - simple – no LOC:
    - motor ie Jacksonian
    - sensory
    - ANS
    - psychic ie personality changes
  - complex – brief LOC:
    - psychomotor – aura, chewin, swallowing movements
    - cog symptoms – confusion, bizarre behaviour, purposeless behaviour
    - compound – tonic-clonic seizures
  - partial with 2ndary generlisation:
    - unilat symptoms
- generalised – convulsive or non convulsive with widespread involvement both cerebral hemispheres
  - tonic clonic
  - tonic – systained contractions
  - clinic – dysrhythmic contractions
  - myoclonic – no LOC, isolated clonic contractions
  - absence – brief LOC, no confusion
  - atonic – head drop or falling down
- infantile spasms

AntiEpileptic Therapy

- 70% pts controlled with monotherapy
  ↳50% of rest will respond to 2 or 3; rest people refractory epilepsy

Choice of Drug

- generalised tonic clonic – valproate>carbamazepine
- generalised absence seizures – valproate>lamotrigine
- generalised myoclinic – valporate>lamotrigine
- partial (simple or complex) – carbamazepine>phenytoin

Special Situations

Women

- ↑seizure frequency during menstruation
- antiepleptics (AED) ⇒ ↓effectiveness of OCP
- no AED safe in pregnancy:
  - x2-3↑teratogenic abnormalities in fetus with AEDs
  - but seizures in preg>risk than SEs of AEDs
- ↑intake of folic acid 5mg/d prior to conception may ↓spina bifida
- lactation not contraindicated although monitor infant for drowsiness
- eclampsia:
  - pre-eclampsia in 5% preg
  - diazepam, phenobarbitone, phenytoin given IV as AED & sedatives
  - Mg also CNS depressant but risks of ↓mmtone & resp depression in neonate
  - monitor mother 2/7 post delivery as risk seizure remains

Elderly

- lower doses:
  - ↓metabolise of drugs
  - ↓renal excretion
  - ↓ed albumin ∴ more free drug of highly protein bound drugs ie phenytoin, valproate
- ↑interactions

Kids

- febrile seizures not prevented by cooling or paracetamol
- Valproate & lamotrigine best. Avoid phenytoin
- <2yrs with valproate have risk of hepatoxicity
- neonates from mothers who received phenytoin need vit K to prevent hypoprothrombinaemia

Maintenance Therapy

- cont successful drug regime until seizure free for 2-3yrs
- if seizure free >2yrs; 70% of people can successfully wean off AEDs with 20yr relapse 12-36%
- taper down dose slowly
- if poly AEDs – stop each drug seperatly & slowly over several months

Drugs which Cause Seizures

- wide variety:
  - anticholinesterases
  - antipsychotics
  - antihistamines
  - interferons
  - quinolones & some other Abxs
  - SSRIs, MAOIs & TCAs
  - OCP
  - aspirin
  - social drugs – acohol, caffeine, cocaine

Use in Neuropathic Pain

- incompletely understood mechanism

Mechanisms of Action

- complex & incompletely understood
- different types:
  - enhance GABA inhibition – benzo's
  - inhibit Na channel function – carbamazepine, phenytoin, valproate, lamotrigine
  - inhibit Ca channel function – block glutamate via NMDA receptor

Interactions of AEDs

- phenytoin:
  - ↑conc of othr AEDs
- phenytoin/carbamazepine/valproate:
  - induce metabolising enzymes ⇒ ↓conc of other AEDs, themselves & other drugs eg OCP
- carbamazepine & benzo's:
  - drugs which inhibit CYP3A4 ⇒ ↑level of carbamazepine
    ↳ie protease inhibitors, grapefruit, quinolones
  - drugs which induce CYP34A ⇒↓effects
    ↳ie steroids, rifampicin, some antivirals, St Johns Wort
- Valproate - ↓s platelet aggregation ⇒ ↑bleeding time

Phenytoin

MOA

- blocks voltage dependant Na channels ⇒ ↓propogation of seizures
- also
  - Ca channel blocker
  - Effect on K conduction

Pharmacokinetics

- saturable metabolism ⇒ non linear pharmacokinetics
  ↳small rise in dose ⇒ big rise in conc
- oral absorb slow & variable

- highly bound to albumin in plama
- time to peak serum level 1.5-3hrs
- half life 7-42hrs (av 24hrs)
- steady state after 7-10 days
- inactivated in liver & metabolites excreted in bile & urine
- IV phenytoin is not very soluble & very alkaline ⇒ skin irritation
  ↳fosphenytoin – analogue which overcome this

Uses

- better for partial seizures
- useful
  - post brain surgery
  - head trauma
  - status

Adverse Reactions

- neurotoxic effects >80micromol/L (20mg/L) ie drowsy, dizzy, confused
- minor:
  - hirsuitism
  - gingival hyperplasia with bleeding
  - acne
  - vitamin D abnormalities
- signs of toxicity:
  - visual changes
  - altered mental state incl hallucinations
  - slurred speech
- toxicity with IV use:
  - CVS collapse incl ↓bp
  - ischaemia of distal extremities

  ↳rate vital – don't exceed 25-50mg/min

Cautions/Contraindications

- caution in pregnancy
- other cautions:
  - DM
  - arrhythmias
  - liver/renal damage
- OCP efficacy ↓ed
- reg dental care

Interactions

- many drugs inhibit metab of phenytoin ⇒ ↑half life:
  - amiodarone
  - oral anticoags
  - allopurinol
  - omeprazole
  - azole antifungals

Dose

- 200-500mg daily with careful monitoring
- IV dose never mix with glucose
- Status: 13-20mg/kg with max rate 50mg/min

Carbamazepine

MOA

- also blocks Na channels
- similar MOA to phenytoin

Pharmacokinetics
- oral absorb slow
- onset action hours to days
- posseses auto-induction:
  - induces higher levels of the enzyme that metabolises it
  - takes ~1 month to reach steady state
- metab in liver – has 1 active metabolite
- excreted by kidneys

Uses
- useful in all types of seizures
- also used for:
  - neuropathic pain
  - bipolar disorder

Adverse Reactions
- CNS depression
- severe hypersensitivity reactions:
  - skin reactions
  - ↓WCC
  - ADH like effects

Interactions
- enzyme inducer ∴ ⇒ ↓effectiveness of many drugs:
  - warfarin
  - other AEDs & itself
- carbamazepine & benzo's:
  - drugs which inhibit CYP3A4 ⇒ ↑level of carbamazepine
    ↳ie protease inhibitors, grapefruit, quinolones
  - drugs which induce CYP34A ⇒↓effects
    ↳ie steroids, rifampicin, some antivirals, St Johns Wort

Sodium Valproate

MOA
- not fully established
- ?MOA:
  - competitive inhibition of reuptake of GABA by axon terminals & glial cells ⇒ ↑GABA levels in CNS
  - block Na, K +/- Ca channels

Pharmacokinetics
- Na valproate converted in stomach to valproic acid ⇒ rapid absorb from GI tract
- ∴ food delays absorb
- variable time to onset
- half life 6-16hrs

Uses
- generally used AEDs
- also used in bipolar & migraine

Adverse Reactions
- mild:
  - drowsy
  - tremor
  - gastric distress
  - hair thinning
  - weight gain
  - irreg menstruation

- hepatotoxicity – esp <2yrs
- pancreatitis

Interactions

- CNS depressants eg alcohol GAs, barbiturates
- anticoags & aspirin
- ↓metab of itself & other AEDs at low doses
- displaces phenytoin from protein binding
- ↑risk of congen malformations incl spina bifida

Lamotrigine

- acts on presynaptic neuronal membrane
- stabilises the inactive Na channels ∴ ⇒ ↓release of excitatory transmitters (glutamate & aspartate)
- hepatic metabolism to inactive conjugate
- its rate of metab:
  - ↑ed by inducing drugs eg phenytoin & carbamazepine
  - ↓ed by valproate
- high risk severe skin reactions – SJS/TEN

Gabapentin

- MOA is uncertain –
  - structurally similar to GABA but does not interact with GABA receptors
  - bind to Ca channels within the brain
    ↳ does not bind to Na channels
  - may also:
    - NMDA antagonist
    - ↓release of monoamine neurotransmitters
    - ↑release of glutamate decarboxylase (this converts glutamate ⇒ GABA)
    - ↑synpatic release of GABA
- uses:
  - role in chronic pain ⇒ ↑GABA mediated inhibition
    ↳may improve sleep in sleep in neuropathic pain
  - anticonvulsant
- effect:
  - enhances effect of coadministered opioids
- PK:
  - OBA 60% - bioavailability of drug ↓s with ↑s doses
    ↳ helps to ↓toxicity
  - peak plasma levels 2-3hrs post admin
  - CNS levels ~20% of plasma levels
  - not PPB
  - t1/2elim 5-7hrs
  - excreted unchanged ∴ does not interfere with other other anticonvulsants

Histamine Agents

Distribution of Histamine

- naturally occurring in all body tissues
- highest concentrations in
  - skin
  - lung
  - GI tract (most)

(see physiology neurophysiology for further info)

Histamine Receptors

- sensitivity to histamine: guinea pig>human>mouse
- 3 receptors
  - H1 (**Gq**) $\Longrightarrow$ ↑PLC $\Longrightarrow$ ↑IP3/DAG $\Longrightarrow$ ↑Ca
    - -ve heart: coronary vasoC/-ve chronotrope
    - skin – pruritis
    - resp:
      - bronchoconstriction
      - ↑mucus
    - vasculature:
      - ↑permeability
      - ↑PGI ⇒ vasoD, ↓platelets, ↑airway resistance
    - CNS – post synaptic excitatory
  - H2 (**Gs**) $\Longrightarrow$ adenyl cyclase $\Longrightarrow$ ↑cAMP $\Longrightarrow$ ↑PKA
    - ↑gastric acid
    - +ve heart: inotrope/chronotrope/vasoD
    - CNS – post synaptic inhibitory
  - H3 -
    - research
    - neural tissue = most presynaptic

Histamine Action – By Organ

- gastric acid:
  - (H2) ⇒ ↑gastric acid via activation fo HKATPase
  - see ↑volume & ↓pH
  - impt in peptic ulcers
- smooth mm (outside CVS):
  - H1 effects (mostly)
  - bronchi & bronchioles contraction – more prominent in reactive airways disease
    ↳ NB H2 ⇒ bronchodilation
  - contraction of ileum & uterus – but only in extremely high conc
- CVS:
  - summation of bothe receptor effects = +ve inotropy
- skin:
  - lewis triple response:
    - reddening = dilation of arterioles + precapillary sphnicters (H1)
    - wheal = ↑permeability of post capillary venules
    - flare = axon reflex
      - stim of sensory nerve fibres +
      - vosdilator mediator (ATP & substance P) ⇒ antidromic impulses through neighbouring branches of same nerve
  - pruritis – stim of sensory nerve endings of C fibres
- CNS:

- effects not fully understood.
- role in motion sickness
- presnyamptic H3 complicates issue

AntiHistamines

H1 Receptor Antagonists

- 2 main categories:
  - older more sedating
  - newer less sedating
- called antihistamines but have widespread effects incl:
  - anticholinergic
  - antidopaminergic
- examples:
  - piperazines = cyclizine
  - phenothiazines = promethazine
  - alkylamines = chlorpheniramine
  - cetirizine
  - non sedating ie ↓penetration of bbb

MOA

- drugs resemble histamine – contain a substituted ethylamine
- = reversible selective antagonists for histamine at H1 receptors
- many have LA properties – but only in v high concs

Pharmacokinetics

- onset action 15-60mins
- metab in liver; excreted in kidneys

Uses

- allergic reactions – although limited role when response not due to histamine releasing drugs as histamine only one of many mediators in anaphylaxis eg leukotrines, kinins
- skin disorders
- vertigo
- motion sickness
- nausea
- sedation - premed

Adverse Reactions

- anticholinergic –
  - classic side effects (note gastric secretion not effected)
- antidopaminergic – esp phenothiazines
  - Extra-pyramidal symptoms ie Parkinson like movmts
- sedation:
  - esp in older/lipophlic drugs which ↑cross bbb
  - may see paradoxical hyperexcitablility in kids
- photosensitivity (promethazine)
- jaundice

Cautions/Contraindications

- contraindicated:
  - ↓K
  - liver impairement
  - prostatic hypertrophy/urinary retention

Interactions

- alcohol, CNS depressants - additive CNS depressant effect especially if CNS depressant has anticholinergic effects
- anticholinergics, psychotrophs - ↑CNS depressant & ↑anticholinergic

- levodopa – phenothiazine antihistamines antagonise levodopa

H2 Receptor Antagonists

see GI section

Hypnotics & Sedatives

Definitions

- conscious sedation
  - = drug induced depression of consciousness during which patients respond purposefully to verbal commands or light tactile stimuli
    ↳eg withdrawal from pain (GCS M4 is too sedated)
  - no interventions should be required to maintain patent airway, spont ventilation or CVS stability
- sedation = where drug or dose of drug decreases acitivity, soothes & calms and moderated excitement without inducing sleep
- hypnosis = where drug induces near natural sleep on EEG (although REM sleep is supressed)
- anxiolysis = drug reduces anxiety without impairing other cerebral or motor functions ie minimal GCS alteration
- Joint commission of accredited healthcare organisations (JCAHO) on sedtation:
  - continuum with unpredictable individual responses:
    - minimal = anxiolysis
    - mod = conscious sedation
    - mod/deep = hypnosis
    - deep = GA
  - seditionist must be able to rescue pts whole level of sedation is deeper than intended
- dependence:
  - psychological dependence = compulsive drug seeking behaviour in which person uses drug in higher doses + more frequently than recommended.
    ↳ preceeds physical dependence but does not always lead to it
  - physical dependence = when withdrawl of drug produces symptoms + signs frequently te opposite of those sought by the user

Conscious Sedation/Monitored Anaesthetic Care (MAC)

- performed for procedures under LA/sedation
  ↳ eg paeds, endoscpy, eyes, dentistry
- issues:
  - unwell population – not fit for GA
  - difficult IV access
  - who sedates
  - monitoring
  - cost
  - NBM guidelines
- identified risks to disaster:
  - od drug
  - lack of appreciation of drugs interactions
  - poor pt selection
  - lack of emerg equipment
  - lack of adequate monitoring
  - premature d/c – chloral hydrate!
  - failure to recognise difficulty

Ideal Sedative

- generally:
  - high therapeutic index (LD50/ED50)
  - predictable effects
  - easily titrateable

- but doesn't really exist:
  - midaz = high therapeutic index but large interindividual variation
  - propofol = predicatble effects, but low therapeutic index
  - chloral hydrate – low therapeutic index and very variable inter-person dose effect

Classification of Hypnotics & Sedatives

- by drug class:
  - benzodiazepines
  - 5-HT1A agonists eg buspirone
  - barbituates eg pentobarbitone
  - others:
    - non barbiturate anaesthetics eg propofol & ketamine
    - chloral hydrate
    - alpha 2 agonists eg clonidine, dexmedetomidine
    - phenothiazines + antihistamines
    - zopiclone
    - mepobramate
    - cholesistokinine antangonists
    - paraldehyde

Receptors & Transmitters

(see GA section)

Benzodiazepines

Table 17.1. Kinetics of some benzodiazepines.

	Diazepam	Midazolam	Lorazepam
Protein binding (%)	95	95	95
Elimination half-life (h)	20–45	1–4	10–20
Volume of distribution ($l.kg^{-1}$)	1.0–1.5	1.0–1.5	0.75–1.30
Active metabolites	yes	yes	no
Clearance ($ml.kg^{-1}.min^{-1}$)	0.2–0.5	6–10	1.0–1.5

- widely used hypnotic agents
- advantages over barbituates, alcohol:
  - specific dose related anxiolytic action
  - lower fatality following overdose
  - lower potential for abuse
  - favourable SE profile
  - fewer drug interactions
  - specific antidote – flumazenil

Chemical

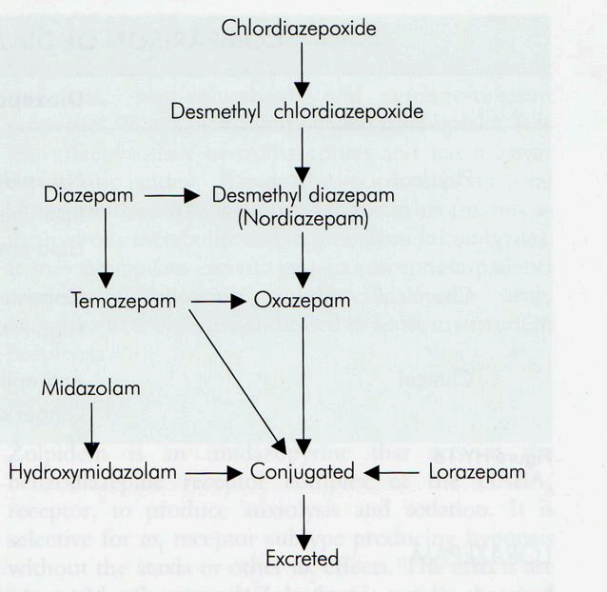
- at least 2 rings:
  - benzene ring
  - diazepine ring

  ↳most have a 3rd ring

Classification

- 1,4 benzodiazepines – diazepam, temazepam, lorazepam
- substituted 1,4 benzodiazepines – triazolam
- 1,5 benzodiazepines – clobazepam

- imidazo-benzodiazepines – midazolam, flumazenil



MOA

- act on γ-aminobutyric acid (GABA) receptors:
  - $GABA_A$ – 19 diff subtypes
    - all are ligand gated Cl channels in post-synaptic membrane
    - mediate fast inhibition ie ↑frequency of Cl channel opening and NOT duration
    - GABA activation of receptor ⇒ influx of Cl into cell ⇒ hyperpolarisation ⇒ ↓excitability
    - receptors have several sites of drug action:
      - benzo's act at particular modulatory site ⇒ facilitation of GABA binding to $GABA_A$
      - other drugs act at diff mod sites on same receptor
        ↳eg barbituates, steroid metabolites, neuropeptides
- limbic system =
  - regulation of emotional behaviour
  - high density of benzo binding in amygdale

  ↳pts with pathological anxiety have ↓ed no GABA-benzo receptor complexs here

Uses

- indications:
  - (days) Rx of anxiety – long acting benzo eg diazepam, lorazepam
  - panic disorder – 2nd line Rx after CBT: eg clonazepam
  - insomnia:
    - 2nd line to education
    - benzo 2-4wks only
    - eg temazepam
  - alcohol withdrawal
  - mm spasm & spasticity - diazepam
  - premeds – diazepam, lorazepam, midazolam
  - seizure termination

Pharmacokinetics

- half live 2-60hrs
- most lipid soluble & good absorb from GI tract
  ↳midaz = water soluble & short duration action
- wide volume of distribution
- redistribution from CNS to periph tissues ⇒ ↓duration of action
  ↳eg diazepam has long duration but short antiepileptic action

- multiple doses:
  - accumulation of drug in fluid & tissues
  - become storage depots ⇒ prolonged sedative actions
- high protein bound (>85%)
- metabolised in GI tract & Liver:
  - hydroxylated or demethylated to
    - active metabolites - most
    - inactive metabolites – lorazepam ∴ preferred in elderly & liver disease
- onset of action post IV dose 1-5mins

Drug Interactions

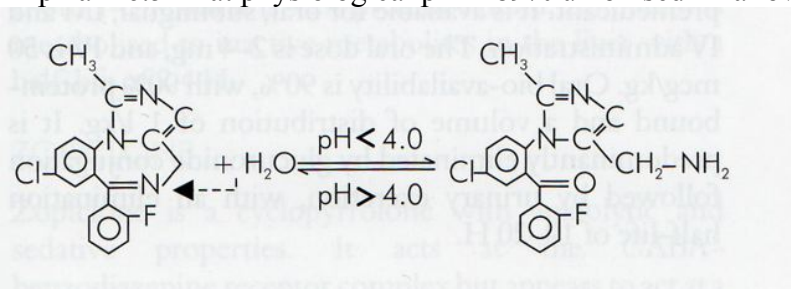
- CNS depressants ⇒ additive effect of CNS depression
  ↳eg alcohol, anti Hs, opiods, psychotropic agents, antidepressants
- many drugs inhibit metab of benzo's (CYP3A4)
  ↳eg azole antifungals/cimetidine/verapamil/omeprazole/macrolides/fluoxetine
- drugs incr metab of benzo's eg carbamazepine, phenytoin, rifampicin, St Johns wort
- stimulants may ↓sedative effects of benzo's
  ↳eg theophylline

Midazolam

- developed 1978

Chemical

- = water soluble imidazo-benzodiazepine (base)
- displays dynamic iseomerism (tautomerism):
  ↳ presented at pH 3.5
  - imidazole ring at nitrogen position 3 – opens and closes
  - ph <4 =
    - ring is open yielding a NH3 positive charged gp
    - ∴ water soluble
  - pH >4 =
    - ring closes ⇒ highly lipid soluble
- pKa = 6.5 ∴ at physiological pH = 89% unionised ⇒ allowing it to cross lipid membranes



- impt as means midaz does not need solubilising agent (eg propylene glycol) when mixed with other agents eg Ringers lactate, acid salts (opioids or anticholinergics)

Presentation

- clear solution of midazolam hydrochloride in 1mg/ml or 5mg/ml
- also contains:
  - 0.8% NaCl
  - 0.01% disodium edetate
  - 1% benzyl-alcohol
  ↳preservatives

Pharmacokinetics

A

- OBA ~44%

- IM 80-100%

D

- 96% protein bound
- Vd 0.8-1.5 l/kg
- Vd may double in critically ill

M

- in Liver:
  - 2 routes:
    - 95% metab by hydroxylation to 1-α hydroxyl-midazolam
      - then conjugated with glucuronic acid
      - ⇒ renal excretion
    - 5% ⇒ oxazepam
- metabolites pharmacologically active
- alfentanil metabolised by same P450 enzyme (3A3/4) ∴ used together ⇒ prolonged action

E

- shows short clinical duration due to combo of:
  - high lipid solubility
  - high metabolic clearance
  - rapid rate of elim
- via urine as hydroxylative derivatives
- ∴ renal impairment has little effect
- clearance 5-9ml/kg/min
  ↳larger than diazepam & lorazepam ∴ effects wear off quicker
- t1/2 elim 1.5-3.5 hrs

Pharmacodynamics

- main actions:
  - hypnosis
  - sedation
  - anxiolysis
  - antergrade amnesia
  - anticonvulsant
  - mm relaxation

Mechanism of Action

- via αγ receptor of $GABA_A$ receptor

Adverse Reactions

- CNS:
  - ↓cerebral O2 requirement & ↓CBF
  - antinoticeptic effects if given neuroaxally
  - ↓s MAC of volatiles by ~15% if used premed
- CVS:
  - ↓SBP ~5%
  - ↓DBP ~10%
  - ↓SVR ~15-30%
  - ↑HR ~18% (as compensation for vasoD)
- Resp:
  - ↓Vt but offset by ↑RR ⇒ little change in MV
  - apnoea – in 10-70% when used as an induction agent
  - blunted response to CO2
- GIT: ↓hepatic & renal blood flow
- others:
  - response to stress:

        - ↓adrenergic response
        - no change in cortisol or renin
    - sig inhibition of phagocyotisis & leucocyte bacteriocidal activity
    - pain on injection

Reversal

- clinical effects/OD can be reversed by:
    - flumazenil
    - physostigmine
    - glycopyrrolate

Dose

- premed: IM 0.07 mg/kg
- IV sedation: 0.07mg/kg titrated
- PO:
    - variable depending on age/cormobidites
    - ~7.mg adult, 3.75mg elderly
    - time to effect ~20mins
- intranasal: use conc solution 0.5mg/kg

Diazepam

- developed 1960

Chemical

- =1,4 benzodiazepine (weak base)

Presentation

- many forms:
    - tabs
    - syrup
    - suppositories
    - solution for rectal admin
    - IV form
- Iv preparation:
    - diff types:
        - clear yellow solution
        - white oil in water emulsion:
            - polyethylene glycol (solubiliser)
            - alcohol
            - bezyl alcohol (antimicrobial preservative)
            - sodium benzoate acid pH 6.2-6.9
- drug = highly lipid soluble:
    - ∴ need for solubilisers (in opposite to midaz)
    - rapid CNS effects
    - large Vd
-

MOA

- facilitates GABA mediated CNS inhibitory pathways

Pharmacokinetics

A

- OBA ~86-100%
- IM injection absorption is slow & erratic

D

- 95% PPB
- Vd 0.8-1.4 L/kg

M

- liver metabolism to active products
- one of longest duration of action 20-70hr half life
- metabolised to active metabolites
    - desmethyldiazepam = major metabolite with t1/2 >100hrs
    - temazepam - <5% metab to oxazepam
    - oxazepam,

E

- metabolites excreted in urine as the oxidised + glucoronide derivatives
- <1% unchanged diazepam excreted
- clearance = 0.44ml/kg/min
    ↳ lowest of all BDZ's
- t1/2 elim 20-40hrs

Adverse Reactions

- CNS –
    - same as midaz
    - may see paradoxical excitement
    - depresses spinal reflexs
    - ↑NDNMBs
- CVS:
    - transient ↓bp & CO after IV administration
    - ↑coronary flow due to coronary artery vasoD
    - ↓myocardial VO2
- resp:
    - large dose ⇒ ↓Resp
    - hypoxic drive effected more than hypercarbic drive
- tolerance & dependence quickly (few days)
- withdrawal:
    - CNS stim – anxiety, sleep disorders, aching limbs, palps, seizures if prev high doses
    - ↓dose 10-20% week
    - rebound insomnia usual but lasts 2-3days

Toxicity

- rash
- GIT upset
- urinary retention
- tolerance
- IV may be irritant to veins (oil in water less so)

Toxic OD Rx

- O2
- promote diuresis with IVF
- hypotension may need vasopressors
- flumazenil – care if on benzo's chronically – withdrawl & seizures
- dialysis of little value

Pharmacodynamics

- main actions & mode of action same as midaz

Cautions/Contraindications

- contraindicated:
    - COPD
    - resp/liver disease
    - sleep apnoea
    - myasthenia gravis
    - dependence other drugs
- short term script only – rapid depenadance requiring prolonged weaning

- caution:
    - glaucoma
    - liver/kidney probs
    - psychoses/depression
    - old or young
    - during preg/lactation

Interactions

- additive CNS depressant effect with other
    - sedatives/hypnotics
    - anti-Hs
    - anaesthetics
    - antidepressants
    - AEDs
- anticholinergic effects of other drugs potentiated
- many drugs inhibit metab of diazepam ⇒ prolonged effect
  ↳eg cimetidine, omeprazole

Dose

- oral 1-10mg
- IV/IM or suppository

Lorazepam

Chemical

- = 1,4 benzodiazepine

Presentation

- tabs of liquid
- clear colourless 4mg/ml

Pharmacokinetics

A

- OBA 90%

D

- 90% PPB
- Vd 1 L/kg
  ↳ ie slightly less than diazepam which explains diazepams longer duration of action

M

- conjugated directly in liver to glucuronide ⇒ inactive water soluble metabolite

E

- 80% as gluuronide
- Cl = 1ml/kg/min
- t1/2 elim 8-25 hrs unaffected by renal impairement

Pharmacodynamics

- CNS – usual benzo effects
- CVS – devoid of any effects
- resp – milder ↓resp – only a prob if severe lung disease
- GIT - ↓pentagastrin stimulated acid secretion
- other: ↓cortisol & glucose levels

Adverse Reactions

Dose

- oral 1-4mg/d in divided doses
- IV = 0.025-0.05mg/kg

Flumazenil

Chemical

- = imidazo-benzodiazepine
- presented as clear colourless solution 100mcg/ml

Pharmacokinetics

A

- well absorbed orally (but high 1st pass metabolism so not given by this route)

D

- 50% PPB
- Vd 0.9ml/kg

M

- extensive liver metab:
  - inactive metabolites= carboxylic acid + glucuronide

E

- 95% renally excreted
- <0.1% unchanged
- Cl 1L/min
- t1/2 elim ~53mins

Pharmacodynamics

- competitive reversible antagonist at benzo site on $GABA_A$ receptor
- only intrinsic effect is slight anticonvulsant effect
- uses:
  - selective reversal agent of benzo sedative effect
    ↳reversal of resp depression not seen
  - other Rxs:
    - wakeup test in scoliosis surgery
    - hepatic encephalopathy
    - alcohol intoxication
- action in 1-2mins; duration of action 1-3hours
  ↳∴ need repeated doses to prevent relapse

Adverse Reactions

- SEs:
  - minor:
    - headache/visual symptoms/↑anxiety/N&V
  - major:
    - can cause dangerous convulsions if:
      - benzo's being taken for epilepsy
      - mixed ODs with CNS stimulants & antidepressants
    - seizures & severe withdrawal if taking benzo's chronically

Dose

- 200mcg over 15sec;
- then 100mcg at 60sec intervals IF required
- don't give >1mg/5mins or max 3mg /1hr
- question diagnosis if no response to repeated doses

Barbituates

- used to be common prescribed for hypnotic & sedative effects
- been replaced by benzos & AEDs
- examples:
  - phenobarbitone – used as AED

- thiopentone – used in GA induction

Zopiclone

- unlike benzo's but has similar pharmacological properities
- hypnotic for Rx of short term insomnia
- rapid absorb, distributed & metabiolised
- half life 5-7 hrs
  ↳extended in old & liver dysfunction
- similar SEs to benzo's and also:
  - thyroid dysfunction
  - alter taste sensation ⇒ bitter taste
- avoid in preg & lactation

Zolpidem

- non benzo
- binds to $GABA_A$ subunit with more selectivity than benzo's
- lacks AED, mm relaxant, antianxiety effects of benzo
- rapid onset of action, short half life
- SEs – similar to benzo's and also:
  - diarrhoea
  - myalgia
  - CNS effects – hallucinations, amnesia, sleep walking
    ↳esp with alcohol

Paraldehyde

- polymer of acetaldehyde
- colourless liquid
- CNS depressant effect similar to alcohol, barbituates, chloral hydrate
- used for IM anticonvulsant in:
  - status
  - convulsions from tetanus
  - toxicity from convulsant drugs
- metab in liver to acetaldehyde

Alcohols

Ethanol

- chemically = hydrocarbon derivative where –H gp replaced by hydroxyl group –OH
- clinically alcohol refers to ethanol

MOA

- denatures proteins by precipitation & dehydration
- CNS depressant causing progressive depression in:
  - cerebrum
  - cerebellum
  - medulla
  - spinal cord
- impairs transmission of impulses at synapses ?MOA
- ?targets:
  - ↑GABA mediated inhibition ⇒ ↓Ca entry into nerve cells
  - antagonise glutamate (which is excitatory)
  - NMDA
  - 5HT
  - Ach (nicotinic)
  - some K channels
- action of alcohol depends on:
  - blood alcohol level
  - ind tolerance
  - rate of ingestion & gastric contents
- CNS effects well documented as euphoria, ↑confidence then ↓ing concentration, judgemnt & memory
- other organ effects:
  - CVS –
    - VD in skin
    - chronic ⇒ HTN, cardiomyopathy & arrhythmias
  - GI –
    - ↑stim of acid gastric juice
    - chronic ⇒ gastritis, pancreatitis, liver damage
  - endocrine –
    - ↑adrenocorticotrophic hormone levels
    - ↓ADH ⇒ dehydration
    - ↓oxytocin ⇒ delayed labour
    - ↓testosterone ⇒ feminisation & impotence
  - lipid metab –
    - low daily intake ⇒ ↑HDL which good

Pharmacokinetics

- very small molecule (weight 46)
- absorb without digestion
- readily diffuses through lipid membranes despite being water soluble
- small amount absorb from stomach; most from small intestine
- peak blood level 30-60mins after ingestion
- distributed to all body tisues: volume of distribution 35L for 70Kg adult
- metabolism:
  - 90% metab in liver by
    - alcohol dehydrogenase: alcohol ⇒ aldehyde
    - aldehyde dehydrogenase: aldehyde ⇒ acetaldehyde
      ↳Asians lack one of enzyme isoforms

        - acetaldehyde ⇒ Aceitc acid ⇒ Acetyl Co A
        - Acetyl Co A enters citric acid cycle ⇒ CO2 & water
    - 10% excreted by lungs, sweat, kidneys
- as plasma levels ↑ ⇒ saturation of alcohol dehydrogenase pathway:
    - max metab 120mg/kg/h
    - ∴ clearance & half life are dose dependant
- plasma levels higher in women in equivalent doses
  ↳smaller level of alcohol dehydrogenase & smaller volume of distribution for water soluble drugs
- heavy exercise may ⇒ slight ↑rate of elimination
- chronic use can ⇒ ↑rate of liver enzyme metabolism BUT then liver damage ⇒ slowed metab
- tolerance:
    - pharmacokinetic – induction of drug metab enzymes
    - pharmacodynamic – adaptation to depressant effects
    - ↑opioid neurotransmission ⇒ euphorant & reinforcing effects of alcohol
- FH of alcohol dependence: ↑release of endorphins in response to alcohol dose

Levels

- subclinical - 30-100mg/dl – slight deterioration in function
- emotional instability = 100-200 = ↓inhibitions, slowing reflexs, sigsn of intoxication
- confusion = 200-300 - ↓pain, staggering gait, slurred speech
- stupor = 300-400 = marked ↓pain, unco approaching paralysis
- coma/death = >400 – LOC, ↓reflex & resp, hypothermic, ↓circulation possible death

Uses

- antidote for methanol & ethylene glycol poisioning

Adverse Reactions

- diuretic effect:
    - ↑fluid intake
    - inhibition of ADH
- chronic alcohol use:
    - hyperlipidaemia
    - liver damage – fatty liver, alcoholic hepatitis, cirrhosis
- alcohol abuse:
    - social problems
    - neuropathies – periph & central
    - myopathies – skeletal & cardiac
    - hepatotoxcity ⇒ oesophageal varices &death
    - GI or haematological toxicity
    - korsakoff's psychosis, alcohol dementia, cerebellar degen
- hangover:
    - headache, nausea, vertigo, pallor, sweating, tachycardia, nystagmus
    - caused by:
        - hypoglycaemia
        - dehydration – antiADH effect
        - electrolyte imbalances
        - persistent lactic acid & acetaldehyde in blood

Cautions/Contraindications

- pregnancy risk ⇒
    - fetal alcohol syndrome = mental retardation & craniofacial dysgenesis
    - growth retardation

  ↳esp 1st trimestere >2g ethanol/kg/day
- avoid if lactation

Interactions

- antiH, antidepressants, opiods, hypnotics/antipsychotics: additive effect sof enhanced CNS depression

- some cefalopsorins, oral DM drugs, metronidazole:
    - inhibit aldehydr dehydrogenase ⇒ ↑levels of acetaldehyde ⇒
        - flushing, stomach pain, D&V
        - ↑HR, ↓bp
        - mild to severe hypoglycaemia
- phenytoin ⇒ ↑liver metabolism ⇒ ↓anticonvulsant action
  ↳can see opposite in acute ingestin ⇒ ↑phenyton levels
- warfarin ⇒ ↓liver metab ⇒ ↑INR
- additive effects:
    - salicylates – GI irritation & bleeding
    - GTN – VD & syncope
    - paracetamol - ↑ed hepatic tox of paracetamol

Dose

- av drink contains 5-20grams of ethanol

Methanol

- toxic dose 100-200mls
- permanent blindness seen in as little as 10mls
- methanol metab different to alcohol:
    - methanol ⇒ formaldehyde ⇒ formate
      ↳inhibits respiration & glycolysis in retina

- metabolites more toxic and take longer to metabolise & are strongly acidic
  ↳(formic acid 2-3 days)

Chemotherapeutic Agents

- anaesthetists:
  - rarely involved with dministration of these drugs
  - do have to assess pts on these drugs & deal with toxicity of them
- impt when pt presenting for surg while on or after course of chemo
- generally chemotherapy drugs ⇒ bone marrow suppression ie
  - anaemia
  - thrombocytopaenia
  - neutropaenia
- pts recently finished chemo may have norm counts but will be unable to mount a response to surgical stress or blood loss

Agents

Vinca Alkaloids or platinum Agents

- eg vincristine
- major SEs:
  - peripheral neuropathy ⇒ document carefully & position carefully
  - SIADH

Anthracyclines

- eg doxorubicin + Adriamycin
- major SEs:
  - cardiomyopathy:
    - related to total cumulative dose
    - usually not reversible
    - get cardiac assessment if not already done eg gated pool scan or ECHO
      ↳ = nuclear medicine Ax of RV & LV
  - ECG changes
  - arrhythmias: SVT or ventricular
  - heart block

Bleomycin & Busulfan

- major SEs:
  - pulmonary fibrosis:
    - = dose dependant
    - Ax by PFTs & CXR
  - Avoid FiO2 >30% in pts recently exposed to bleomycin
    ↳ can promote lung injury or ARDS

Cisplatin, Hydroxurea + Methotrexate

- [All]:
  - renal insufficiency
- [Cisplatin]:
  - peripheral neuropathy – cisplatin
  - significant electrolyte abnormalities - ↓Kg, ↓Mg
- [methotrexate]:
  - pneumonitis – esp in RA
  - interstitial lung disease
  - hepatic impairement
  - GIT disturbances
  - mucositis/mouth ulcers

Others

- cyclophosphamide:

    - cardiac toxicity
    - prolongs sux duration
- mitomycin: interstitial pneumonitis

AntiMicrobials

Agents

- Classifications
    - Antibacterial
    - Anti viral
    - Antifungal
    - Antiprotozoal
    - Antiparasitic

Bactericidal vs Static

- Eg bacteriocidal :
    - Penicillins
    - Cephalosporins
    - Aminoglysosides
    - flouroquinolones
- Use these when :
    - Bacterial endocarditis
    - Immuno-surpressed pts

Renal & Hepatic Insufficiency

- Must reduce dose if present esp:
    - B-lactams
    - Aminoglycosides
    - Tetracyclines (except doxycycline)

Therapeutic Monitorring

- Must to ensure avoid toxicity esp:
    - Aminoglycosides
    - Vancomycin

Mechanism of Action

- On cell wall –
    - penicillins,
    - cephalosporins,
    - carbapenems – imipenem
    - glycopeptides eg vancomycin
- inhibitors of protein synthesis –
    - macrolides ie erythromycin
    - lincosamides eg clindamycin
    - aminoglycosides – gent
    - tetracyclins
    - chloramphenicol
    - oxazolidinones eg linezolid
- inhibitors of folate synthesis: sulphonamides & trimethoprim
- inhibitors RNA synthesis – rifampicin
- inhibitors DNA synthesis – quinolones, metronidazole
- misc: eg metronidazole, nitrofurantoin

Resistance to Antibiotics

- Can be result of:

  - Failure to reach target site – failure to permeate membrane eg penicillins in gram –ve
  - Enzyme inactivation – eg B-lactamase enzymes
  - Alteration of target site – eg single point mutations in penicillin binding protein
  - Active extrusion of antibiotics

- Commonly caused by:
  - Conjugation – plasmid passes resistance factor during direct bacteria contact
  - Genetic mutation

β Lactam Agents

Penicillins

- 6-amino-penicillanic acid:
  - thiazolidine ring bound to ß lactum ring
- βlactam ring:
  - essential for MOA
  - resistant bacteria that posses β lactamase ⇒ target ß lactum ring ⇒ inactivate penicillin

MOA

- bacterial cell wall =
  - rigid cross linked structure of peptidoglycan
  - glycan chains consisting of amino sugars
  - thickness of wall varies:
    - gram +ve = 50-100molecules thick
    - gram –ve = 1-2 molecules thick
- pencillins bing to penicillin binding proteins (PBPs)
- penicillins :
  - weaken cell wall by **inhibiting transpeptidase enzyme** responsible for cross linking glycan strands
  - inactivation of an inhibitor of autolytic enzymes
- if penicillin successful ⇒ intracellular osmotic pressure then bursts cell open ⇒ lysis
- penicillins = bactericidal time dependant drugs:
  - kill bacteria
  - action influenced by βlactamase enzymes & inhibitors of β lactamase
    ↳eg clavulanate in augmentin
- generally more effective on gram +ve than gram –ve
  ↳adjuncts such as β lactamase inhibitors make more effective

Causes of Resistance

- ß lactamases:
  - = >50types – impt in staphs, haemophilus, N gonnorrhea
    ↳ but not streptococci
  - use B lactamase inhibitors to prevent:
    - clavulanic acid
    - sulbactam
    - tazobactam
- ↓permeability of outer membrane – esp in gram –ve
  ↳ outer membrane limits penetration of hydrophilic antibiotics
- modified penicillin binding sites eg MRSA
- defective autolytic enzymes

Naturally Occuring Penicillins

Narrow Spectrum

- 3 major types:
  - benzylpencillin & penicillin V
  - procaine penicillin } must not be given IV otherwise severe neuromuscular damage & CNS effects eg hallucinations, anxiety

  - benzathine penicillin
- = naturally occurring
- major disadv's is
  - susceptibility to ß lactamases
  - poor absorption in GIT
  - short half life
- action:
  - gram +ve & -ve cocci
  - some gram –ve rods

Semi-Synthetic Penicillins

- created by adding different chains on nucleus (R_1)

Narrow Spectrum Penicillinase-Resistant

- = resistant penicillins with antistaphylococcal activity
- eg fluclox
- chemical alteration in structure means resistant to penicillinase produced by staph
- not effective against methicillin-resistant bacteria

Broad Spectrum β lactamase sensitive Aminopenicillins

- eg amoxicillin & ampicillin
- ∴ destroyed by ß lactamase
- similar spectrum to penicillins BUT greater efficacy against selected gram –ve bacteria ie H. influenzae
- need to combine with ß-lactamase inhibitor eg clauvanic acid to be effective against staph aureus & e coli ⇒ ie augmentin ↳ both β lactamase producing bacteria

Extended Spectrum Penicillins (Antipsuedomonal)

- eg piperacillin; piperacillin-tazobactam (tazocin)
- ↑ed potency against gram –ve ie anti-pseudomonal activity

Pharmacokinetics

A

- different degrees of oral absorption
- wide distribution into all body tissues incl across placenta
- hydrophilic ∴ does not cross bbb unless meninges inflamed

E

- =mainly renal
- 90% by active tubular secretion into proximal tubule
- secretion can be blocked by probenecid ⇒ ↑serum concentration & ↑ed t1/2

Drug Interactions

- allopurinol – amoxicillin ⇒ ↑risk rash
- antiplatelet drugs – high dose IV penicillin ⇒ inhibition platelet aggregation
- COCP – combined with amoxicillin & penicillin V ⇒ ↓effectiveness OCP
- probenecid - ↓ed renal tubular secretion of penicillins ⇒ ↑plasma conc & half life penicillins

Adverse Reactions

- rare direct toxicity
- GI: alter gut flora ⇒
  - disturbance
  - superinfection with other organism not sensitive to penicillin
- hypersensitivity reactions:
  - I: anaphylxis
  - III: serum sickness reaction – rash, joint pain, fever

  ↳ 10-15% who reacted, will react again
- rare:
  - cholestatic hepatitis esp fluclox & augmentin

- leucopaenia
- mental disturbances – procaine penicillins
- convulsions
- platelet dysfunction with taz

Warnings & Contraindications

- caution:
  - IV penicillins contain large amount of Na – caution in heart failure
- contra in:
  - penicillin hypersensitivity
  - bleeding disorders
  - congestive heart failure
  - CF
  - GI disease
  - EBV

Cephalosporins

- isolated from sea sewerage outlet
- chemical modification of central active component & addition of side chains have altered activity
- divided into 1st,2nd, 3rd, 4th generation:
  ↳ through 1st – 3rd generations see ↓ing gram +ve cover & ↑ing gram –ve cover
- widespread use has led to MRSA & C diff

MOA

- same as penicillin: inhibit bacterial cell wall synthesis
- bacteridal
- resistance mechanisms = same as penicillin
- rapidly dividing bacteria most effected
- 1st gen eg cephazolin, cephalexin –
  - most active against gram +ve & non-enterococcal streptococci
  - inexpensive & well tolerated
  - commonly used for peri-op prophylaxis
- 2nd gen eg cefuroxime, cefaclor –
  - ↑ed activity against gram –ve incl H influenza
  - cefuroxime = only 2nd gen effective in meningitis
- 3rd gen eg ceftriaxone–
  - ↑ed ability to resist ß lactamass of many gram –ve bacilli eg e coli, klebsiella, proteus, H influenza ↳ but less active against gram +ve
  - only gen to achieve therapeutic levels in CSF
  - ceftriaxone =
    - esp effective against Neisseria & haemophilus
    - longest t1/2 elim
- 4th gen eg cefepime – same as 3rd but ↑ing resistance to βlactamase

Pharmacokinetics

- cephalexin & cefaclor 95% bioavailability
- cefuroxime 50% bioavailability

Uses

- used for penicillin allergic pts but is cross reactivity of 5-15%
  ↳∴ avoid if anaphylaxis

Adverse Reactions

- GI
- rash, oedema
- thrush
- Stevens-Johnson Syndrome

- haemolytic anaemia
- neurotoxicity ⇒ seizures
- thrombocytopaenia & bleeding

Cautions/Contraindications

- caution in impaired vit K synthesis
- heart failure or Na restriction
- anaphylaxis to penicillins

Interactions

- anticoags & cephazolin or ceftriaxone: ↑risk bleeding. Cephs interfere with vit K metab in liver ⇒ hypoprothombinaemia
- NASIDs & cephazolin & ceftriaxone: additive effect on platelet inhibition
- probenecid - ↓renal tubular secretion of cephalosporins ⇒ extended half life.
  ↳NB doesn't effect secretion of ceftriaxone

Carbapenems

- eg imipenem, meropenem
- related to β lactam Abxs but different structure: have another 5 membered ring in chemical structure

MOA

- bind to penicillin binding proteins ∴ inhibiting bacterial cell wall synthesis

Pharmacokinetics

- imipenem is degraded by renal dipeptidase ∴ has to be given with inhibitor of this enzyme (cilastin)
- IV administration ⇒ rapid peak plasma conc
- half life 1-4hrs
- excreted unchanged in urine

Uses

- have broadest spectrum activity of all the Abx's
- work against gram +ve & -ve & aerobic & anaerobic bacteria eg listeria, (some) pseudomonas, enterobacteria
- not active against MRSA
- drugs expensive & ∴ reserved for nocisomal/life threatening infection
- meropenem – good for meningitis (imipenem not used as ↑s risk of seizures)

Adverse Reactions

- GI
- CNS: confusion, psych problems, insomnia
- Livr impairement – monitor LFTs
- seizures – esp if pre-existing CNS problems

Cautions/Contraindications

- avoid if carbapenem or penicillin allergy
- kidney impairement
- CNS disorders

Interactions

- probenecid ⇒ ↓renal secretion of carbapenems ⇒ ↑risk toxicity
- ganciclovir ⇒ seziures

Glycopeptides

- eg vancomycin & teicoplanin
- ↑ing problems with vanc resistance

MOA

- inhibit bacterial wall synthesis via **inhibition of glycopeptidase synthase**
- bactericidal – unless against streptococci
- synergises with aminoglycosides

- primarily active against gram +ve incl MRSA

Pharmacokinetics

- poor absorption for GI tract – only used this route for pseudomembrnaous colitis
- Vd large
- vanc half life 4-6hrs
- teicoplanin half life 100hrs
- ~100% kidney excretion ∴ need close dose adjustement in renal impairment
- levels monitored in vanc; not in teic unless Rxing severe infection eg endocarditis

Uses

- guidelines to ↓resistance:
  - MRSA & MRSE infections
  - C diff – unresponsive or relapse to metronidazole
  - antibacterial prophylaxis for endocarditis before surgery/procedures in penicillin allergic people
  - surg prophylaxis for major procedures if hosp has high rate of MRSA/MRSE

Adverse Reactions

- rash, itching, chills,fever
- ototoxicity, nephrotoxicity
- rare:
  - red man syndrome – caused by too rapid infusion (with mostly vanc) ⇒ widespread histamine release ⇒
    - chills, fever
    - tachycardia
    - pruritis with red rash over whole body

Cautions/Contraindications

- contra:
  - glycopeptides hypersensitivity – is a cross reaction between teic & vanc
  - deafness or Hx of hearing loss
  - renal disease

Interactions

- aminoglycosides ⇒ ↑otoxocity & nephroxicity
- bile acid binding resins (cholstyramine) & oral vanc ⇒ ↓efficacy of drug
- mm relaxants/GAs & vanc ⇒
  - ↑neuromuscular blockade by both types mm relaxants
  - ↑vanc SEs

  ↳complete infusion prior to GA

Inhibitors of Protein Synthesis

- summary MOA:
  - macrolides, lincosamides: (BS⇒BC) 50S blockers ribosome subunit
  - chloramphenicol: (BS for most): inhibit 50S
  - tetracyclines: (BS) reversible block 30S
  - aminoglycosides: (BC) irreversible block 30S

Macrolides

- contain a many membered lactone ring which has one or more sugar molecules attached
- eg azithromycin, clairthromycin, erythromycin, roxithromycin

MOA

- bind to 50S ribosomal subunit ⇒ effects translocation
- bacteriostatic in mod concentrations ie inhibit growth

  ↳at high conc may have limited bactericidal properties

Resistance

- change in binding site – 50S subunit

Pharmacokinetics

A

- claryith & azith = more acid stable than eryth
- peak plasma conc 2-4 hours (roxithromycin 1-2hrs)
- good oral absorb 30-50%

D

- most fluid compartments incl placenta
- does not cross bbb

M

- liver metab:
  - erythro partly inactivated
  - clarythro – converted to active metabolite
  - azithro – resistant to inactivation
- excretion:
  - azithroymcin – bilary
  - clarithryo – urinary
  - erythro – bilary
  - roxithro – faeces
- T1/2:
  - erythro = 90min
  - clarithro = 3hrs
  - azithro = 24hrs

Uses

- similar actions against gram +ve & gram –ve
- used when pencillin allergies
- clarithromycin (& PPI & amoxicillin) used in H pyrlori eradication

Adverse Reactions

- azithro:
  - GI, dizzy & headache.
  - rare: interstitial nephritis
- clarithro:
  - anorexia, GI, severe anaemia, abnormal taste
  - rare: C diff, liver failure, ↓platelets
- erytho:
  - GI, vag thrush
    ↳↓s GI transit time via action on motilin receptors
  - rare: hearing loss, pancreatitis, liver failure
  - Rapid IV dose ⇒ vent arrhythmias
- roxithro:
  - GI, rash, angiooedmea, asthma & bronchospasm

Cautions/Contraindications

- caution in:
  - liver disease
  - hearing loss (erythro)
  - kidney impairement (clarithro)
  - cardiac arrythmias (erthro)

Interactions

- macrolides inhibit CYP3A4 ⇒ ↑ levels other drugs
  - ↑benzo's
  - ↑carbamazpeine
  - ↑dig
  - ↑theophylline

- ↑warf

- erythro most drug interactions whereas azithro least

Lincosamides

- eg clindamycin

MOA

- same as macrolides
  - ↳bind to ribosome 50S subunit preventing peptide bond formation
  - ↳bacetiostatic & cidal at high doses

Pharmacokinetics

- well absorb – take with full glass of water
- rapid distribution does not cross bbb
- t1/2 elim 21hrs
- peak conc in approx 1hr of oral administration (3hrs IM injection)
- metab in liver, active metabolites
- excreted in bile (10% unchanged) & urine

Uses

- potent Abx for
  - gram +ve cocci = serious strep & staph infections
  - anaerobes eg bacteroides
- Rx bone/joint, pelvic infection, abdo, skin & soft tissue infection

Adverse Reactions

- GI distress – pain, D&V
- candiasis
- neutropaenia
- ↓platelets
- pseudomembranous colitis & C Diff:
  - most limiting factor in use
  - overgrowth of C Diff ⇒ release of toxins ⇒ inflam of colon
  - risk gps incl elderly, immunocompromised, pre-existing inflam bowel disease

Cautions/Contraindications

- caution in high risk gps

Interactions

- chloramphenicol or erythro – antagonise effects of clindamycin
- NMJ blockers - ↑ed blockade ⇒ weakness & resp paralysis

Dose

- oral clindamycin 15-450mg 6-8hrly

Aminoglycosides

- include gentamicin, tobramycin & neomycin (oral aminoglycoside)

MOA

- irreversible binding to 30S ribosome subunit
- interferes with mRNA ribosome complex ⇒ miscoding ⇒ defective bacterial proteins ⇒ cell death
  - ↳∴ bactericidal

Resistance

- bacterial enzymes
- failure of penetrations ⇒ can overcome with concomitant use of penicillin +/- vanc
- lack of binding to ribosomes (rare)

Pharmacokinetics

A

- highly polar - 1% absorb from GI tract

- rapid IM absorb – peak conc 30-90mins

D

- strongly polar molecules (hydrophilic) ∴ don't cross bbb
  ↳ but may cross placenta

E

- entirely elim by kidneys
- 50% excereted unchanged in 24hrs
- plasma half life 2-3 hrs
- plasma conc monitoring essential to prevent adverse reactions
  ↳if therapy >48hrs:
- have significant post Abx effect:
  - concentration dependant killing – od large dose ⇒ bactericidal levels
  - inhibit growth of organisms after conc fallen below min inhibitory conc line
  - ∴ once daily dosing has been shown to be as good as bd/tds dosing

Uses

- for serious or life threatening infections
- monotherapy –
  - very effective gram –ve
    ↳eg pseudomonas, E coli, proteus, klebsiella
  - limited gram +ve activity
- combo with β lactam agents provide synergistic effect against eg listeria & staph aureus
  ↳combo enhances aminoglycosides penetrations into cells

Adverse Reactions

- GI
- tinnitus & ototoxicity (cochlear & vestibular):
  - irreversible damage to sensory cells in cochlea & vestibular organ
  - vestibular damage (streptomycin, gent) ⇒ vertigo, ataxia
  - cochlear damage (neomycin, kanamycin) ⇒ hearing loss

  ↳ ototoxicity:
    - neomycin the least
    - concomitant use of other ototoxics make it worse eg loops
- nephrotoxic:
  - ie tubular damage
  - reversible if drugs stopped
  - more likely in pre-existing renal disease
  - ↑risk with other nephrotoxics eg cephalosporins
- optic nerve dysfunction – seen with streptomycin
- NMJ blockade ⇒
  - v rare by self
  - more likely with concurrent NDNMBs
  - caused by inhibition of Ca uptake which is required for exocytotic release of Ach

Cautions/Contraindications

- extreme caution:
  - dehydrated – renal function
  - myasthenia gravis
  - parkinsonism
  - hearing impairement

Interactions

- multipharmacy of aminoglycosides: ↑risk oto & nephrotoxicity & NMJ blockade
  ↳hearing los may progress or reverse after stopping drug
- loops - ↑risk irreversible hearing loss
- all mm relaxants - ↑blockade or NMJ

- NSAIDs – effect on renal function ⇒ ↑levels of aminoglycosides
- penicillins & cephalosporins – Abx action of aminoglycoside enhanced 2nd to greater penetration
  ↳must not mix preparations as not compatible

Dose

- gent & tobramycin 4-7mg/kg IM/IV once daily

Tetracyclines

- eg doxycycline, minocycline, tetracycline

MOA

- bacteriostatic for many gram –ve & gram +ve
- exhibit cross sensitivity & cross resistance
- inhibit protein synthesis by reversibly blocking 30S ribosome subunit ∴ preventing access of tRNA to mRNA ribosome complex
  ↳same as aminoglycosides but reversible binding

Pharmacokinetics

A

- oral variable absorb – better on empty stomach (doxy fully absorbed)
- some drugs chelate metal ions ⇒ ↓absorption if taken with milk/antacid/Fe supplements
  ↳ doxy encouraged to take with mik ⇒ ↓gastric SEs

D

- conc in CSF 10-25% of plasma conc after IV dosing
- cross placenta & breast milk
- drugs localise in teeth, liver, spleen, tumours, bone

E

- doxy metab in liver ⇒ elim via bile
- rest are excreted in kidneys
- doxy half life 12-24hrs, tetracycline 6-12hrs

Uses

- 1st choice: mycoplasma, chlamydial, cholera, rickettsial
- other:
  - gr+ve & gr –ve infections
  - acne
  - anthrax
  - UTI
- mixed resp infections eg bronchitis

Adverse Reactions

- doxy:
  - oesophagitis
  - ataxia
  - GI – modifies gut flora ⇒ vit B deficiency +/- supra infection – C diff ⇒ pseudomembranous enterocolitis
  - photosensitivity – can occur 3days post sun exposure
  - bones/teeth: chelate Ca ⇒ dental hypoplasia +/- bone deformities
    ↳ ∴ contraind in pregnant & kids
  - fungal overgrowth
- renal failure – can exacerbate renal failure
- rare:
  - liver/pancreatitis
  - beign ↑ICP

Cautions/Contraindications

- contra:

- kids <8 – teeth
- pregnant women >18/40

Interactions

- antacids, Ca/Fe/Mg supplements ⇒ formation non absorbable complex ⇒ ↓absorb
  ↳separate from Abx by 2-3hrs
- bile acid binding resins ⇒ ↓absorb
- oestrogen OCPs: ↓contraceptive effectiveness & breakthrough bleeding

Dose

- doxy – 200mg od (day 1); then 100mg od thereafter

Chloramphenicol

MOA

- inhibit protein synthesis by binding to 50S ribosome subunit
- bacteriostatic for most organisms bactericidal for H influenza

Uses

- reserved for serious infections:
  - multi resistant H influenza
  - meningitis whene penicillin CI'ed
  - topical

Resistance

- production of chloramphenicol acethyl-transferase

Pharmacokinetics

- complete & rapid oral absorption ⇒ peak 2hrs
- wide distribution in body fluids incl CSF
- 30-50% PPB
- liver metab
- 10% excreted unchanged in renal
- T1/2 2hrs

Adverse Reactions

- BM depression (rare)
- grey baby syndrome =
  - incomplete inactivation + excretion
  - D&V
  - flaccidity
  - hypothermia
  - grey colour
- hypersensitivity reactions

Interactions

- aminoglycosides – inhibits penetration of aminoglycoside into cell

Fusidic Acid

- narrow spectrum steroid Abx
- used against gram +ve bacteria
- inhibits protein synthesis
- well absorbed
- some metabolised, some excreted in bile
- used in combo with fluclox for serious staph infections esp osteomyelitis
  ↳ orthopods like to use it in joint transplants

Inhibitors of DNA Synthesis

Fluroquinolones

- cipro, moxifloxacin, norfloxacin, ofloxacin

MOA

- synthetic broad spectrum agents with bactericidal activity
- interfere with bacterial topoisomerase II (DNA gyrase) & IV
  ↳these involved in supercoiling of DNA required for bacteria DNA duplication/transcription/repair
- similar enzyme exists in human cells but only inhibited at mugh higher quinolone conc

Pharmacokinetics

- oral bioavaiable:
  - cipro 50-70%
  - 86 moxifloxacin
  - 30-40 norfloxacin
  - 95-100% ofloxacin

  ↳ Mg & aluminium interferes with absorption ie antacids
- widely distributed – does not cross bbb
- cipro & moxifloxacin only ones for IV use
- partly metab in liver & excreted by kidneys
  ↳ ofloxacin = mainly renaly excreted

Uses

- broad gram +ve & gram –ve (especially)
- excellent against:
  - H influenza & enterobacteriaceae
  - N gonnorhea
  - pseudomonas
  - campylobacter
- NB:
  - weak inhibition of streptococci & pneumonococci
  - high resistance with staphs ie avoid in MRSA
- individual quinolones vary in activity eg cipro – not active against strep pneumoniae

Adverse Reactions

- damage cartilage <18yrs old
- GI
- photosensitivity
- dizzy & drowsy
- Rare:
  - CNS stim – psychosis, confusion, hallucinations, tremors
  - steven johnson syndrome
  - face/neck swelling
  - SOB
  - interstitial nephritis
  - tendon rupture - ↑risk if also steroids or >60yrs

Cautions/Contraindications

- caution with CNS disorders eg epilepsy

Interactions

- antacids, ferrous sulphate - ↓absorb cipro
- nitrofurantoin – antagonises quinolone effect
- theophylline & xanthines – cipro & norflox ⇒ ↓metab of theophyllines ⇒ ↑plasma level theophylline
- warf – with some quinolones ↑warfarin levels

Inhibitors of Folate Synthesis

Sulphonamides

- eg commonly used in combo = trimethoprim-sulfamethoxazole (co-trimoxazole)

MOA

- both bacteriostatic
- structurally similar to PABA
- [sulphonamides]:
  - competitively inhibits bacterial enzyme dihydropteroate synthetase
    ↳this incorporates PABA into dihydrofolic acid
  - ↓ed amount dihydrofolic acid ⇒ ↓of tetrahydrofolic acid ⇒ ↓synthesis of purines, thymidine ∴ DNA
- [trimethoprim]:
  - folate antagonist
- susceptible bacteria are sensitive because they need to synthesise their own folic acid
- combo of trimethoprim & sulfamethoxazole is synergistic:
  - blocks 2 steps in synthesis of folic acid

  ↳although ↑ed SEs and often no ↑efficacy

Pharmacokinetics

- absorption:
  - trimethoprim quicker 2hrs
  - sulfamethoxazole 4hrs
- trimeth ⇒ into tissues(large Vd); sulfa remains in ECF (Vd variable depending on PPB)
- both cross bbb
- excretion:
  - sulphonamides: metab in liver ⇒ urine excretion
  - trimethoprim: weak base ∴ elim via kidneys is enhanced by acidifying the urine

Uses

- use has declined because of bacterial resistance
- prophylactic against pneumocystis carinii eg AIDS pneumonia
- otherwise:
  - uncomplicated UTIs
  - epididymo-orchitis & prostatitis

Adverse Reactions

- [sulph]:
  - N&V & headaches
  - metHb – rare
  - hepatitis
  - hypersensitivity reactions
  - BM depression + crystaluria
- [trimeth]:
  - N&V & skin rashes
  - megaloblastic anaemia – folate deficiency

Cautions/Contraindications

- caution in
  - HIV people - ↑ed risk of allergic reactions
  - renal impairement
- contraindicated:
  - people prev allergic reaction to sulphonamide or related drugs eg thiazides, parecoxib

Interactions
- LA procaine antagonises effects of sulphonamides
- cyclosporin : sulfonamides ⇒ ↑nephrotoxicity
- methotrexate: sulfonamides ↓renal clearance of MTx
- phenytoin: metab of phenytoin inhibited ⇒ ↑phenytoin levels
- warf: warf metab inhibited ⇒ ↑warf levels

Dose
- ration trimeth:sulfa 1:5
- 80/400mg-160/800mg every 12hrs

Misc Abx's
Metronidazole
MOA
- drug reduced within anaeaerobic microbe cells to short acting cytotoxic agent
- agent interacts with DNA ⇒inhibition of bacterial synthesis ⇒ cell death
- selectively toxic to many anaerobes & protozoa
- bactericidal

Pharmacokinetics
- oral met well absorb & distributed throughout body
- good tissue penetration incl bbb, vag secretions, sminal fluid, saliva, breast milk
- peak plasma conc 1-2hrs, half life 8hrs
- 50% metab in liver
- excreted in kidney

Uses
- preop prophylactic regimens for elective colorectal surgery
- amoebiasis (intestinal & extraintestinal)
- bone infections
- brain abscess
- CNS infections
- endocarditis

Adverse Reactions
- Gi effects incl anorexia, dry mouth, change taste
- CNS toxicity - dizziness/headache/seizures
- adverse reactions with alcohol – disulfiram like effects
- leucopaenia
- neuropathy/pancreatitis

Cautions/Contraindications
- caution:
  - renal/liver disease
- avoid:
  - blood diseases
  - severe liver disease
  - active organic CNS disease

Interactions
- alcohol – interferes with metab of alcohol ⇒ accumulation of acetaldehyde ⇒ disulfiram effects:
  - flushing
  - headaches
  - N&V & abdo distress
- warf – inhibits warf metab ⇒ ↑levels
- barbituates – induce metab of metronidazole ⇒ ↓effectiveness of Abx

- disulfiram – avoid within 14days of Abx

Nitrofurantoin

- bacteriocidal
- MOA not fully understood
- resistance in susceptible organisms = rare
- avoid combo with quinolones
- caution in G6PD deficiency
- 100% OBA, then rapid renal excretion (filtered & secreted)
  - ↳ ∴ therapeutic conc in urine & not plasma
  - ↳ renal failure ⇒ toxic plasma levels
- acute allergic pneumonitis can occur within days of Rx:
  - fever
  - cough & SOB
  - CP
  - rash

  ↳more common middle aged women
- chronic use >6/12 ⇒ interstial pulmon fibrosis

PhotoSensitivity Comparison

- most likely to cause (top to bottom)
  - doxycyline
  - amiodarone
  - chlorpromazine
  - sulphonamides
  - captopril
  - enalapril
  - BFZ
  - carbamazepine

Surgical Antibiotic Prophylaxis

- indicated whenever complicating infection would be associated with significant morbidity/mortality
- in order for max effect antibiotic must be
  - at therapeutic conc in tissues prior to inicison
  - must administer prior to tourniquet inflation
  - remain there for duration of procedure:
    - cefazolin t1/2 1.8 hrs ∴ for proceudres >8hrs should consider further doses
- can use oral regimine but must be initiated 24hrs prior
- should use broad spectrum Abx – generally cephlasporins used
  - should avoid 3rd generation as
    - no ↑ed efficacy & associated with ↑microbial resistance
    - altered gut flora
  - actual drug should be based on local prevalence of resistant bacteria MRSE/MRSA
- Abx should not be continued >24hrs post op
- single dose prophylaxis has advantages:
  - cheaper
  - less bacterial resistance
  - evidence to suggest more efficacious

Antiseptics & Disinfectants

- goal is to supress or prevent microbial infection

Definition

- antiseptic = applied to living tissue
- disinfectants = applied to inanimate surfaces
- same compound can act as both depending on:
  - drug conc
  - conditions of exposure
  - number of organisms

Ideal Agent

- broad spectrum
- potent germicidal activity
- rapid onset, long lasting
- withstand range of environmental factors eg pH, temp, humidity
- retain activity in face of pus, necrotic tissue, soil
- high lipid solubility
- high dispersibility
- non-toxic to host & not impair healing
- non staining

MOA

- most agents exert activity by
  - denaturation of intracellular protein
  - alteration of cellular membrane - often by extraction of membrane lipids
  - enzyme inhibition

Categories

Alcohols

- MOA:
  - denature protein
  - damage cell membrane
- not effective against spores
- isopropyl alcohol vs ethyl alcohol:
  - iso = greater bactericidal
  - ethyl = less toxic

Biguanides

- eg chlorhexidine
- MOA: disrupts cytoplasmic membrane
- potent against most gram +ve, and some gram –ve
  - 0.1% solution in 15 sec bactericidal against staph aureus, Ecoli, psuedomonas
- not active against spores
- activity is enhanced by alcohols & ammonium compounds
- one of most widespread used antiseptics:
  - 0.5% solution with 70% isopropanol
- newly developing risk of anaphylaxis
- shouldn't be used with anionic detergents ie soap

Oxidising Agents

- eg Hydrogen peroxide:
- MOA:
  - liberates oxygen when in contact with catalase present on wound & mucosal surfaces
  - $\Rightarrow$ alters microbial proteins
- short acting germicidal effect

- limited tissue penetration
- no action on spores
- uses:
    - 3% for cleaning antiseptic
    - 58% for sterilisation of instruments

Halogen Containing Compounds

- iodine:
    - potent germicide, low toxicity to tissues
    - solution with 50ppm iodine kills:
        - bacteria 1min
        - spores 15min
    - added to ethanol ↑s antibacterial activity
- chlorine:
    - limited in humans due to irritation to skin & mucous membranes

Metals

- silver:
    - can be irritant to tissues but excellent antibacterial effects
    - 0.1% solution = bactericidal, 0.01% = bacteriostatic
    - colloidal silver compound 0.5% dressing used in burns:
        - slow release silver ions
        - sustained bacteriostatic effect
        - non irritant

Surface Active Compounds

- surfactants ⇒ ↓surface tension of an aqueous solution & are used as :
    - wetting agents
    - detergents
    - emulsifiers
    - antiseptics
    - disinfectants
- classified based on position of hydrophobic moiety in molecule:
    - anionic surfactants:
        - = soaps
        - generally dissociate in water into
            - hydrophilic K+, Na+ ions
            - lipophilic fatty acid ions
        - tend to be alkaline pH8-10 ⇒ irritant to skin/mucosa
        - action by emulsifying surface dirt, epithelium, bacteria & then rinse away
        - added antiseptics sometimes added in
        - are incompatible with cationic surfactants
    - cationic surfactants:
        - = gp of alkyl or aryl substitutes quaternary ammonium compounds
        - active at cell membrane where are absorbed & ↑permeability
        - inactivated by anionic surfactants
        - limited value except on skin
        - not active against viruses & spores
        - toxic to mucous membrane >1%
        - may form a film under which microorganism can survive

Antivirals

- to be most clinically effective antiviral drugs must be started before disease appears
  ↳ onset of symptoms replication of virus reached peak
- viruses lack any metabolic capability
  ↳are DNA or RNA contained within a capsid
- 2gps of antivirals:
  - antiviral (non-retroviral)
  - anti-retroviral used in HIV

Non-Retroviral Drugs

- subgps:
  - DNA polymerase inhibitors eg acyclovir, famciclovir, ganciclovir
  - neuraminidase inhibitors – oseltamivir, zanamivir
  - misc antivirals eg foscarnet, ribavirin

DNA Polymerase Inhibitors

Aciclovir

MOA

- selectively taken up by HSV infected cells
- drug converted by several enzymes (incl thymidine kinase) to active triphosphate form
- acyclo-GTP inhibits viral DNA synthesis by 2 actions:
  - inhibits incorporation of norm deoxyguanosine into viral DNA by viral polymerase
  - acyclo-GTP instead incorporated into DNA chein ⇒ termination of synthesis

Pharmacokinetics

- orally poorly absorbed 15-30%
- widely distributed incl CSF & herpetic vesicular fluid
- conc in CSF ~50% that of plasma
- half life 2.5hrs; 20hrs in anuric patients
- 15% metabolised by liver; rest excereted unchanged in kidney

Uses

- prophylaxis & Rx of
  - genital herpes infections
  - varicella
  - HSV encephalitis
  - AIDS

Adverse Reactions

- with oral dose:
  - GI
  - CNS – headache, dizzy
- IV form:
  - phlebitis
  - acute renal failure
  - encephalopathic alterations – confusion, hallucinations, convulsions, trmoes

Cautions/Contraindications

- caution:
  - kidney probs
  - CNS probs
  - dehydrated people – risk precipitation of crystals in kidneys

Interactions

- probenecid ⇒ ↑aciclovir plasma conc
- theophylline – ↑plasma conc of theophylline

Dose
- genital herpes 400mg tds 5-7days

Ganciclovir
- Very similar to aciclovir but has HIGH toxicity risk
- Only used for life/sight threatening cytomegaly virus infection

Foscarnet
- Inhibits viral DNA polymerases
- Also used for herpes viruses
- Toxicity to renal damage limits use

HIV INfection

Virology
- HIV = double stranded RNA retrovirus
- Enters cell ⇒ viral reverse transcriptase enzyme makes a DNA copy of it's RNA genome
- Viral integrase enzyme integrates this into host DNA
- Core viral proteins intially synthesised as large polypeptides
  ↳cleaved by viral protease enzyme into enzymes of virus
- Completed virions then released from host by characteristic budding
- No. of circulating viruses predicts ⇒ AIDS
  ↳aka viral load

Antiretrovirals
- HAART = combining 2 NRTIs with a PI or NNRTI

Nucleoside analogue reverse transcriptase inhibitors (NRTI)
- Prevent HIV virus transcripting RNA into DNA.
- Eg **zidovudine**

Protease Inhibitors (PI)
- Slow cell to cell spread & lengthen time to first clinical event
- Prevent HIV from copying itself by interfering with protein processing required to make new virus RNA
- All metabolised by P450 in liver
- Eg **indinavir**

Non-nucleoside reverse transcriptase inhibitors (NNRTI)
- Prevent HIV virus transcripting RNA into DNA.
- Eg **nevirapine**

Vasopressin

Endogenous Vasopressin

- see chp 39 renal physiology notes

Exogenous Preparations

- lypressin (lysine vasopressin) –
  - 60% vasoC effect of ADH
  - 80% anti-diuretic effect of ADH
- desmopressin (DDAVP) –
  - 0.4% vasoC effects of ADH
  - x12 antidiuretic effects of ADH
- POR-8 – vasoconstrictor
- felypressin:
  - vasoC
  - minimal anti-diuretic effect
- terlipressin:
  - protracted vasoC

Uses

- neurogenic DI:
  - DDAVP or lypressin
- shock/sepsis
  (↳ cardiac arrest – now out of guidelines)
- haemophilia prophylaxis & some forms of vWD – DDAVP
- enuresis – DDAVP – intranasally
- bleeding oesophageal varices: vasopressin, terlipressin, lypressin
- with Las for vasoC: felypressin (with prilocaine)

Pharmacokinetics

A

- vasopressin – IVI, Sc, IMI
- DAP + lypressin – nasally, IVI
- terlipressin – IVI

M

- metab by tissue peptidases

E

- 1/3 of vasopressin renal elimination
- t1/2elim 10-20mins (except DDAVP which is less subject to tissue peptidase ⇒ t1/2 elim 75min)

Adverse Effects

- cardiac – angina/MI/HTN/arrhythmias
- GIT – bowel ischaemia/necrosis
- other:
  - hyponatraemia
  - hypersensitivity reactions
  - bronchospasm
  - VTE
  - peripheral gangrene

Vasopressin in Shock

- physiological role in normal health = maintaining water balance
- shocked state ⇒
  - ↑vasopressin ⇒ vasoconstriction (V1a)

- prolonged shock ⇒ exhaustion of endogenous vasopressin

CVS Actions of Endogenous VP

- diversion of blood to vital organs:
  - ↓flow to skin, skeletal mm, small bowel, fat
  - ↑flow to heart + brain
- cardiac:
  - in vitro: +ve inotrope
  - in vivo:
    - [low dose] ↓CO due to ↑SVR
    - [high dose] ↓↓CO due to coronary vasoC
- no effect on renal flow (unlike adrenaline)
- splachnic: ↓flow, ↓portal venous pressure

Clinical Uses

- shock – may reverse irreversible shock 2nd to hypovolaemia (4mcg/kg/min
- sepsis:
  - catecholamine vasopressors may restore MAP but as expensive of regional ciculations eg splachnic
  - use of concurrent VP shows marked enhancement of catecholamines ∴ can ↓dose ⇒ better survival of regional circulations
  - 0.04mcg/min
- CPB:
  - CPB induces inflame response similar to sepsis
  - see SIRS induced hypotension 2nd to ↓SVR & ↓response to catecholamines
  - response greatest in hypotensive gps

Diabetes Drugs

Drugs which cause ↑↓glucose

Hyperglycaemia	Hypoglycaemia
Diuretics	ACEI
Phenytoin	α & β blockers
Oral contraceptives	Ethanol
Quinolones	Quniolones
Sympathomimetics	MAOIs
Thyroid hormones	
TCAs	

Insulin

- = 51aa polypeptide
- now made from recombinant DNA technology
- previously sourced from:
  - pork insulin – 1 aa different
  - bovine – 3 aa different

  ↳ not used now as ↑ed chance of resistance/allergy/lipodystophy
- human insulin – absorbed faster & shorter duration of action than animal insulin

MOA

- see physiology section

Pharmacokinetics

- wide variety of insulins available allows titration of dose to control glucose carefully

  ↳ add zinc or protamine to retard absorption ∴ prolong duration of action
- very poor PPB
- Vd 0.075L/kg
- insulin metabolised & inactivated rapidly in most tissues (liver, muscle & renal):
  - disulfide bonds are cleaved
  - peptide chains broken down into amino acids

  ↳but biological activity continues longer
- metabolites appear in urine
- t1/2 elim 1.6-3.4min (5-7min in diabetic pt)

Uses

- DM I & II
- emerg Rx of hyperkalaemia (if norm pancreas can give sugar alone & pancreas will create enough insulin)
- during pregnancy
- adjunct to oral hypoglycaemics

Adverse Reactions

- very rare with human insulin
- otherwise allergy & lipodystrophy
- overdose: signs of hypo:
  - presyncope
  - sweating
  - tremor

Cautions/Contraindications

- caution in:
  - liver/kidney disease
  - high fever
  - infection

- hyperthyroid
- adrenal/pituitary disorders
- diarrhoea/intestinal obstruction
- recent surg or trauma

Interactions

- see table above for drugs effect glusocse levels
- beta blockers can
  - mask symptoms of hypo
  - prolong hypo by blocking gluconeogenesis

  ↳better with cardio-selective blockers ie metoprolol

Dose

- depends on pts weight, diet & lifestyle & type of insulin
- typical dose 50 units/day or 0.7units/kg/day split into 2-4injections

Time preparations

- ultra short acting – 2 or 3 amino acids have been changed
- short acting
- intermediate acting – formulated as hexamers. need to be converted to monomers prior to absorption
- long acting – protamine added
- premixed formulations

Dosage Regimes

- basal-bolus:
  - short acting prior to each meal
  - intermediate or long acting nocte
- split mixed:
  - total daily dose estimated then split 1/3 short acting & 2/3 intermediate or long acting
  - 2/3 taken before breakfast & 1/3 before evening meal

Administration

- s/c 15-30mins
- rotate injection sites
- vials all 100units/ml
- insulin pumps

Time to Onset (standard insulin prep)

- IV: 15mins onset; 1-2hrs duration of effect
- s/c: 1hr to onset; 1-5hrs duration of effect

Pregnancy

- insulin used to control diabetes
- insulin requirements drop 24-72 hrs after delivery & slowly return to prepreg levels 6/52

DM Type II Management

Drugs

- metformin 1st line therapy unless contraindicated:
  - renal/cardiac/hepatic disease
  - very elderly
- sulfonylurea is alternative or adjunct
- insulin –
  - 3rd line if oral hypoglycaemics not effective
  - bedtime intermediate/long acting
  - 50% of type II require insulin in 10yrs of diagnosis
- classification:
  - biguanides – metformin
  - sulphonylureas:
    - 1st gen = tolbutamide

        - 2nd gen = glipizide, gliclazide
    - Thiazolidinediones = pioglitazone & rosiglitazone

Biguanides – Metformin

MOA

- not completely understood but:
    - ↑insulin sensitivity via ↑ed receptors & ↑ed affinity of receptors
    - ↑gluc uptake & utilisation in skeletal mm (ie ↓ed insulin resistance)
    - ↓hepatic glucose production ie ↓gluconeogenesis
    - ↓LDL & vLDL synthesis
    - ↓glucose absorption from gut
- does not affect islet β cells ∴ does NOT :
    - ↑insulin release
    - hypoglycaemia

Pharmacokinetics

- slow absorb along length of Gi tract
- OBA 50-60%
- unbound to proteins
- peak in plasma 2-3hrs; half life 5-10hrs
- no metab: excreted unchanged in urine
- t1/2 elim ~3hrs

Uses

- uncomplicated type II >10yrs age where not controlled by diet & exercise
    ↳ esp if obese
- PCOS

Adverse Reactions

- causes ↓weight & better lipid profile
    ↳sulphonyureas cause ↑weight
- generally rare serious complications
- ??can cause hypoglycaemia- although ↑↑↑ed risk with sulfonylureas
        ↳ debate – a lot of texts state cannot cause hypoglycaemia
        ↳especially if renal disease or exacerbates ↓BSL caused by other drugs
- lactic acidosis – uncommon but need to consider in certain gps with ↑ed risk:
    ↳because blocks gluconeogenesis
    - liver/kidney diseae
    - elderly
    - alcohol or drugs which ↑metformin levels
- other:
    - Gi upset
    - acute hepatitis
    - vit B12 anaemia

Cautions/Contraindications

- caution in:
    - GIT problems
- avoid in:
    - liver/kidney disease
    - lactic acidosis
    - cardiac disorders
    - severe burns/dehydration/severe infections
- pregnant people should switch to insulin

Interactions

- alcohol ⇒ ↑ed risk lactic acidosis
- drugs that affect ↑↓glucose – see table at start of section

- drugs which compete for renal transport mechanisms ⇒ ↓clearance metformin:
  - cimetidine
  - Ca channel blockers
  - digoxin
  - morphine
  - ranitidine
  - trimethoprim
  - vanc
- warf may also ↓metformin clearance

Dose

- 500mg-1g bd or tds

Sulfonylureas

- developed from spin off from sulphonamide antibacterial agents
- diff generations:
  - 1st gen = tolbutamide
  - 2nd gen = glipizide, gliclazide

MOA

- bind to receptors in B cell in islets & block ATP sensitive K channels:
  - normally open when K is low ⇒ ↑K conductance ⇒ inhibition of insulin secretion
  - block of channel ⇒ ↓K efflux ⇒ cell depolairsation ⇒ ↑Ca entry ⇒ insulin secretion
- ∴ need partially functional pancreatic ß cells
- see ↑in basal & stimulated insulin secretion
- ↑ed insulin secretion ⇒
  - ↓glycogenlysis
  - ↓gluconeogenesis
  - ↓serum glucose
- prolonged Rx ⇒ ↑tissue cellular sensitivity of insulin
- indirect inhibition of glucagon release

Pharmacokinetics

	Rel pot	Dur act	PK aspects	Comments
Tolbutamide	1	6-12h	some active/some Inactive met's. Renal excr	rel safe(less chance ↓↓ BSL) can ↓ thyroid iodide uptake CI'ed in liver failure
Glibenclamide	150	18-24	some act met's→ Renal excr . 50% unch in faeces	can cause ↓↓ BSL + active met accum in RF (NB caution in elderly / RF)
Glipizide	100	16-24	most→inact met's→ Renal excr 12% in faeces	can cause ↓↓ BSL diuretic action only *in*active met's acc in RF

- duration of action long >16hrs ∴ if OD must admit for obs
- all are highly protein bound 95-99%
- 2nd gen ⇒ hepatic & renal impairement ⇒ ↑risk of hypoglycaemia

- they cross placenta ∴ contraindicated in preg

Adverse Reactions

- hypoglycaemia
- stimulate appetite ⇒ weight gain
- GIT probs 3%
- taste disturbance
- rashes
- bone marrow damage – rare but severe

Interactions

- ↑action of sulfonylurea: drugs metabolised in same pathway OR displacement from PPBs
  - warf
  - sulfonamides
  - NSAIDs
  - alcohol
  - MAOIs
  - some antibiotics eg sulpha's, chloramphenicol, trimeth, fluconazole
- ↓action of sulfonylurea:
  - diuretics – loops & thiazides
  - corticosteroids

PeriOp

- usually stop 24-48hrs preop

Dose

- taken with food to ↓hypoglycaemic risk

Thiazolidinediones (Glitazones)

- eg pioglitazone & rosiglitazone

MOA

- ↑sensitivity of periph tissue & liver to insulin ∴ ↓insulin resistance
- activation of PPAR-gamma receptor:
  - nuclear receptor which regulates gene transcription esp in adipocytes
  - regulates glucose & lipid metab via proteins:
    - GLUT-4
    - lipoprotein lipase & transport & binding proteins for fatty acids
      ↳∴ ↓circulating free fatty acids

Pharmacokinetics

- peak plasma conc 1hr; half life 3-24 hrs
- peak action 6-8wks
- protein bound >99%

Adverse Reactions

- anaemia
- periph oedema
- weight gain
- ↑ed risk heart failure
- ↑risk periph limb fractures
- pioglitazone safer in pts with ↑ed CVS risk factors
  ↳rosiglitazone ↑s triglyceride & LDL levels
- must monitor liver function
- if no improvement in glycaemic control at 8wks ⇒ stop and start insulin

Glucocorticoids

Comparison Steroids

- hydrocortisone = gold standard corticosteroid
- Relative potencies:

	Anti-inflammatory	Na-retention	Duration (h)
Hydrocortisone(cortisol)	1	1	8-12
Cortisone	0.8	0.8	8-12
Prednisone/prednisolone	4	0.8	12-36
Methylprednisolone	5	minimal	12-36
Dexamethosone	30	minimal	36-72
Betamethasone	30	-	36-72
Beclomethasone (inhaled/top)	+	-	-
Budesonide (inh/top)	+	-	-
Fludrocortisone	15	150	8-12
Aldosterone	-	500	-

- short acting = hydrocortisone 8-12hrs (half life 1.5-2)
- intermediate acting :
  - prednisolone 24-36hrs (half life 3-4hrs)
  - fludrocortisone 1-2days (half life 0.5-3hrs)
- long acting:
  - dexamethasone 2-3 days (half life 3-4hrs)

Physiological Effects

- 2 main roles of steroids in physiology:
  - permissive ie action in resting state permit/facilitate homeostatic functions
  - stress ie actions in response to stress are crucial for survival
- endogenous = secreted from Z fasiculata of adrenal cortex
- also see some crossover mineralocorticoid effect because specificity of 2 types of steroid not absolute
- generalised effects:
  - general metabolic
  - anti-inflammatory
  - immunosuppressant
  - negative feedback on hypothalamic-pituitary-adrenal axis (HPA axis)

General Metabolic Effects

- carbohydrate metab:
  - ↓glucose uptake into cells
  - ↑gluconeogenesis
  - ↑insulin resistance

  ↳∴ hyperglycaemia & glycosuria ie diabetogenic
- protein metab:
  - breakdown of protein in mm & extrhepatic tissue ⇒ ↑serum amino acids levels

  - ↑trapping of amino acid in liver & deamination of amino acids

  ↳ ⇒ delay protein synthesis ⇒ delay wound healing/mm wasting/osteoporosis/↓growth in young

- fat metab:
  - ↑mobilisation fatty acids from adipose tissue ⇒ ↑plasma levels
  - long term steroid ⇒ redistribution of fat (moon face, buffalo hump) 'Cushingoid'

  ↳ permissive action via catecholamines
- Ca balance:
  - ↓Ca absorb from gut
  - ↑Ca excretion from kidneys

  ↳overall –ve Ca balance ⇒ ↑osteoclastic activity to normalise serum Ca level ⇒ osteoporosis

Anti Inflammatory/ Immunosuppressant

(suppress all vascular & cellular events in inflam response ie immediate events & late processes)

↳ ∴ overall see ↓chronic inflamm & ↓autoimmune reactions

- vascular:
  - inhibit extraneuronal uptake of catecholamines ⇒ ↑VC action of NA

    ↳∴ without glucocorticoids ↓bp
    - stress response:
      - acute & chronic stress ⇒ ↑vasopression & ACTH (via CRH) release from ant pituitary
      - simultaneous release of adrenaline & NA from adrenal medulla
      - protective mechanism to prevent hypotension or shock
  - ↓fluid exudation
- cellular:
  - acute inflam: ↓ numbers & activity of leucocytes
  - chronic inflam:
    - ↓activity of mononuclears
    - ↓prolif of blood vessles
    - ↓fibrosis
  - lymphoid areas:
    - atrophy of thymus ⇒ ↓clonal expansion of T+B cells in blood
    - ↓action of cytokine secreting T cells ⇒ inhibited integrated immune repsonse
- inflamm + immune mediators:
  - ↓action & production of cytokines (IL, TNF)
  - ↓generation of eicosanoids & PAF
  - ↓complement system
  - stabilise lysosomal membranes
  - prevent movement of neutrophils
  - prevent release of proteolytic enzymes during inflam

Regulatory Suppression of HPA Axis

- high levels of plasma corticosteroids have –ve feedback on HPA ⇒ ↓CRH & ∴ ↓ACTH release ⇒ ↓glucocorticoid from adrenals & atrophy of adrenals in long term
- creates problems if encounter new:
  - stress
  - infection
  - immune challenge

Uses

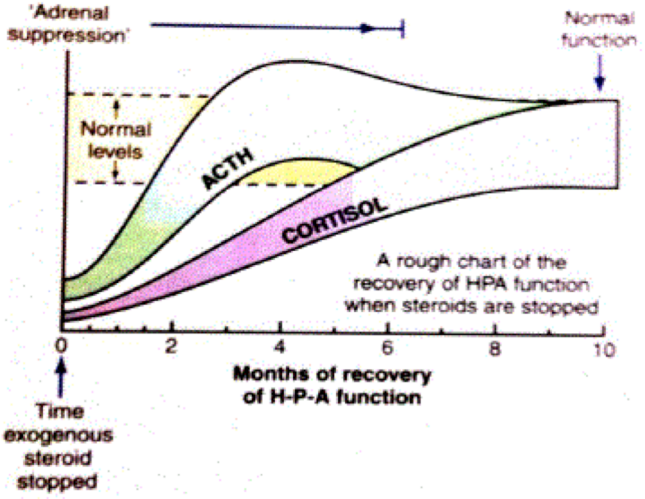
- low (physiological doses) – replacement therapy eg addisons, hypopituitarism, adrenal insufficiency

  ↳stress/sick day dose – double or treble dose
- high (pharmacological doses) –
  - anti-inflam & immunosuppressant effects
    - prevent allograft rejection
    - haem malignancies – suppress WCC, ↓size lymph nodes

        - allergic reactions
        - autoimmune disorders eg RA
        - chronic inflam conditions
        - neoplastic disease:
            - eg ↓cerebral oedema
            - combine with cytotoxics eg Hodgkins/ALL
        - severe migraine & headaches
        - ↓N&V

Adverse Effects

- long term use ⇒ suppression HPA axis:
    - unpredictable but unlikely if <7.5mg pred or Rx <3weeks
    - HPA suppression only really problem if:
        - stop exogenous steroid
        - intercurrent illness/stress
    - can take months to recover
- excessive dosing ⇒ Cushingoid effects
- GI:
    - Pancreatitis
    - Candidiasis
    - Oesophageal ulceration
    - Peptic ulceration
- M/S:
    - Myopathy
    - Osteoporosis
    - #'s
    - growth surpression
- endocrine:
    - adrenal suppression
    - iatrogenic cushing's syndrome
- CNS:
    - Aggravated epilepsy
    - Depression/euphoria
    - Psychosis
- Eye:
    - Cataracts
    - Glaucoma
    - Papilloedema
- Immune:
    - ↑infection susceptibilty & severity esp chicken pox



Pharmacological Action

- = steroids at level higher than normal physiological doses

MOA

- steroids work via 2 main pathways:
    - genes & transcription factors
    - via signalling pathways & mediators
- genes & transcription MOA:
    - entry into target cell & binding to specific cytoplasmic receptor
        ↳usually glucocorticoid receptor alpha (GRα)
    - steroid-receptor complex undergoes conformational change ⇒ exposure of DNA binding domain
    - dimmers of complex translocate to nucleus

    - in nucleus bind with glucocorticoid response elements (GRE) in promoters of target genes
    - ⇒ induction or inhibition of transcription of specific mRNAs ∴ ↑↓specific protein synthesis
- signalling pathways & mediators MOA:
    - many forms of GR receptor
    - many genes targeted
    - ↑synthesis of many
        - kinase enzymes
        - anti-inflam mediators eg lipocortin
    - ↓synthesis of
        - COX 2
        - collengase
        - proinflam mediators eg eicosanoids, histamine
- specific to anti-inflammation:
        - stim production of lipocortin ⇒ inhibit phospholipase A2 which blocks aracnoiodic acid pathway ie ↓PGs, ↓Thromboxane, ↓prostacyclin, ↓leukotrienes

Pharmacokinetics

- alternate day dosing preferred if possible – less SEs of:
    - HPA axis suppression
    - growth suppression
    - raised BSL
    - bone loss
    - infections
    - mineralocorticoid effects
- well absorbed
- lipophilic ∴ diffuse well into cells
- cortisone & prednisone are prodrugs:
    - cortisone hydroxylated ⇒ hydrocortisone before active
    - prednisone ⇒ prednisolone
- fluorinated adrenocorticoids more slowly metabolised than other compounds
- 90% bound to protein
- metab in liver & most body tissues by hydroxylation & glucuronidation
- metabolites excreted via kidneys
- half life & duration of action depend on type of steroid

Cautions/Contraindications

- caution in
    - HTN
    - colitis/diverticulosis
    - open angle glaucoma
    - liver/kidney disease
    - endocrine disturbances incl SLE
    - hypoalbuinaemia
    - psych disease
- should carry alert card
- contraindications:
    - HIV/AIDS
    - heart disease/failure
    - chicken pox/measles or systemic fungal infections or TB
    - ulcers/oesophagitis
    - myasthenia gravis
- cross into breast milk

Interactions

- antacids - ↓steroid absorb
- anti-DM drugs – antagonising
- antifungals – hepatic inhibitors ⇒ ↑steroid levels
- dig – steroid mineralocorticoid effect ⇒ ↓K ⇒ ↑dig toxicity
- diuretics – Na retaining effects of steroids antagonise effects of diuretics
- hepatic enzyme inducing agents ⇒ ↓steroid effect
- vaccines – not advised if on immunosuppressant doses of glucocorticoids

Steroid Resistance

- may see developed resistance to steroid in conditions which require chronic steroid eg asthma, COPD, Inflammatory Bowel Disease
- mechanisms of steroid resistance:
    - mutations in gene coding for glucocorticoid receptor (GR)
    - altered no's of GR
    - altered affinity of steroid for GR
    - ↓affinity of GR complex to bind DNA
    - altered expression of transcription factors

PeriOp Steroid Use

- if steroids stopped within 3/12 Rx as if currently on steroids
- action based on their long term dose of pred:
    - <10mg/d ⇒ assume norm HPA axis response ⇒ no additional cover
    - >10mg:
        - Minor surg (eg hernia)- routine steroid that day or hydrocort 25mg IV @ induction
        - Mod surg (eg hysterectomy) -
            - routine pre op steroid
            - Hydrocort 25mg Iv @ induction AND 6hrly for 24hrs
        - Major surg -
            - Routine preop steroid
            - Hydrocort 25mg @ induction and then 6hrly for 48-72hrs
            - High dose immunosupression:
    - High dose immunosuppression ⇒ give usual doses during peri-op period
- Convert usual oral steroid dose to hydrocort, then revert back to oral dose when able

Dose

- hydrocortisone :
    - physiological adult: 20mg in morning; 10mg nocte
    - pharmacological 100-200mg IV

Mineralorticoids

- =other gp of steroid hormones secreted by Z Glomerulosa (adrenal cortex)
- natural hormone = aldosterone
- liquorice has mineralocorticoid actions ⇒ ↑bp
- function to affect water & electrolyte balance
  ↳ can be entirely separated from glucocorticoid actions

Aldosterone

Secretion & Control

- synthesised in adrenal zona glomerulasa
- regulated by
  - renin-angiotensin system:
    - ↓arterial volume or pressure
    - low Na in kidney tubules

    ↳ stim juxtaglomerular apparatus in renal afferent arterioles ⇒ release of renin:
    - renin = proteolytic enzyme
    - acts on angiotensinogen to form AT1
    - AT1 in lungs & kidneys ⇒ ATII by ACE
  - level of serum K: ↑K (1%) ⇒ ↑aldosterone
  - serum Na levels: ↑Na (10%) ⇒ ↓aldosterone

  ↳ ACTH has role but limited

MOA

- regulates Na/K balance:
  - ↑Na reabsorp via ↑function of
    - Na channels (ENaC)
    - Na/K pumps
  - ↓loss of Cl & HCO3 – follow Na
  - ↑K & ↑H+ secretion by tubular cells in distal & collecting tubules

Clinical Uses

- aldosterone several thousand times more potent as mineralocorticoid than hydrocortisone
- limited use because:
  - cost
  - short half life
  - requires IV administration

  ↳∴ synthetic analogue fludrocortisone
- aldosterone antagonists eg spiro ⇒ Na & water losing actions & K sparing effects

Fludrocortisone

MOA

- potent mineralocorticoid
- strong glucocorticoid
- acts primarily on distal tubule to
  - reabsorb Na ⇒ ↑water reabsorb ⇒ ↑bp
  - ↑excretion of K & H

Pharmacokinetics

- good oral absorb
- half life 3.5hrs
- duration action 1-2days
- highly protein bound
- metab in liver; excreted kidney

Uses

- addisons & orthostatic hypotension

Adverse Reactions

- rare but potentially serious:
  - severe/persistent headaches
  - HTN
  - dizziness
  - oedema of LLs
  - joint pain
  - ↓K
  - ↑weakness
- at low doses should not see glucocorticoid SEs

Cautions/Contraindications

- caution in :
  - pts with oedema
  - acute GN
  - liver disease
  - thyroid disease
  - osteoporosis
- contraindiactions:
  - heart disease
  - HTN
  - kidney disease

Interactions

- main interactions 2nd to cause of ↓K:
  - digoxin
  - diuretics

Dose

- 50-100mcg once or twice daily with food

Thyroid Disease

Hyperthyroid

- drugs used include:
  - thio-urey-lenes
  - radioiodine
  - iodine
  - perchlorate
  - ß blockers (symptomatic) - Propanolol

Thioureylenes

- = most impt of anti-thyroid Rx
- diff drugs:
  - carbimazole – 1st line
  - methimazole
  - pro-pyl-thiouracil (PTA) – reserved for pts intolerant of carbimazole

Presentation

- all oral tabs

Mechanism of Action

- central effect:
  - prevent synthesis of new T3 & T4
  - ↓action of thyroperioxidase ⇒ ↓oxidation of iodide to iodine ⇒
    - ↓iodotyrosine synthesis
    - ↓coupling of iodotyrosines
- periph effect (PTA only): ↓periph conversion of T4 ⇒ T3

Uses

- hyperthyroidism (diffuse toxic goitre) – with 1yr of Rx recurrence >50%
  ↳ can continue on them
- pre-surg for toxic goitre
- part of Rx in thyroid storm – PTA preferred due to perph action

Pharmacokinetics

- carbimazole
  - = prodrug:
  - rapidly converted to active methimazole in liver
  - distributed through body water
  - t1/2 6-15hrs
- norm dose ⇒ 90%↓ of hormone production within 12hrs
  ↳ clinical response takes 2 weeks due to large store of hormone & T4 has long t1/2
  ↳ PTA may act faster due to periph action
- both active drugs cross placenta & appear in breast milk
  ↳ PTA less so as has ↑ed PPB – both
- renal excretion of metabolites

Adverse Reactions

- granulocytopaenia –
  - rare but reversible. ?sore throat
  - sl ↑incidence with PTA
- rashes 2-25%
- headaches, nausea, arthralgia, jaundice

Radioioiodine

- orally given ⇒ selective thyroid uptake ⇒ short range beta radiation ⇒ selective damage of follicular cells

- hypothyroidism will eventually occur esp in Graves disease
  ↳ easily Rx;ed with replacement Rx
- best avoided in children + pregnancy

Iodine/Iodide

- given orally in high doses eg Lugols iodine
- when iodide levels are too low or too high ⇒ abnormal thyroid function
- ↑iodide levels ⇒
  - ↓iodide binding to thyroglobulin ⇒ ↓iodination of thyroglobulin ⇒ transiently ↓secretion of hormones ⇒ ↓symptoms in 1-2days
    ↳ effect is greatest when iodide transport is ↑ed ie in thyrotoxicosis
  - inhibits effect of TSH on thyroid gland ⇒ ↓size of gland
  - inhibits proteolysis of thyroglobulin
- over 1-2 weeks: ↓↓vascularity & size of gland
- only see short term changes – new equilibrium reached with chronic use with loss of effects
- ∴ mainly used:
  - preparation of operation
  - thyroid storm

Perchlorate/other ions

- some inorganic anions compete with iodide for uptake at thyroid
- not used clinically

ß Blockers (Propanolol)

- symptomatic control of thyroid storm ie –ve inotropy & chronotropy
- other useful actions:
  - ↓periph conversin T4 ⇒ T3
  - block hypersensitivity to catecholamines

Hypothyroidism

Thyroid Replacement Therapy

- no drugs exist which ⇒ ↑synthesis/release of thyroid hormones
- ∴ (if not iodine deficiency) use replacement therapy

Chemical

- synthetic T4 (thyroxine) = oral Rx
- lio-thyronine (T3) = IV – reserved for hypothyroid coma due to rapid onset

MOA + Effects

- see physiology section for MOA

Pharmacokinetics

- T3 & T4 both well absorbed
- in plasma >99% bound to albumin & thyroxine binding globulin
- some T4 converted (liver & kidneys) ⇒ T3 or inactive reverse T3
- metab in liver
- excretion:
  - 60% in bile as inactive metabs
  - 40% renally unchanged

By Adam Hollingworth

Octreotide

- =synthetic analogue of GHRIF (somatostain) (inhibiting)
  ↳somatostatin has a longer half life than octreotide (1.5hr vs 3hr)
- potent agent that also inhibits secretion of many GI hormones:
  - insulin
  - glucagon
  - gastrin
  - Vasoactive intestinal peptide (VIP)

Pharmacokinetics

- rapid absorb after s/c injection
- peak levels 0.4hrs; duration action 12hrs; elim half life 1.5hrs
- excreted in urine (32% unchanged)

Uses

- lowering blood levels of growth hormone & IGF-1 (insulin like growth factor) in acromegaly
  ↳in failed surg or radiotherapy
- Rx symptoms of carcinoid tumours ie flushing/severe diarrhoea
- prevent complications in pancreatic surg
- Rx bleeding oeseophageal varices ⇒ ↓splachnic blood flow ⇒ ↓portal venous pressure
- hypoglycaemia

Adverse Reactions

- local injection site reactions
- GI disturbances
- headache
- thyroid disfunction – must monitor long term
- gallstone formation ⇒ may need cholecystectomy

Cautions/Contraindications

- caution in:
  - DM
  - GI tract tumours
  - severe kidney impairement
  - pregnancy
- contraindicated in breast feeding

Interactions

- effects fluid, electrolys & glucose balance ∴ widespread interactions

Dose

- depends on use – acrogmegaly 0.2-0.3mg daily s/c

By Adam Hollingworth

Anti-Emetics

Vomiting Reflex

(from physiology notes)

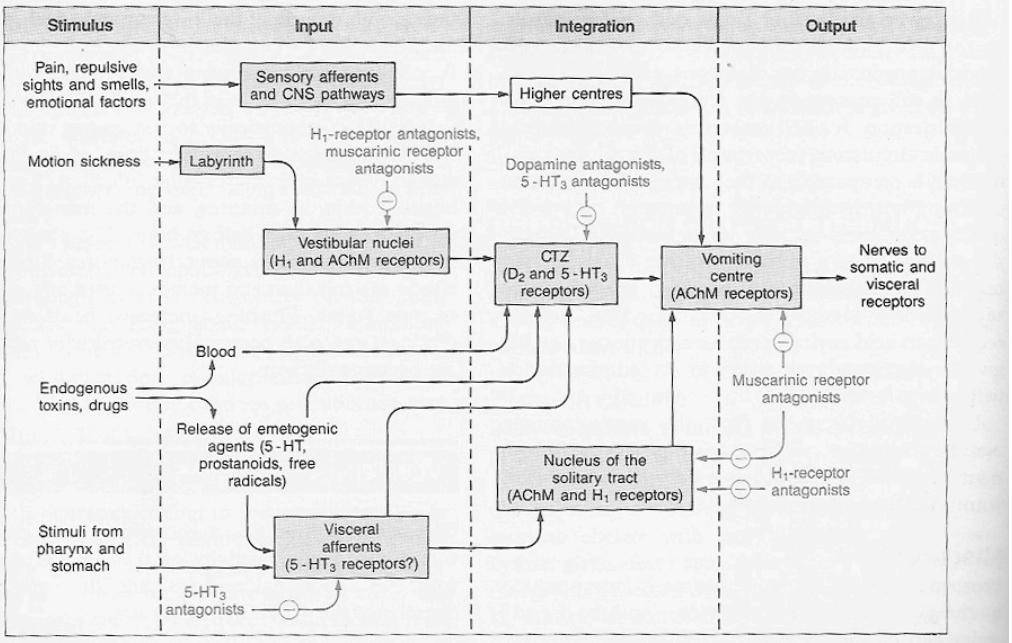


Fig. 19.8 Schematic diagram of the factors involved in the control of vomiting, with the probable sites of action of anti-emetic drugs. The cerebellum may function as a second relay or gating mechanism in the link between labyrinth and CTZ (not shown). (CTZ = chemoreceptor trigger zone; H_1 = histamine H_1; M = muscarinic; D_2 = dopamine D_2; 5-HT_3 = 5-hydroxytryptamine$_3$) (Based partly on a diagram from: Borison et al. 1981)

- afferent limb
  - inputs from:
    - CTZ (see below for triggers)
      - located in area postrema in lat walls 4th ventricle ie outside BBB
      - responds via neurotrasmitters: ACh, 5HT, Histamine, DA
    - vestibular apparatus/cerebellum ⟹
      - afferent to vomit centre 2 routes:
        - directly
        - via CTZ eg dopamine (CTZ blocker) does not block motion sickness
    - higher centres – pain/smell/sight
    - organs eg
      - heart via vagal
      - testes,
      - GI tract - mucosal irritation/distension via SNS & PNS (vagal) afferents

  ↳ generally most common trigger is bowel or brain
- induction of vomiting coordinated response from 1+1 areas:
  - vomiting/emetic centre – reticular formation of medulla [MAIN]
  - chemoreeptor triggr zone (CTZ) –
    - very close integration with emetic centre
    - neurotransmitters vital ie ACh, 5HT, Histamine, DA
- efferent to:
  - CN 5, 7, 9, 10, 12 to upper GIT
  - Spinal nerves to diaphragm, abdo muscles

CTZ

- CTZ activated by:
  - CSF & blood borne emetics eg chem. toxins & drugs
  - 5HT neurotransmitter from afferent nerves from stomach & small intestine receives input from vestibular apparatus
  - higher centres – smells, emotions, pain
  - ↑ICP
  - endocrine disturbances
  - radiation & chemotherapy
- CTZ cannot initiate vomiting alone
- CTZ very close physically to resp centre ∴ difficult to full abolish vom without effecting RR
- vomiting action comes via efferent nerves from emetic centre (not CTZ)

Receptor Locations

- dopamine-2 (D2):
  - CTZ in area postrema (main)
  - NTS
  - Dorsal vagal nucleus (DMVN)
- Muscarine:
  - NTS, DMVN, nucleus ambigus (NA)
- Histamine:
  - NTS, DMVN, vestibular nuclei
- 5HT3:
  - central = AP, NTS, cerebral cortex, hippocampus
  - periph = GIT, nerve endings, afferent fibres

Classification of Anti-Emetics

- need to be careful cos many drugs are not receptor selective
- work by blocking neurotransmitters:
  - Ach ⇒ M receptors in vestibular & emetic centres
    ↳anticholinergics ie hyoscine hydrobromide
  - histamine ⇒ H1 receptors in vestibular & vomiting centres
    ↳antihistamines ie promethazine, cyclizine
  - dopamine ⇒ D2 in stomach & CTZ
    ↳dopamine antagonists ie domperidone, droperidol, metoclopramide, haloperidol, prochlorperazine
  - substance P ⇒ Neurokinin-1 receptors (NK_1) in CNS
    ↳NK1 antagonist ie aprepitant, fosaprepitant
  - serotonin ⇒ $5HT_3$ in GI tract, CTZ & vomiting centres
    ↳5-HT3 antagonists ie granisetron & ondansetron

Receptor site affinity

Drug group	Dopamine(D2)	Muscarinic	Histamine(H1)	5-HT3	NK1
Phenothiazines					
-chlorpromazine	4 +	2 +	4 +	+	
-**prochlorperazine**	4 +				
Butyrophenones					
- **droperidol**	4 +		+	+	
- haloperidol	4 +		+		
- domperidone	4 +				
Antihistamines					
- promethazine	2 +	2 +	4 +		
- **cyclizine**	+	2 +	4+		
Anticholinergic					
- scopolamine	+	4 +	+		
Benzamide					
- **metoclopramide**	3 +		+	2 +	
Antiserotonin					
-**ondansetron**				4 +	
-granisetron				4 +	

Receptors & Agonists

Dopamine

- D2 = classic receptor in CTZ in AP
- other receptors in CTZ may exert action via dopamine
- D2 agonists:
  - apomorphine, bromocriptine
- D2 antagonists:
  - eg metoclopramide, droperidol, prochlorperazine, domperidone
  - limited by extrapyramidal SEs ∴ ideal agent is one with ↓ed brain penetrance

5-HT

- 5HT-3:
  - peripheral & central distribution
  - impt role in:
    - radio & chemo therapy
    - PONV
- $5HT_{1A}$ also involved:
  - agonists block emetogens eg morphine, cisplatin, motion sickness
- $5HT_4$:
  - difficult to study
  - animal studies suggest role in N&V
  - metoclopramide agonist here

Ach

- Ach = agonist at muscarinic & nictonic cholinergic receptors in para ns
- muscarininc receptors found:
  - centrally –
    - NTS, DMVN, NA
    - mediate vestibular initiation of motion sickness
  - peripherally – mediate GI motor aspects of vomit
- anti-emesis achieved by diff mechanisms:
  - central = ↓motion sickness
  - periph =
    - ↓salivary & gastric secretions
    - antispasmodic
    - prevention of relaxation of sphincters
- Scopolamine (l-hyoscine) =
  - central acting ie crosses bbb
  - x10 more potent than atropine
  - poorly OBA ∴ used S/L or transdermal
  - SE: drowsiness, confusion

Opioids

- dual effect:
  - emetic actions: mu receptors (+D2) in AP of CTZ
  - antiemetic:
    - unsure but maybe mu or delta receptors – esp at high doses

Adrenergic

- α stim = emetic effect in animals via α2 in AP
  ↳ although clonidine may be antiemetic

Encephalin

- AP = rich in encephalin receptors
- encephalin also ⇒ ↑ dopamine release

Neurokinins

- tachykinins = emetic effects
- eg apretitant = NK-1 antagonist used in chemotherapy emesis

GABA

- Benzo's potentiate inhibitory GABA interneurons (found in hippocampus, cerebellum, cortex)
- may ↓PONV & N&V from chemo Rx - ?due to anxiolytic, hypnotic, amnesic effects

Histamine

- H_1 receptors concentrated in NTS, DMVN, vestibular nuclei
- centrally acting antiHs often demonstrate anticholinergic effects

Calcitonin

- = polypeptide hormone derived from C cells
- synthetic calcitonin ⇒ N&V

Cannabinoids

- humans have endogenous cannabinoids with central & periph receptors
- cannabis = antiemetic
  ↳ MOA via psychotropic effects in forebrain which inhibit emetic pattern generator via descending pathways
- synthetic cannabinoid nabilone used in cancer Rx for antiemetic effects
  ↳ SEs: euphoria, sedation , incoordination

Ginger

- active ingredient & ?mechanism of action

- unproven efficacy in N&V

Steroids

- addition of dex is effective in chemo & PONV where ondansetron alone has been unsuccessful
- MOA is unknown - ?↓ed central PG production
- dosing is controversial
  - 8mg min dose if on morphine PCA
    ↳alternative is to add 0.1mg/ml droperidol to PCA

Capsaicin

- capsaicin ⇒ desensitisation of vagal afferent C fibres
- resinferatoxin (RTX) =
  - naturally occurring analogue
  - x1000 more potent than capsaicin
  - does not have cardiorespiratory SEs
  - blocks emesis in animals
  - MOA ?via depletion of substance P or CGRP at central point in pathway ?NTS

Glutamate

- glutamate antagonists can block cisplatin induced emesis - ?act at AP
  ↳ esp non-NMDA antagonists

Benzodiazepines

- lorazepam used as antiemetic in chemo
- amnesic & sedative properties
- MOA uncertain:
  - modify central connections to vomit centre
  - prevent anticipatory nausea seen with repeated chemo

Acupuncture

- some RCTs show benefit over placebo in:
  - pregnancy
  - chemo & rado Rx
  - PONV
- ?most effective in awake pt

Drugs & Vomiting in Pregnancy

- try and avoid
- low fat, high carb, small & reg meals
- most in 1st trimester 7-12wks
- 1-2% hyperemesis gravdium
- drugs safe incl metoclopramide, prochlorperazine, promethazine

Drugs in Chemotherapy induced Vomiting

- vomiting 4hrs Rx, peak 10hrs, subsides 12-24hrs
- cisplatin ⇒ delayed vomiting 3-5days
- should use antiemetics prophylactically prior to chemo
- polypharmacy of antiemetics to achieve control

PONV

- 20-30% despite modern drugs/regimes/antiemetics
  ↳ used to be 75-80% in ‘ether era’
- intractable only in 0.1% of cases

Risk Factors

[use a score predictor]

- Patient:
  - Age:

        - ↑children:adult
        - >50 = ↓ risk
    - Female = x3 risk
    - Previous PONV or motion sickness = x2-3 risk
    - Smoker = ↓ 0.6% risk (liver enzyme induction ∴ faster breakdown of emetogens)
    - ASA 1-2 > 3-4
- Surgical –
    - high risk procedures = breast, strabismus repair, ENT, gynae, laprascopic, laparotomy, craniotomy (post fossa), genitourinary, shoulder surgery
    - duration of operation
- Anaesthetic:
    - Premedication:
        - ↓risk = benzo & clonidine
        - ↑ risk = opiates
    - Type - GA x11 than regional
        - TIVA < volatile
    - Intraop drugs:
        - ↑risk =
            - opiods,
            - NO, volatiles,
            - induction agents of ketamine, etomidate, thio
            - Neostigmine - muscarininc effects on GI tract
        - ↓risk =
            - Propofol
            - Adequate IV hydration
- post op factors:
    - ↓bp
    - dehydration
    - premature ambulation
    - pain
    - opioids

Apfels Criteria

- score for predicting PONV using inhalational anaesthesia
- adults RFs:
    - female
    - Hx PONV/motion sickness
    - non smoker
    - use of post op opioids
- children RFs:
    - age >3yrs
    - surgery >30min
    - strabismus surg
    - Hx of PONV in relatives

No risk factors	⇒	10% incidence of PONV
1	⇒	20%
2	⇒	40%
3	⇒	60%
4	⇒	80% - 90%

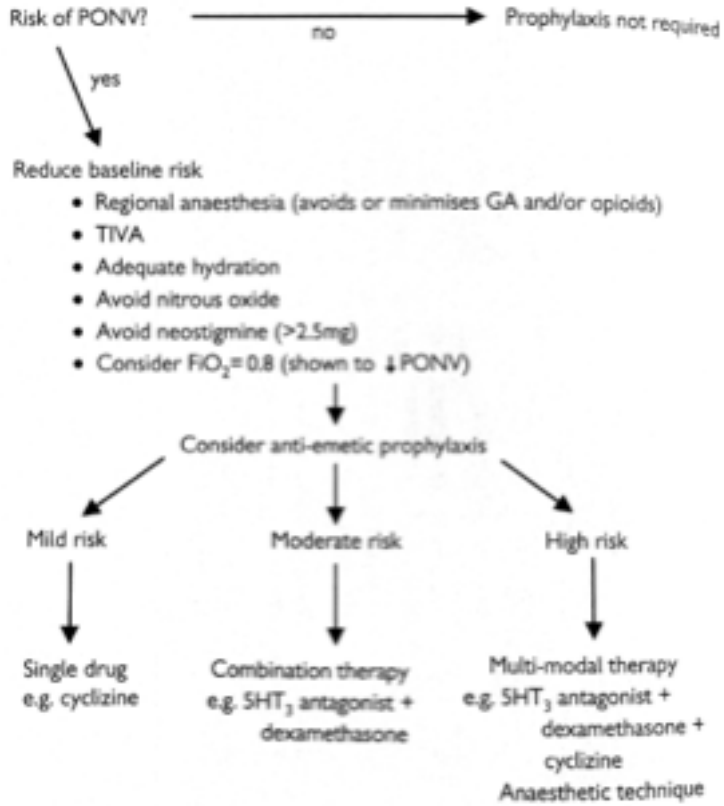
- ∴ ≥ 2 RFs should use prophylactic regimen:
    - medium = use 2 drugs

  - high risk = use > 2drugs
- all common drugs equally effective & each ↓risk by 25-30%
  ↳ droperidol, 5-HT3 antags, dex, cyclizine, sclopolamine
- if use x4 prophylaxis still ~20% PONV
- duration of surg is impt – each 30mins ↑s risk by 60% ie 30min surg with no RFs = 16%

Management

- Multi-modal approach
- ↓baseline risk:
  - premed – anxiolytic
  - LA/regional if able
  - avoid inflating stomach with bag mask vent
  - hydration, supplementary O2 therapy peri-op
  - consider TIVA/avoid N20
- Prophylaxis vs treatment is controversial
- High risk patients where PONV >33% ondansetron prophylaxis cost effective
- Combo Rx eg dex & ondansetron
- Look for surgical cause
- Start using different classes:
  - Anticholinergic eg hyoscine or scopoderm
  - Antihistamine – cyclizine, (promethazine 6.25mg)
  - Antidopaminergic - prochlorperazine, metoclopramide, droperidol or haloperidol
  - 5HT3 antagonist
  - Steroid - dex

Flow Chart for PONV



Individual Drugs

Dopamine Antagonists

Prochlorperazine

- =phenothiazine derivative
- inhibitory action in emetic centre & CTZ
- main D2 blockade but also:
  - antihistamine
  - antimuscarinic
- used for vomiting in:
  - migraine
  - vertigo eg Meniere syndrome
- adverse effects similar to metoclopramide & also:
  - cholestatic jaundice
  - periph oedema
  - blurred vision
  - skin rash
- safe in lactation

Domperidone

- same class as metoclopramide
- doesn't cross bbb ∴ less likely to cause EP side effects
- IV prep withdrawn due to arrhythmias
- 2nd line for GORD in infants

Metoclopramide

- = a benzamine

MOA

- controversy over efficacy – if use conventional dose ie 10-20mg evidence to suggest placebo as good
  ↳ better if give 20mg at end of op
- central action:
  - blocks D2 in CTZ
  - [high doses] partial block of 5-HT3
- peripherally – via muscarinic cholinergic systems in GIT:
  - ↑speed gastric emptying ⇒ ↓reflux from duodenum & stomach
  - ↑motility of upper GI tract

Pharmacokinetics

- OBA 30-90%
- peak plasma
  - oral - 30-180mins
  - IM 10-15mins
  - IV 5-20mins
- liver metab
- half life 2.5-5hrs
- 70% liver metab; kidney excretion

Uses

- diabetic gatroparesis
- GORD
- IV – chemo/radiotherapy antiemetic
- IV – opiate induced
- adjunct:
  - GI radiological exams ⇒ ↑speed gastric emptying
  - facilitate small intestine intubation on OGD

Adverse Reactions

- younger women – dystonic reactions
  - ↳ Rx with anticholinergic – rebalances Ach/D agony
  - ↳ eg benztropine, diphenhydramine
- GI
- CNS – (up to 72hrs post administration
  - sleepy, restlessness
  - extrapyramidal
  - tardive dyskinesia
  - neuroleptic malignant syndrome
- CVS – tachy & hypotension
- rare - agranulocytosis

Cautions/Contraindications

- contra:
  - phaeochromocytoma – risk of HTN crisis
- caution:
  - Parkinsons ⇒ worse symptoms
  - depression ⇒ worse symptoms
  - renal impairement ⇒ ↓dose 25-50%
  - children - ↑ed risk extrapyramidal symptoms

Interactions

- CNS depressants – additive depression CNS
- cyclosporine & dig – altered plasma conc with metoclopramids
- succinylchline - ↓inactivation of sucs ⇒prolonged NMJ blockade

Dose

- 10mg qds
- children 0.1mg/kg max bd

Droperidol

Chemical

- = bu-tyro-phenone
- IV or tablets

Mechanism of Action

- MOA via receptors:
  - D2 – (main) antagonism at CTZ
  - Anti H1
  - anti 5HT3
  - α blocker

Effects

Uses

- prevention & Rx of PONV –
  - best given towards end of op – similar to ondansetron
  - more effective in females
  - 0.5-1.25mg (paeds 10-15mcg/kg) or 50mcg/1ml in PCA
- neuroleptanalgesia or neuroleptanaesthesia (with fentanyl)
- psychosis
- peri-op hiccoughing
- sedative

Pharmacokinetics

- A: well absorped from IMI
- D: 90% PPB

- M: extensive liver met
- E: 80 % via renal (only 1% is unchanged); 20% faecal route
- T1/2 elim ~ 2hrs
-

Adverse Reactions

- CNS:
  - neuroleptic = dissociative state
    ↳ sedation, anxiolysis, ↓motor activity, indifference to external environment
  - ↑seizure threshold
  - extra-pyramidal

  ↳ can develop >12hours post administration

  25% patients may experience anxiety 12-48hrs
- CVS:
  - can ↓bp due to α blocker effect
  - possible rare ↑QTc & Torsade
- GIT
- other: hyperprolactinaemia
- allergies

Muscarininc Receptor Antagonists (anticholinergics)

- at normal doses effectively selective muscarinic antagonists
  ↳ but do have some activity at nicotinic receptors

	Hyoscine	Atropine	Glycopyrrolate
Antiemetic potency	++	+	0
Sedation/amnesia	+++	+	0
Anti-sialagogue	+++	+	++
Mydriasis	+++	+	0
Placental transfer	++	++	0
Bronchodilation	+	++	++
Heart rate	+	+++	++

- atropine not used as antiemetic due to CVS side effects

Hyoscine HydroBromide

Chemical

- racemic mixture – only L-hyoscine is active

MOA

- competitive antagonist of Ach ⇒ ↓conduction in labyrinth of inner ear

Pharmacokinetics

- OBA 10-50%
- transdermal successful delivery method
- partial metab in liver; excreted in kidney

Uses

- motion sickness

Adverse Reactions

- related to antimuscarinic effects:
  - common: dry mouth, tachycardia, blur vision
  - rarely: constipation, fatigue, restlessness, irritablke

Dose
- 30mins prior to travel

5-HT3 Antagonists
Ondansetron
Chemical
- = synthetic carbazole

MOA
- selective 5-HT3 antagonists –located:
  - peripherally in GIT (stomach/small bowel) – prevents afferent vagus nerve info ⇒ CTZ ⇒ 5HT release
  - central – CTZ
- cancer chemo ⇒ release of stored 5-HT from enterochromaffin cells in GIT ⇒ stim 5-HT3 receptors in vagus nerve ⇒ CTZ stim

Effects
- CNS: anti-emetic & anxiolytic. no sedation
- GIT: ↑large bowel transit time ⇒ constipation (gastric motility not affected)
- CVS: prolong QTc
- Resp: nil

Side Effects
- headache, flushing
- anaphylaxis – rare
- constipation
- ↑ed QTc

Pharmacokinetics
- oral bioavailability 60%
- peak plasma conc 1-1.5hours post oral
- PPB 75%, Vd 2l/kg
- 90% metab in liver by multiple CYP enzymes ⇒ inactive metabolites
  ↳ if one inhibited, others will take over
- excreted urine (10% unchanged)
- plasma half life 3-4hrs

Uses
- nausea with cytotoxic agents & radiotherapy
- PONV: prophylaxis & Rx
- pruritis from neuraxial opioids

Cautions/Contraindications
- caution in liver impairment

Interactions
- enzyme inducers eg rifampicin ⇒ ↑metab ondansetron ⇒ ↓efficacy
- tramadol - ↓analgesic effect

Dose
- 8hrly dosing
- kids 0.1mg/kg up to 4mg
- oral dose 24mg 1-2hrs prior to chemo

Histamine Antagonists

Cyclizine

Chemical

- = piper-azine derivative
- IV prep made with lactic acid at pH 3.2 ∴ painful if injected IM

Mechanism of Action

- = centrally acting competitive reversible H1 antagonist
- also works as an antimuscarinic

Effects

- CNS:
  - some sedation
  - addiction potential
- CVS: tachycardia 2nd to antimuscarinic effects
- GIT: ↑tone of LES
- resp: does not completely reverse anaphylactic bronchospasm
  ↳ suggesting this caused by leukotrines rather than histamine

Uses

- PONV prophylaxis/treatment – most effective against opioid & tramadol N&V
- motion sickness
- menieres
- chemo/Radio Tx

Pharmacokinetics

- OBA 80%
- metab in liver (N- dealkylation
- t1/2elim 10hrs

Adverse Reactions

- full anticholinergic profile eg dry mouth, sedation, blurred vision, tachycardia

Promethazine

- antihistamine with
  - significant anticholinergic properties &
  - sedative effects
- well absorbed from gut but high 1st pass metab ∴ OBA 25%
- duration of action 3-6hrs
- metabs eliminated entirely in urine

NK_1 Antagonists

Aprepitant

MOA

- substance P widely distributed in CNS
- involved in pain & emetic pathways
- act centrally

Pharmacokinetics

- CYP3A4 liver metabolism

Uses

- very effective if used in combo:
  - 5-HT3 antagonist
  - dexamethasone

Adverse Reactions

- GI
- fatigue
- hiccups
- angio-oedema
- urticaria

Cautions/Contraindications

- ?preg ?kids ?lactation

Interactions

- inducers/inhibitors of CYP3A4:
    - ketoconazole – inhibitor ⇒ ↑levels of aprepitant
    - dexamethasone – substrate for CYP3A4 ⇒ half dose of dex if used together

Steroids

Dexamethasone

MOA

- unknown
- theory:
    - inhibit prostaglandin synthesis – especially E series
    - ↓5HT turnover in CNS
- should be given early in case
- has long lasting effect
- optimum dose 4-5mg (paeds 150mcg/kg)
- no side effects with single dose PONV prophylaxis but risk of:
    - tumour lysis syndrome

Gastric Acidity & Volume

Classification of Drugs

Volume Reduction

- prokinetics:
  - metoclopramide –
    - ↑gastric & small bowel motility
    - relaxes pylorus & duodenum (with gastric contractions)
  - cisapride –
    - ↑Ach form myenteric plexus in GIT wall
    - (but causes ↑ed QTc & risk of VT ∴ withdrawn
- anticholinergics:
  - atropine – competitive antag of Ach at M1 receptors ⇒ ↓gastric secretions
- motilin receptor agonists: erythromycin
- emetics – ipecacuanha – direct gastric irritant effect
- sildenafil:
  - reverses diabetic gastroparesis by ↑NO synthase in pyloric mm ⇒ relexation & ↑emptying

Acidity Reduction

- antacids:
  - particulate: Mg salts
  - non particulate: Na citrate
- H2 antagonists:
  - H2 competitve blockade ie ranitidine, cimetidine
  - ↓in basal & stimulated gastric acid
- PPIs:
  - @pH <3: PPI irreversible bind to H/K/ATPase ⇒ ↓HCL secretion in exchange for HCO3
- PG analogues:
  - eg misoprostol
  - MOA:
    - via PG receptor ⇒ ↓histamine mediated stim of parietal cells
    - ↑mucosal bloof flow, ↑mucus, ↑HCO3
  - not as efficacious as PPI/H2 blocker
  - uterine contractions in pregnancy a problem!
- Muscarinic blockers (M1):
  - eg pirenzipine
  - ↓stimulated gastric acid secretion at doses not effecting other classic antimuscarinic organs
    ↳ but has low therapeutic index
  - as effective as cimetidine at healing gastric ulcers

Antacids

MOA

- = chemical compounds which buffer or neutralise Hcl in stomach
- particulate vs non particulate
- major ingredients:
  - aluminium Hcl
  - calcium carbonate
  - Mg salts
  - sodium bicarbonate
- gaviscon contains alginic acid – viscous cohesive foam which adheres to lower oesophagus

Pharmacokinetics

- rapid acting eg sodium bicarb
- less rapid – aluminium
- duration of action:
  - on empty stomach - effect lasts 20-40mins
  - 1hr post food – up to 3hrs
- need chewing first to allow dissolution of antacids in stomach
- unreacted insoluble antacids are excreted

Uses

- relief of symptoms assoc with:
  - peptic ulcer disease
  - gastritis
  - GORD
  - dyspepsia

Adverse Reactions

- magnesium-aluminium compounds most commonly used ⇒ less diarrhoea side effects
- aluminium – phosphate depletion, constipation
- Ca carb – abdo distension, alkalosis, phosphate depletion, milk alkali syndrome
- Na bicarb – met alkalosis (high dose), ↓K, hypervent, tetany, volume overload ⇒ pulmon oedema
- Mg salts – belching, elevated Mg

Cautions/Contraindications

- if renal failure - ↑ed load of cations eg Al3+, Mg2+, Ca2+ ⇒problems
- Na bicarb – absorbed in stomach ⇒ ↑Na load in heart failure/HTN
- concurrent diarrhoea – avoid Mg antacid
- concurrent constipation – avoid aluminium antacid
- safe in preg

Interactions

- generally delay absorption drugs. always take 2hrs separate from drugs
- Mg drugs ⇒ ↑absorp of some hypoglycaemics ⇒ hypoglycaemia
- specifics of antacids on other drugs:
  - bisphosphonates - ↓absorb
  - quinolones – Aluminium & Mg ⇒ ↓absorb
  - tetracyclines - ↓absorb due to complex formation. 3-4 hrs apart

Sodium Citrate

- =non particulate antacid 8.8% with
  - sucrose 6.7%
  - methyl hydroxyl-bezoate 0.2%
- 0.3mol solution with pH 8.4 & unpleasant taste
- in pts risk of reflux/aspiration: 15-30mls 15-30mins preop ⇒ ↑gastric pH & ↓risk with aspiration
- onset of effect quicker than particulate antacids as they need adequate mixing with gastric contents
- no particulates means safer if aspirated
- buffers H ions

Sucraflate

- = aluminium salkt of sulphated sucrose
- used in PUD & prevention of stress ulcer in critically ill
- minimally absorbed (3%) & no metab of that which absorbed ∴ GIT drug
- MOA:
  - weak intrinsic antacid effect
  - at acidic pH:
    - forms a viscous paste adhereing preferentially to ulcer by ionic binding
    - forms complex with proteins at ulcer surface which resist hydrolysis

↳ ie physical barrier protection
- only real SE is constipation

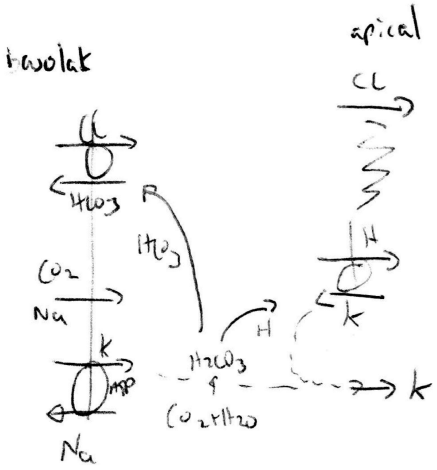
PPIs

Omeprazole

- compromises R-omeprazole & S-omeprazole (esomeprazole)
- = substituted benzi-midazole derivative

MOA

- ↓gastric acid secretion by inhibiting proton pump H,K,ATPase enzyme system at secretory surface of parietal cells
- drugs accumulate in highly acidic environment (pH0.8) of secretory canaliculi of parietal cells
- drugs converted to thiophilic sulphonamide (permanent cation) ⇒ covalent interaction with PP
- with sufficient bonding ⇒ block of final step of acid production ⇒ ↓basal & ↓stimulated acid secretion
- covalent bond (irreversible) = why action exceeds plasma half life
- most potent inhibitors of gastric acid - ↓max output by ~65%
  ↳ x2-10 than cimetidine
- stop drug: ↑gastric acid with synthesis of new H,K,ATPase
- NB no effect on gastric emptying rate



Pharmacokinetics

- post single dose: 1hr to ↓gastric acid secretion
- peak effect 2hrs; duration of activity 3-5days
- OBA 40-97%
- PPB 95% - albumin & α1 acid glycoprotein
  ↳ ∴ not effected by dialysis
- Vd 0.3-0.4 L/kg
- plasma half life 30mins (esomeprazole has slightly longer half life 1hr)
- extensive liver metab; metabolites excreted in urine (80%) and faeces (20%)
- no dose adjustment needed in organ failure

Uses

- premed (H2 antagonists slightly faster at ↓acidity)
- peptic ulcer disease – shows better healing than with H2 antagonists
- prevention of NSAID peptic ulceration
- erosive oesophagitis from GORD
- long term hypersecretory conditions eg zollinger ellison

Adverse Reactions

- generally well tolerated ie ↓endocrine effects as seen with cimetidine
- minor:
  - abdo pain ⇒ constipation!
  - D&V
  - dizzy/headache
  - gynaecomastia
- rare:
  - agranulocytosis/pancytopaenia/thrombocytopaenia
- ↓B12 absorb with chronic dosing

Cautions/Contraindications

- cautionin liver disease

Interactions
- omeprazole is inhibitor of CYP2C19 enzyme ⇒
  - ↑phenytoin levels
  - ↑diazepam levels
  - ↑warf level
- can ↓bioavailability of drugs which require acidic environ for absorb eg ampicillin, iron, digoxin

Dose
- 20-40mg for 4-8weeks for GORD
- hypersecretory conditions 20-120mg daily

H pylori Rx
- 3 drugs bd for 1/52 (?extended to 10 or 14days)
- best = PPI, clarithromycin, amoxicillin (>90% erad)

H2 receptor Antagonists

MOA
- histamine made in enterochromaffin like cells of the oxyntic mucosa
- released histamine acts on H2 receptors ⇒ ↑gastric acid secretion
- H2 antagonists competively block histamine from stim H2 receptors on gastric parietal cell ⇒ ↓50-60 % acid production esp nocturnally

Uses
- as PPI

Interactions
- ↓acidic levels in stomach ⇒ ↓absorbtion some drugs – see PPIs

Ranitidine

Chemical
- =furan derivative
  ↳ ie furan ring replaces the imidazole ring
- =x5-10 more potent than cimetidine

Effects
- ↓basal secretion by up to 90% after single dose
- ↓gastric volume, HCL & pepsin content
- longer anti-secretory action than cimetidine
- dose related ↑ in LES tone

Pharmacokinetics
- crosses placenta but no adverse effects reported
- OBA 50-60%
- 15% PPB
- Vd 1.5L/kg
- 30% metabolised ⇒ 40% excreted unchanged in urine
  ↳ need dose adjustment in renal disease
- t1/2elim 3hrs
- removed by diaylsis

Adverse Reactions
- no CVS, anti-androgenic effects as seen with cimetidine
- less drug interactions as x5-10 less binding to cP450 than cimetidine
- anaphylactoid – rare
- reversible confusion
- ↓WCC, ↓plts

Cimetidine

Chemical

- retains the imidazole ring of histamine
- has an extra bulky side chain on this ring ⇒ competitive antagonist

Effects

- as ranitidine but:
  - no consistent effect on LES or rate of emptying
- longest period of basal acid secretion = at night
- nocturnal dosing ⇒
  - ↓nocturnal acid
  - no change daytime acid
  - ulcer healing = faster

Pharmacokinetics

- OBA 70%
- 20% PPB
- Vd 1L/kg
- 30% liver metab ⇒ 70% excreted unchanged in urine
  ↳ ∴ dose adjust in renal dysfunction
- t1/2elim 2hrs
- removed by dialysis

Adverse Reactions

- CVS: bradycardia/arrhythmias esp with rapid IV infusion
- renal – may cause ↓creat clearance
- endocrine: weak antiandrogenic ⇒ impotence, ↓sperm count, gynaecomastia
- immunomodulative effect ⇒ pituitary inhibition
- multiple drug interactions specific to cimetidine (=inhibitor of mixed hep oxidases & C-P450 system):
  - ⇒ ↑plasma levels of:
    - benzo's
    - warf
    - phenytoin
    - theophylline
    - nifedipine
    - flecanide
    - metoprolol
    - lignocaine
    - TCAs
    - OCP
- dizziness
- confusion
- rashes
- leucopaenia
- pancreatitis, ↑LFTs

Analgesia

Mediators of Pain

- include:
  - glutamate
  - GABA
  - endogenous opiods
  - 5HT
  - NA
- modulation of these transmitters responsible for pain relief drugs:
  - opiods
  - NSAIDs
  - LAs
  - GABA agonists
  - NMDA antagonists
  - tachykinin antagonists
  - cannabinoids
  - Ca channel blockers
  - α2 agonists

Endogenous Opiods

- natural enkephalins & endorphins (larger polypeptides)
  ↳esp in
    - periaqueductal grey matter midbrain
    - limbic system
    - interneurons dorsal horn areas
- endorphin release higher after acupuncture & TENS
- placebo ⇒ ↑release endorphins

Prostaglandins

- acute inflammation from direct tissue damage
- arachidonic acid produced from damaged cell membranes
- COX enzyme system ⇒ prostaglandins ⇒ ↓threshold of nociceptors to other mediators
- NSAIDs inhibit prostaglandin production

Tachykinins

- =fast acting polypeptides incl substance P & neurokinins A & B
- involved in inflam & neuropathic pain

Nociceptive Pain

- =physioligcal pain
- stim of nociceptors by noxious stim eg injury or inflam
- somatic nociceptive pain =
  - well localised
  - from skin, mucosa, bones, joints, pleura, peritoneum
  - Rx with NSAIDs
- visceral nociceptive pain =
  - from walls of visceral organs
  - deep & aching pain
  - poorly localised & often referred
  - Rx with opiods
- muscle spasm nociceptive pain =
  - skeletal or smooth mm – mediated by PGs
  - worse on movement or colicky pain (stretch of smooth mm)

- Rx mm relaxants & NSAIDs

Neuropathic Pain

- from primary lesion/alteration/dysfunction in PNS or CNS pathways
- eg spinal nerve root compression
- assoc parasthesia, hyperalgesia, allodynia (pain due to stim wouldn't norm cause pain)
- responds less well to opiod analgesics
- Rx adjuncts:
  - TCAs or SNRI (serotonin/noradreanline reuptake inhibitor) eg venlafaxine
    - ↳ ⇒ enhanced NA & 5HT mediated descending inhibition of painful stim
    - ↳ TCAs ⇒ sleep enhancing
  - anticonvulsant eg gabapentin or carbamazepine
    - ↳ ⇒ enhanced GABA mediated inhibition
  - LA – lignocaine ⇒ ↓Na channel mediated transmission of pain
  - tramadol – both opiod & selective 5HT reuptake inhibitor activities

NSAIDs

- classification:
    - non specific cox inhibitors
        - salicylates
        - para-aminophenols (paracetamol)
        - acetic acid derivatives
            - diclofenac
            - ketorolac
            - indomethacin
        - pyrazolones ie phenylbutazone
        - proprionic acids ie ibuprofen
        - oxicams ie tenoxicam
    - preferential cox-2 inhibitors ie meloxicam
    - specific cox 2 inhibitors ie valdecoxib & parecoxib

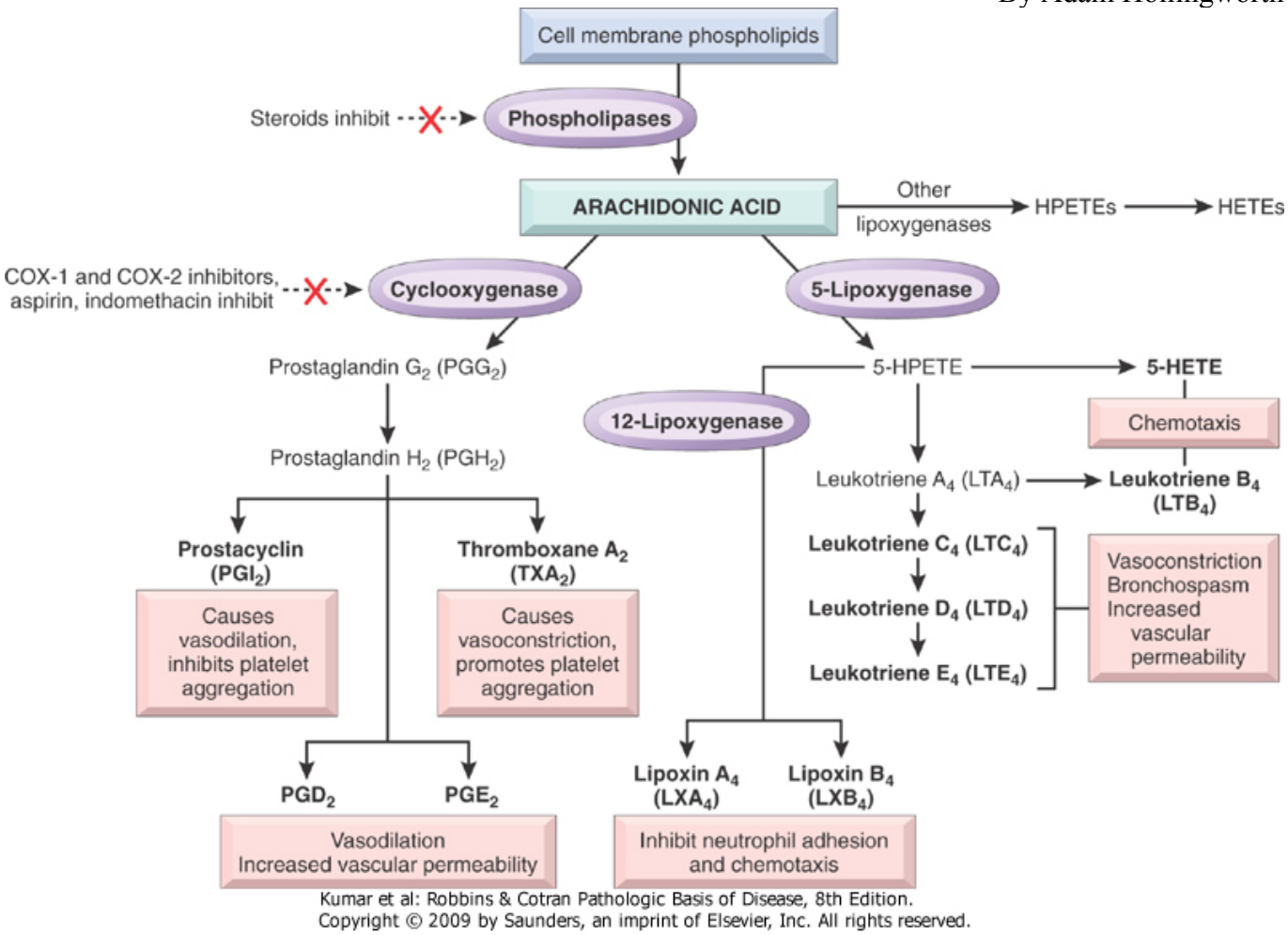
MOA

Analgesic

- inhibition of COX isoenzymes ⇒ ↓PGs at site of injury
- PGs sensitise nociceptors to actions of bradykinin & other pain mediators
- COX1 & COX2 catalyse synthesis of PGs involved in pain
    ↳also GI side effects of which COX2 shows less of
- analgesic action is peripheral

Antipyrexic

- inhibition of PG synthesis in hypothalamus



(from physiology – endocrine section)

Generic Side Effects

- GI side effects:
  - due to ↓synthesis of mucoprotective PGs by systemically absorbed NSAIDs
  - incl: dyspepsia, N&V, gastritis, constipation/diarrhoea
- renal damage:
  - ↓ed vasodilator PGs
  - esp in elderly on long acting NSAIDs
- asthma
- skin reaction – uritcaria
- Na retention ⇒ heart failure & HTN

Table 9.6. Clinical and kinetic data for some NSAIDs.

Drug	Maximum daily dose	Elimination half-life (h)	Plasma protein-binding (%)	Analgesic and antipyretic activity	Anti-inflammatory activity
Aspirin	4 g	variable*	85	+++	++
Paracetamol	4 g	2	10	+++	++
Diclofenac	150 mg	1–2	99	+	+++
Ketorolac	40 mg	5	99	++	+
Indomethacin	200 mg	6	95	+	+++
Phenylbutazone	300 mg	50–100	98	+	++++
Tenoxicam	20 mg	72	99	+	++
Meloxicam	15 mg	20	99	+	++
Ibuprofen	1.8 g	2–3	99	+	+

* When obeying first-order kinetics the $t_{1/2}$ elimination of aspirin is short (15–30 min). However, this is significantly prolonged when enzyme systems become saturated and its kinetics become zero-order.

1. Salicylates - Aspirin

- see CVS notes
- = non specific COX inhibitor

2. Para-aminophenols (Paracetamol)

- safer than aspirin because:
  - adverse effects & allergic reactions rare with therapeutic doses
  - low risk gastric upset
  - plasma protein binding negligible ∴ no displacement & less drug interactions
  - no sig drug interactions eg can take concurrently with anticoagulants
  - safe in children – no Reye's syndrome
  - safe in preg & lactation

MOA

- inhibition of some COX isoenzymes ⇒ ↓PGs at site of injury
- exact MOA are not clear
- does inhibit COX in some tissues in some species
- ??acts as prodrug with one of its active metabolites activating cannabinoid receptors in CNS

Pharmacokinetics

- orally – rapidly absorbed – peak plasma 15-60mins
- elim half life 1-3hrs
- metabolised in liver:
  - norm pathway: metabolised to glucuronide & sulfate derivatives
  - high dose/toxic pathway:
    - saturation of normal pathway
    - metabolised to benzoquinone intermediates (BQI)
    - BQI has 2 pathways of metab depending on available glutathione:

- enough glutathione ⇒ paracetamol-mercapturic acid derivative (non toxic)
- depleted glutathione ⇒ formation protein derivatives, lipid perioxidation, oxidative stress ⇒ liver cell death

↳N acetylcysteine is a synthetic analogue of glutathione

Uses

- effective
  - antipyrexic
  - analgesic
- very limited anti-inflamatory

Adverse Reactions

- rare at normal levels
- nausea & rash have been reported
- overdose can lead to serious liver/renal damage

Managing Paracetamol OD

- Measure levels after 4hrs
- Severe liver damage in normals if take >150mg/kg or >10g or 20tabs
- Fatal dose usually >20-30g
- Pts above Rx line within 24 hrs should get N-acetylcysteine
- ALL pts presenting with deranged LFTs or symptoms >24hr after taking >10g paracetamol should get antidote
- Pts also taking enzyme inducing drugs should have lower threshold to Rx:
  - Rifampicin

  ↳those on enzyme inhibitors not at high risk eg omeprazole
- Repeat paracetamol levels 4hrs after initial level

  ↳?delayed absorption
- INR most sensitive indicator of liver damage
- Features:
  - Generally asymptomatic <24hrs except mild nausea/vomit/anorexia
  - Then:
    - Hypoglycaemia – 2nd to liver failure
    - GI bleeding
    - Lactic acidosis – early (within 12hr) or late
    - Pancreatitis – alone or with liver failure
    - Hepatic necrosis
      - Apparent 24-36hrs, peaks at day 3-4
      - RUQ pain, Jauundice, vomiting
      - those on rifampicin, St John Wort or anticonvulosants at greatest risk
    - Acute renal failure – 1-10% incidence

      ↳chronic alcoholics & pts on phenytoin more susceptible
    - Confusion & encephalopathy: 36-72hrs
- Liver unit referral
  - pH <7.32
  - INR >1.5
  - (shock 80 systolic)
- Indications for transplant:
  - Late acidosis (>36hr) <pH 7.3
  - PT >100sec
  - Grade 3 encephalopathy = confused, distressed
  - Creat >300

Acetylcysteine

- Encephalopathic pts always get despite length from taking it

- Acetylcysteine given by IV infusion in 5%dex
- 1st : 150mg/kg in 200ml dextrose over 15mins
- 2nd : 50mg/kg in 500ml over 4hrs
- 3rd : 100mg/kg in 1l over 16hrs

↳ SEs – usually in 1st hr:

- rash around infusion site
- angiooedema
- bronchospasm
- hypo/hyper tension

↳ stop, give antihistamine, then restart at slowest infusion rate

- factors ≈ Rx under high risk line:
  - enzyme inducing drugs eg carbamazepine, phenytoin, rifampicin, alcohol
  - malnourished eg anorexia, alcoholism, HIV

Methionine

- useful if pt refuses IV Rx
- give oral tabs 2.5g ev 4hrs to toal of 10g
- no siginifcant SEs
- less effective than parvolex esp if:
  - Vomit
  - >8hrs after ingestion
  - had activated charcoal

3. Acetic Acid Derivatives

Diclofenac

Chemical

- = phenyl-acetic acid derivative

Presentation

- IV (give over 30mins), oral, rectal

Mechanism of Action

Effects

- GIT – less irritation than indomethacin & aspirin at comparable doses
- pain – IV formulation should be used with caution:
  - highly irritant & painful esp IM injection ⇒ mm damage
  - local thrombosis
- class effects ie ↓platelet function, acute renal impairement

Uses

- used alone or to ↓opioid need
- esp useful in renal colic
- non specific COX effects limit its use peri/intra-op

Pharmacokinetics

- well absorbed
- PPB 99%
- small VD
- hepatic hydroxylation & conjugation ⇒ inactive metabs
- excreted in
  - urine 60%
  - bile 40%

Interactions

- ↑plasma conc of lithium & digoxin
- generally dose not effect oral anticoagulants or hypoglycaemic agents

Dose

- paed 1mg/kg tds
- max adult dose = 150mg/day in divided doses

Ketorolac

- characteristics:
  - potent analgesic activity
  - potent antipyretic
  - limited anti-inflam activity
- class like side effecrs
- oral or IV prep

Indomethacin

- potent anti-inflam but less analgesia
- rectal use peri-op:
  - ↓opioid requirement
  - ↓platelet function ⇒ wound haematoma & blood loss
- use to promote closure of PDA in premature infants by inhibiting prostaglandin synthesis
- class side effects AND ↑ed headache risk
- may impair hepatic function
- may cause ↓effect of diuretics & ACEIs
- OBA 80%
- metabolised to inactive metabs
- 5% excreted unchanged
- elim via renal & bile

4. Pyrazolones – Phenylbutazone

- = potent anti-inflam agent
- limited use to severe anky spond pts due to high risk haematological side effects
  ↳ agranulocytosis & aplastic anaemia
- adverse reactions incl:
  - ↓hepatic function
  - rash
  - sodium & water retention

5. Proprionic Acids – Ibuprofen

- not recommended for children <1yr old
- has lowest incidence of side effects of most commonly used NSAIDs

6. Oxicams – Tenoxicam

- exhbits many class like features
- 2 specific features make it useful periop:
  - IV dosing ⇒ rapid onset
  - long elim half life (72hrs) ⇒ long duration of action & once daily dosing
    ↳ although bad if side effects become significant
- high OBA
- metab to inactive metabolites
- excreted via:
  - urine 66%
  - bile 33%

7. Preferential COX-2 inhibitors

Meloxicam

- tablets & suppositories
- = x3-50 potent against COX2 than COX1
- shows ↓ed GI side effects (but same renal)
- OBA 90% but slow absorption
- bound to albumin
- 97% liver metab to inactive metabolites

- excreted via:
  - renal 50%
  - bile 50%
- t1/2elim 20hrs

8. Specific COX-2 Inhibitors

- a lot of drugs from this class have been withdrawn due to concerns of ↑incidence of MI & stroke
- thought initial benefit was as shown in table:

Comparison of NSAIDs and COX-2

	NSAIDs	COX-2
Efficacy for moderate to severe acute pain (numbers needed to treat—NNT)	Diclofenac 50mg (2.3) Ibuprofen 400mg (2.4) Ketorolac 10mg (2.6)	Celecoxib 200mg (4.5) Parecoxib 20mg (3.0) Valdecoxib 20mg (1.7)
Renal function	Can affect renal function postoperatively	Similar adverse effects on renal function
Gastrointestinal	Acute gastroduodenal damage and bleeding can occur. Risk increased with higher doses, history of GI ulceration, long-term use, and elderly	Less clinically significant peptic ulceration than NSAIDs (VIGOR and CLASS studies)
Platelet function	Inhibit platelet function but do not significantly increase surgical blood loss in normal patients. Associated with higher incidence of post-tonsillectomy haemorrhage	Do not impair platelet function
Aspirin-exacerbated respiratory disease	10–15% of asthmatics affected when given aspirin. Cross-sensitivity with NSAIDs	Do not produce bronchospasm
Bone healing	Impaired in animal models. No good evidence that clinically important	Similar to NSAIDs

- ie no bronchospasm, no effect on bleeding, ?↓GI effect
  ↳ GI effect may be true as long as not taking for >12months

Parexocib

Chemical

- = a prodrug which is then converted to active moiety valdecoxib
- valdecoxib withdrawn due to serious dermatological side effects ie TEN, SJS, angioedema (8/million)
  ↳ not seen in parecoxb yet ?due to short term use
- COX1:COX2 inhibitory ratio of 1:61

Pharmacokinetics

M

- parecoxib ⇒ valdecoxib by liver enzymatic hydrolysis
- valdecoxib hep metab by cytochrome & glucuronidation to many metabolites
- one of the metabolites antagonises COX-2

E

- hepatically eliminated ∴ renal impairement does not effect kinetics
- parecoxib plasma t1/2 = 20mins
- valdecoxib t1/2 elim = 8hrs

Interactions

- ↓dose of parecoxib with fluconazole due to inhibition of CYP2C9

Celecoxib

- tablets
- for RA & OA only
- COX1:COX2 inhibitory ratio of 1:30

Adverse Reactions

- no ↑ed risk in stroke & MI
- similar incidence of GI upset although ?slightly lower

Pharmacokinetics

- peak plasma conc after 2-3hrs
- t1/2 elim 8-12hrs
- 97% PPB
- Vd 5.7L/kg
- near complete liver metab to inactive metabolites
- drugs which effect CYP2C9 will effect plasma conc:
    - inhibit = omeprazole⇒ ↑plasma conc
    - induce = carbamazepine ⇒ ↓plasma conc

Opioids

- unique compounds in their ability to produce analgesia without loss of
  - touch
  - proprioception
  - consciousness (dose dependant)

Definitions

- opiate = any substance derived from opium
  ↳∴ excludes peptides & synthetically derived agonists
- opioids = substances that bind to opioid receptors
  ↳∴ includes all natural, synthetic & endogenous compounds
- alkaloids = basic compound of plant origin, contains nitrogen
- narcotic = greek for stupor or to be numb
- Morpheus = Greek god of dreams

History

- naturally occurring opioids (or opiates):
  - morphine
  - codeine
  - papaverine
- morphine can be synthesised but much easier & cheaper to derive it from opium

Classification

- split:
  - endogenous
    - endorphins
    - enkephalins
    - dynorphins
  - exogenous:
    ↳ can be subclassifed by either:
    - Nature:
      - natural
      - synthetic
    - Action at opioid receptor
      - agonist
      - agonist-antagonist
      - partial agonist
      - antagonist

Nature

- naturally occurring ie alkaloids of opium:
  - phenanthrenes:
    - morphine
    - codeine
    - thebaine (precursor of etorphine + naloxone)
  - Benzyl-iso-quinolines:
    - papvaerine
    - noscapine
- semi-synthetic – from simple modification of morphine molecule
  - heroin
  - apomorphine
  - hydro-, oxy- ….. morphine
  - oxy-, hydro- ….. codone
  - papaveretum

- synthetic – contains phenantrene nucleus of morphine but are fully synthesised :
  - phenyl-piper-idines:
    - pethidine
    - fentanyl, alfentanil, sufentanil, remifentanil
    - tramadol

    ↳have similar mw, pKa's to amide LA's
  - benzomorphans:
    - penta-, phena-, cycla- ….. zocine
  - di-phenyl derivates:
    - methadone
  - morphinan derivatives:
    - levorphanol

Action

- full agonists ie activation of all receptor classes but different potencies:
  - morphine
  - morphine derivatives: naturally occurring, semi synthetics, morphinan derivatives
  - phenyl-piper-idines
  - methadone
  - benzomorphans - phenazocine
- agonist-antagonists ie agonist at 1 receptor but antagonist at others:
  - benzomorphans: pentazocine, bremazocine
  - buprenorphine
- partial agonists ie lacks full intrinsic activity
  - buprenorphine = partial agonists at mu, antagonist at kappa
- antagonists ie devoid of receptor activity at all types ie zero efficiacy
  - naloxone
  - naltrexone
  - nalmefene

Ideal Property for Opioids

- physic-chemical:
  - high lipid solubility – faster onset, less delayed resp depression via spinal route
  - stable in solution
  - compatible with other drugs
  - cheap
- pharmacokinetic:
  - high OBA eg oxycodone 60% vs morphine 30%
  - non active metabolites
  - non cumulative
  - organ independent, non saturable clearance eg remifentanyl
- pharmacodynamics:
  - high specificity & potency
  - rapid onset & offset
  - duration of action according to needs
  - high TI
  - induce well being/euphoria
  - lacks dependence/tolerance/dysphoria
  - lack of adverse effects

Common Side Effects as a Group

- CNS:
  - dysphoria + psychomimetic effects

    ↳esp if given in opioid naïve and not in pain
  - tolerance

  - physical & psychological dependence
  - stim of DTZ ⇒ N&V
  - convulsions (nor-pethidine)
- Resp:
  - Resp depression
  - thoracic rigidity – high doses only
- Autonomic NS
  - sphincter spasm – does include Odi
  - constipation
  - ↓bladder tone
  - pruritis – esp if given spinally
- CVS:
  - hypotension
  - bradycardia (morph/remi) / tachy (pethidine)
- Histamine release (via several mechanisms eg direct, complememt, HS reaction)
  - CVS & resp SEs
- Drug interactions: MAOI <> pethidine

Structure – Activity

- alkaloids (basic):
  - pKa ~8 ⇒ 90% ionised at body pH
    ↳ except alfentanil pKa 6.5 = 10% ionised
- T shape
- tertiary, basic nitrogen atom
  ↳∴ binds receptor in ionised form
- complex structures with a number of enantiomers:
  - S-isomers are most active
- diff no of rings:
  - phenantrenes – 5 rings
  - morphinans – 4 rings
  - benzomorphans – 3 rings
  - phenylpiperidines – 2 rings

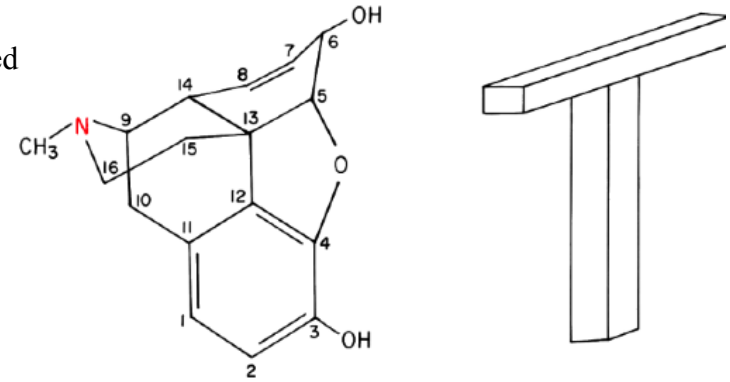


Fig. 12-2. The T-shaped molecule of morphine. (From Thorpe[40] with permission.)

Opioid Receptors

- receptors where opioids function
- opioid receptors are GPCRs (**Gi**). Activation ⇒
  - [all] inhibit adenylate cyclase ⇒↓cAMP levels
  - [Mu+delta] ↑opening K channels ⇒ ↑K out
  - [kappa] ↓opening of Ca channels ⇒ ↓Ca in
  ↳∴ overall effect ↓neuronal excitability & ↓release of excitatory pain transmitters
- tolerance due to:
  - loss inhibitory functions
  - ↑excitatory signalling – upregulation of adenylate cyclase
- withdrawal due to rebound ↑cAMP levels via delta opiod receptors
- significant correlation between analgesic potency & affinity for Mu receptors
- only a small degree of receptor occupancy required ⇒ analgesia
- large doses of opioids 'spill over' to other receptors ⇒ additional effects

Mu Receptor

- strong agonists – morphine & fentanyl
- partial agonist – buprenorphine
- weak agonist – pethidine
- Mu_1 response:

  - good:
    - supraspinal & peripheral analgesia
    - euphoria
    - low abuse potential
  - bad:
    - bradycardia
    - hypothermia
    - urinary retention
    - miosis
- Mu_2 response:
  - good:
    - euphoria,
    - spinal analgesia
  - bad:
    - hypoventilation
    - constipation (severe)
    - physical dependence

↳antagonist naloxonazone was used to differentiate mu1 & mu2 (sensitive mu2 & insensitive mu2)

Kappa

- agonist – morphine, endogenous opiates
- little/no acivity – methadone, pethidine
- response:
  - good:
    - Supraspinal analgesia (k1 + K3)
    - spinal analgesia K1
    - sedation ∴ low abuse potential
    - ? role in ↓ing addiction potential by ↑dopamine2 receptors in nucleus accumbens
  - bad:
    - dysphoria + hallucinations
    - resp depression
    - miosis
    - diuresis (↓ADH release)

Delta

- agonist – endogenous opiates, morphine
- response:
  - good:
    - supraspinal analgesia (D1)
    - spinal (D2)
  - bad:
    - hypovetilation
    - constipation (minimal)
    - physical dependence
    - urinary retention
    - rebound in withdrawal

(sigma)

- stim by partial agonists eg buprenorphine
- only –ve response: dysphoria, hallucinations, confusion

Receptor summary by Symptoms

- good:
  - supraspinal analgesia = Mu1, K1 +K3, D1
  - spinal analgesia = Mu2, K1, D2
  - peripheral analgesia = Mu1

  - euphoria – Mu2
  - sedation - kappa
- bad:
  - dysphoria = kappa
  - hypoventilation = Mu2, Kappa, delta
  - constipation = Mu2 (severe), Delta (minimal)
  - urinary retention (Mu1, Delta) ⇒ kappa causes diuresis
  - dependence = Mu2, delta

Endogenous Opioid Peptides

- all = peptides
- classified as:
  - endorphins
  - enkephalins
  - dynorphins
- from inactive polypeptide precursors:
  - pro-enkephalin ⇒ enkephalins
  - pro-dynorphin ⇒ dynorphins
  - pro-opio-melano-cortin (POMC) ⇒ beta-lipotropin ⇒ beta-endorphin

Endorphins

- binds preferentially to mu
- more potent & stable than enkephalins
  ↳∴ long lasting analgesia (hrs)
- POMC precursor also precursor of 3 non opioids:
  - ACTH
  - α-MSH
  - ß-lipoprotein

  ↳∴ in response to stress concentrations of these also ↑

Enkephalins

- selective affinity for delta
- antagonised by naloxone
- = neurotransmitter in descending inhibitory pathways
- rapidly hydrolysed ie true neurotransmitter

Dynorphin

- selective affinity for kappa
  ↳but also has action at other 2
- ?modulatory effect on other opioids
- ?role in spinal injuries
- ?new role in Rx of addiction

Opioid Analgesia

- complex system due to:
  - uncertainty of receptor details
  - complex pain pathways
  - development of tolerance
  - anti-opioid systems
  - wide ranges in genetic sensitivity to diff opioid classes
- work by surpressing the subjective component of pain
- each receptor class acts via distinct mechanisms in diff locations within the CNS – both centrally & peripherally
- systemic morphine via mu receptors:
  - supraspinally – primary site of action:
    - via control centres assoc with descending inhibitory pain pathways:

        - peri-aqueductal grey (PAG)
        - nucleus raphe magnus (NRM)
        - locus ceruleus (LC)
    - spinal – mu in dorsal horn
    - peripheral mechanisms eg loperamide mu agonist which does not cross bbb and demonstrates antihyperalgesic effects
- all targets work alone but more effective in combination
  ↳ie profound synergy:
    - eg spinal morphine in mice ⇒ ↓Ed50 of systemic morphine by x100
    - eg epidural drugs enhanced by concomitant systemic drugs
- large inter-indivdual variation in response to specific agent or doses
- opioids not completely cross-tolerant ie tolerant to one agent, may not be tolerant to another

Opioid Tolerance

- = progressive decreasing response to repeated doseage of a drug ie drug becomes less potent
- frequently encountered but can overcome by ↑ing dose or switching to diff drug
- tolerance produces ↓potency **not** ↓efficacy
- can be profound needing up to x100 higher dose – only limited by dose limiting side effects
- mechanism proposed:
    - altered receptor transduction mechanisms
    - upregulation of adenylate cyclase
    - opioid induced hyperalgesia
- NMDA blockade (animal studies):
    - no effect on analgesic activity
    - blocks tolerance effect

  ↳eg ketamine, Mg, methadone has some NMDA blocking effect

Opioid Dependance/Addiction

- physical dependence = propensity to experience a withdrawl syndrome after discontinuation of the drug (or administration of an antagonist)
- addiction (psychological dependence) = chronic state characterised by compulsive use of a substance resulting in harm & contuned use despite this

- physical dependence does not imply addiction
- additction mechanism:
    - ?nucleus accumbens (NA) plays impt role
    - addiction ⇒ ↓D2 receptors in NA
    - pethidines high addictive potential mediated via NA area
    - kappa agonists ⇒ ↑D2 receptors in NA
      ↳eg use dynorphin to Rx addiction
- all pts chronically on opioids become dependent yet v few given them for pain management become addicted
- should not administer agonist-antagonists or antagonists
- can taper opioid dose with no evidence of withdrawal
- signs of withdrawal (sympathetic over-activty):
    - Anxiety/Insomnia
    - Lacrimation/Rhinorrhea
    - Mydriasis (dilation)
    - N&V/Abdo cramp, diarrhoea
    - Myalgia
    - ↑bp
    - Yawning
    - piloerection

- Delirium, seizure, tremor, hallucinations & high fever do not occur ∴ look for something else
- Rarely has serious complications even without intervention
  ↳unlike withdrawal from benzo's

- methadone (long lasting) can have milder but protracted withdrawal period
  ↳taper dose 50% every 2 days without signs of a withdrawal
- Rx include symptom relief:
  - Benzo's
  - Antiemetics
  - Antidiarrhoeal agent
  - Clonidine (alpha 2 adrenoceptor agonist) - ∴ ↓'s symptoms of autonomic dysfunction

Summary of Pharmacokinetics of Opioid Group

Absorption

- OBA:
  - most = well absorped from small intestine
  - weak bases with high pKa (6.5-9.3)
  - ionised in stomach – little absorption here
  - ↑unionised form in relative alkaline small intestine ⇒ ↑absorption
- 1st pass metabolism:
  - all opiods (except methadone) undergo sig 1st pass metab in:
    - gut wall
    - liver (high extraction ratio)
  - ∴ low OBA in general:
    - morphine 20-30%
    - pethidine 45-75%
    - codeine 60-70%
    - oxycodone 50-60%
- absorption from mm:
  - rapid with max plasma conc 15-60mins; duration ~4hrs
  - unpredictable in shock/hypothermia/pain
- multiple other routes of admin

Distribution

- affected primarily by:
  - lipid solubility:
    - most impt factor in penetrating CNS
    - high lipid soluble drugs eg fentanyl ⇒ rapid onset of action (short $t1/2_{keo}$)
    - rpt doses/infusions ⇒ accumulation + prolonged recovery
  - PPB:
    - min effect on drugs entering CNS due to large VD's
    - many are bound to α1-acid glycoprotein:
      - acute phase reactant
      - ∴ free conc will be ↓ed in acute illness
  - degree of ionisation:
    - effects everything else (lipid sol, PPB, portioning b/w tissue & plasma)
    - depends on ambient pH
      - eg hypervent (↓PaCo2) ⇒ ↑pH ⇒ ↑unionised ⇒ ↑rapid onset
      - eg ↑PaCo2 ⇒ ↓unionised ⇒ slower onset
        ↳but is offset by ↑cerebral blood flow caused by ↑PaCO2
    - pKa – alfentnil has lower pKa than fentanyl ⇒ ↑unionised proportion of drug ⇒ faster onset
  - tissue binding:
    - Vd = several times > Total Body Water

Metabolism

- mainly in liver
- reactions:
  - phase 1
  - phase 2 – glucuronide conjugation for morphine
- metabs generally inactive/much less active than parent drug
- sig degree in inter-individual variability in kinetic constants
- t1/2elim does not necessarily relate to clinical duration of action
  - t1/2elim: morphine < fentanyl but has longer duration of action
    ↳cos fentanyl redistributes quicker terminating action

Elimination

- Cl ~ hepatic flow ∴ Clhepatic ~ hepatic flow
  ↳ ie not influenced by PPB or enzymatic activity
  ↳except methadone = restrictive clearance due to easily saturatable P-450 system

	pK	Percent Nonionized (pH 7.4)	Protein Binding (%)	Clearance (ml/min)	Volume of Distribution (liters)	Partition Coefficient	Elimination Half-Time (hrs)	Context Sensitive Half-Time: 4-Hour Infusion (mins)	Effect-Site (Blood/Brain) Equilibration Time (mins)
Morphine	7.9	23	35	1,050	224	1	1.7–3.3		
Meperidine	8.5	7	70	1,020	305	32	3–5		
Fentanyl	8.4	8.5	84	1,530	335	955	3.1–6.6	260	6.8
Sufentanil	8.0	20	93	900	123	1,727	2.2–4.6	30	6.2
Alfentanil	6.5	89	92	238	27	129	1.4–1.5	60	1.4
Remifentanil	7.3	58	66–93	4,000	30		0.17–0.33	4	1.1

	pK	lipid solubility (rel to Morphine)	% unionized
Morphine	8	1	25
Alfentanil	**6.5**	**150**	**90**
Fentanyl	8.5	1000	10
Sufentanil	8	2000	20
Pethidine	8.5	50	**7**

- relative IV opioid potencies:

Morphine	1
Pethidine + Tramadol	0.1
Oxycodone	1
Buprenorphine	20 – 30
Fentanyl + Remifentanil	100
Sufentanil	500 - 1000

↳ remember potency determined by affinity for receptor & pharmacokinetic factors

Substance P

- =neurokinin present esp in nociceptive afferents
- mediates
  - pain
  - inflam
  - smooth mm contraction
  - stim many exocrine glands

Opioid Drugs

Morphine

Structure/Chemical

- = principle phenantrene alkaloid in opium
  ↳opium contains ~9% morphine by weight
- complex 5 ring structure with T bar shape
- gold standard opioid against which others compared
- weak base, pKa 7.9 = 25% unionised
- S-isomer is most active

Presentation

- liquid – as a salt with sulphate or hydrochloride

MOA

- still not entirely clear
- diff actions at diff levels:
  - spinal cord level:
    - stim opiod receptors ⇒ ↓release of substance P from dorsal horn neurons ⇒ ↓afferent transmission of pain
  - supraspinal levels:
    - opiod receptors widely distributed in CNS esp limbic, thalamus, hypothalamus, midbrain
      ↳ ⇒ altered perception of pain – potentiation of descending inhibition

Pharmacokinetics

A

- generally not well absorbed
- OBA 20-30% due to:
  - poor absorption:
    - weak base (pKa 8) in acidic stomach ⇒ ionisation
    - no absorption until reaches alkaline small bowel ⇒ unionised ⇒ absorbed
  - extensive 1st pass metab in liver
- S/C route shows slow absorption due to relatively low lipid solubility
- IM dosing – peak affect 15-60mins lasting 3-4hrs
- IV dosing – peak effect much same as IM due to slow crossing BBB
  ↳low lipid solub, 75% ionized at pH 7.4

D

- PPB 35%
- 25% unionised at pH7.4
- Vd 3-5L/kg (big)
- small fraction crosses bbb:
  - morphine conc in brain falls slowly due to low lipid solubility
  - ∴ plasma conc don't correlate with CNS effects
- post IV dose:
  - plasma conc declines in tri-exponential fashion:
    - initial rapid distribution
    - slower decline ⇒ BBB crossing during this phase
    - very slow exponential decline – correlates with t1/2 elim ~3hrs

  ↳no direct correlation between plasma conc & clinical effects
  ↳in contrast to fentanyl

M

- mostly phase 2 metabolism ie glucuronide conjugation
  ↳ some also N-demethylated ⇒ normorphine

- almost entirely metab'ed in gut wall + liver ⇒ active or inactive
- main metabolites of morphine:
  - morphine-6-glucuronide (M6G):
    - 10%
    - x13 more potent than parent drug
    - 24 hr excretion via kidneys
  - morphine-3-glucuronide (M3G)
    - 75%
    - inactive or possible mu antagonist
    - 10% enters enterohepatic circulation:
      - excreted by bile ⇒ broken down by intestinal bacteria ⇒ release of morphine ⇒ reasorbed for remetabolism

E

- Cl_{hep} =
  - flow dependant
  - hep extraction ratio 0.8
- metabolites are renally excreted:
  - 90% M3G in 24hrs
  - M6G can accumulate in renal failure
- t1/2 elim 2 hrs

Altered Physiology/Special Circumstances

- elderly:
  - ↓Vd ⇒ ↑plasma conc ⇒ more sensitive
  - ↑CNS sensitivity
- neonates: ↓ed conjugating capacity ⇒ ↑sensitivity
- liver cirrhosis:
  - Cl not affected as conjugation mostly spread
  - ↑sensitivity due to PD changes

  ↳ pethidine v bad (nor-pethidine toxic half life)

  ↳methadone may be safer
- hypovolaemia - ↓IM absorbtion
- ↓hepatic clearance seen when ↓liver blood flow eg:
  - SAB
  - halothane
  - BBlockers
  - upper abdo surgery
  - IPPV/PEEP
- acid base changes = complex:
  - resp acidosis = ↑ionised fraction ⇒ ↑receptor binding ⇒ ↑resp depression & ↑CBF ⇒ +ve feedback loop or badness
  - resp alkalosis: ↑non-ionised ⇒ ↑bbb crossing ⇒ ↑effects
- renal disease:
  - extend half life of opioids excreted in an active form

    ↳ eg methadone, pethidine, M6G

Equivalent Dosing

- 30mg oral morphine = 10mg IV

Pharmacodynamics

- CNS effects:
  - analgesia:
    - mu1 & kappa
    - better for dull/poorly localised pain from deep structures
    - ↑s threshold & changes perception of pain ie feel it but don't care

- euphoria – not all pts
- dysphoria (kappa) – esp if no pain present
- sedation (kappa):
  - usually drowsiness
  - if sleep: EEG shift to delta waves & REM supressed
  - sedation scores are better indicators of opioid OD than RR
- pupils (kappa):
  - miosis via stim of Edinger Westphal nucleus (CNIII)
- cerebral metabolic rate: ↓10-25%
- ICP & CBF: in very high doses ↓ed
  ↳ fentanul & sufentanil ⇒ ↑CBF & ↑ICP
- mm rigidity:
  - esp thoracic wall
  - ↓FRC, ↓compliance ⇒ resp compromise
  - can prevent by precurarisation or slow IV injection
  - ?mechanism but:
    - opioid receptrs in substantia nigra ⇒ effect on dopaminergic/GABA pathway
- N&V:
  - due to stim of dopamine & 5-HT3 receptors in CTZ
  - repeated dosing may ⇒ depression of vomiting centre
- seizures – v high doses

- resp effects:
  - central resp depression (mu 2 in brainstem):
    - both rate & depth depressed (rate> depth)
    - max depression within 7mins IV but can occur up to 30mins post IM
    - effects last 3-4hrs
    - ↓sensitvity to $PaCO_2$ (hypoxic stim is unaffecting ∴ O_2 therapy and morphine can be hazardous
    - potentiated by other CNS depressants
    - fetal resp centre highly sensitive to morphine
  - delayed rep depression (seen in all opiates)
    - lack of pain eg post reduction of joint
    - physiological sleep
    - hypothermia
    - redistribution from periph compartments eg fat, mm, lung
    - sequestration in stomach eg 20% of IV fentanyl sequestered in gastric acid ⇒ reabsorb in alkaline small gut
    - spinal admin ⇒ cephalad spread – esp for less lipid soluble drugs
  - antitussive
  - potential bronchospasm (histamine release)
- CVS effects:
  - bradycardia (mild):
    - ?mechanism theories either:
      - ↓symp activity OR
      - direct affect on vagal nuclei in medulla OR
      - direct effect on SA/AV node
    - predisposing factors:
    - halothane
      - rapid injection
      - concomitant BZD;s
      - sux
      - laryngoscopy

- hypotension:
  - usually not significant in norvolaemic supine
  - no direct myocardial depression (as seen in pethidine)
  - ?mechanisms either:
    - histamine release
    - ↓symp activity
    - venoD/vasoD
    - ↑vagal
- histamine release:
  - = from mast cells via direct displacement effect
  - can cause:
    - hypotension
    - bronchospasm
    - pruritis
  - large inter-pt variability
  - not seen with fentanyl or sufentnail

- Urinary tract effects:
  - ↓UO 2nd to ↑ADH
  - ↑tone of urethral sphincter (& detrusor) ⇒ retention
- GI effects:
  - ileus
  - ↓secretions

  ↳both ⇒ constipation

  ↳ see minimal tolerance to constipation effects
  - ↓LES tone & delayed gastric emptying ⇒ ↑risk or reflux
  - ↑other sphincter tones ie pyloric, oddi, bilary tract, anal
    - Oddi spasm =
      - seen in only 3% (fentanyl >morphine>pethidine)
      - can reverse with 2mg glucagon IV with no loss of analgesia
- Hormonal:
  - ↓release of ACTH, prolactin, gonadotrophic hormones

    ↳suf > alf>fent>morph
  - ↑release of ADH
- pruritis:
  - 2 causes:
    - histamine release
    - indep of histamine
  - incidence:
    - 1-2% IVI
    - 10% epidurally
    - ~50% intrathecally – ondansetron or naloxone
- OD:
  - triad of hypoventilation, miosis, coma
  - prevent with vigilance, sedation scores, RR

Interactions

- alcohol or other CNS depressants –
  - additive effect on CNS
  - ↓RR
  - ↓bp
- buprenorphine given with full agonist:
  - additive effect on ↓RR if given concurrently with full agonist
  - ↓analgesic effect of full agonist

  - precipitate withdrawal symptoms
- MAOIs:
  - intensify opiod effects – esp tramadol & pethidine
  - risk of serotonin syndrome
- diltiazem, erythromycin, fluconazole:
  - inhibit metab of alfentanil ⇒ ↑conc
- rifampicin ⇒ ↑metab of morphine, codeine, & alfentanil

Dose

- in IV dosing remains variable plasma conc, rates of metab & elim
- usual adult dose 0.1-0.2mg/kg
  ↳rescue in elderly/frail/resp disease
- acutally a better correlation of dose with age rather than weight

Codeine

Chemical

- =phenantrene
- naturally occurring alkaloid
- = 3-methyl-morphine
- =prodrug of morphine (due to low inherent potency)

Presentation

- not given IV due to ↑↑histamine release

Pharmacodynamics

- codeine has low affinity for opioid receptors
  ↳x10 less potent than morphine
- analgesia created by metabolite = morphine
- effects:
  - constipation – very effective
  - antitussive – seems to be action on specific codeine receptors
- compared to morphine:
  - ↓ed N&V
  - ↓ sedation
  - ↓abuse potential
  - large doses ⇒ CNS excitement rather than depression

Pharmacokinetics

A

- OBA ~60-70% (methyl grp at C3 protects it from conjugation)

D

- 7% PPB

M

- 3 metabolic pathways in liver:
  - 6-hydroxy glucuronidation (main 60-70%) ⇒ inactive metabolites
  - O-demethylation (5-15%) ⇒ morphine
  - N demethylation (10-20%) ⇒ norcodeine (inactive)
- O-demethylation uses CYP2D6 which exhibits genetic polymorphism:
  - poor metabolisers experience little pain relief
  - 30% Hong Kong Chinese or 10% UK

E

- metabolites excreted in kidneys
- 5-15% excreted unchanged
- t1/2 elim 3.5hrs

Dihydrocodeine

- synthetic opioid
- used in chronic pain pts
- x2 potency
- related derivatives of codeine
- greater abuse potential

Heroin (Diamorphine)

Chemical

- = 3,6 diacethylmorphine
- parent drug has no opioid activity
- approx. x2 potent compared to morphine

Pharmacokinetics

A

- well absorbed from gut – high lipid solubitlity
- low OBA due to high 1st pass metab

D

- PPB 40%
- pKa 7.6

M

- on administration rapid metabolism by plasma & tissues esterases ⇒ mono-acethyl-morphine (mam)
- mam = more lipid soluble than morphine
  ↳↑lipophilic ⇒ quicker CNS penetration ⇒ 'rush'
- mam & diamorphine able to cross bbb quickly
- in CNS mam conversion to morphine to provide action

E

- plasma half life of diamorphine itself = 5mins

Pharmacodynamics

- compared to morphine:
  - ↑euphoric effects
  - ↓ed N&V
  - neuraxially:
    - ↓ed delayed resp depression – due to ↑ed lipid solubility
    - ↓ed pruritits
  - ↑↑abuse potential ∴ reserved for palliative care/cachectic pts (as smaller volume needed)

Pethidine

Chemical

- phenyl-piper-idine (2 ring)
- 1st synthetic analgesic used in medicine
- structurally similar to atropine ∴ mild anticholinergic effects
- principle effects reflect morphine

Pharmacodynamics

- potency ~10% of morphine
- equipotent doses show similar analgesia, RR, tolerance + dependence
- morphine differences:
  - CNS:
    - ↓sedation
    - ↑potential for seizure:
      - toxic active metabolite = nor-pethidine

        - not reversible with naloxone
        - accumulates in renal failure
    - ↓N&V
    - ↑euphoria - ↑ed activity at NA ⇒ high addiction potential
    - no EEG changes with single dose
- Eyes: ↓miosis ⇒ mydriasis possible due to atropine like effects
- CVS:
    - sig ↓bp (esp elderly)
    - direct myocardial depressant in large doses
    - α blocking effects
    - tachycardia seen – atropine effects
- Resp:
    - more depressant in adults - ↑ed Vt effect
    - less depressant in neonates
    - less antitussive
- Atropine effects – dry mouth
- Other:
    - duration 2-3hrs
    - ↓ed bilary colic
    - ↓ed constipation & urinary retention
    - has some LA effects – prev been used as sole spinal drug
    - withdrawal – less autonomic symptoms, rapid onset & offset
    - effective Rx of post op shivering ?kappa effect
      ↳ use low dose 25mg

Pharmacokinetics

A

- low OBA 50%
- well absorbed IMI
- more lipid soluble than morphine ⇒ faster onset of action

D

- 5% unionised
- PPB 60-80% (AAG)
- pKa 8.7
- Vd 4L/kg

M

- extensive phase-1 oxidative reactions with no conjugation
- demethylation to:
    - norpethidine
    - pethidinic acid
    - pethidine-N-oxide
- small amount unchanged pethidine eliminated
  ↳can be enhanced with acidification of urine eg in OD scenarios
- norpethidine:
    - t1/2 elim 15-40hrs
    - ~50% of potency of pethidine
    - implicated in generalised seizures

E

- t1/2 elim 3-4hrs
- Cl_{hep} = flow dependant
- hep extraction ratio 0.7
- 70% dose cleared in 24hrs

Special Populations

- use in diff pt populations:
  - neonate: Cl x3 longer
  - elderly: ↓PPB ∴ ↑free plasma concentration
  - alcoholics: ↑Vd ⇒ ↓plasma conc

Obstetrics

- pethidine readily crosses placenta
  ↳little norpethidine crosses but pethidine is metabolised by foetus to create local store of norpethidine:
  ↳ levels peak 4hrs after maternal IM injection, foetal half life x3 as long
- fetal resp centre less sensitive to pethidine than morphine

Interactions

- MAOIs:
  - unknown mechanism
  - severe SEs incl ↓RR, ↑↓bp, convulsions, coma, hyperthermia, serotonin syndrome

Fentanyl

Chemical

- = phenyl-piper-idine
- synthetic opioid
- ↑rapidity of onset

Pharmacokinetics

A

- OBA 30% - can get lollipops
- usually IV/transdermal
- transdermal - plasma levels take 12 hrs to reach equilibrium

D

- 85% PPB (AAG)
- ionised >90% (pKa 8.4)
- Vd 4-5L/kg
- rapid onset ~5min - ↑potency & ↑lipid solubility
- short duration of action 20mins at low doses due to rapid redistribution to inactive tissues (fat, mm, lung)
- initial dose
  - ~75% ⇒ 1st pass pulmonary uptake = large inactive reservoir
  - ~40% ⇒ sequestered in rbcs
  - ~20% ⇒ sequestered in gastric acid (ion trapping)
- high doses/infusion ⇒ saturation of inactive tissues ⇒ plasma conc of fentanyl remains constantly high ⇒ duration of action reflects t1/2 elim ie 3-4hrs

M

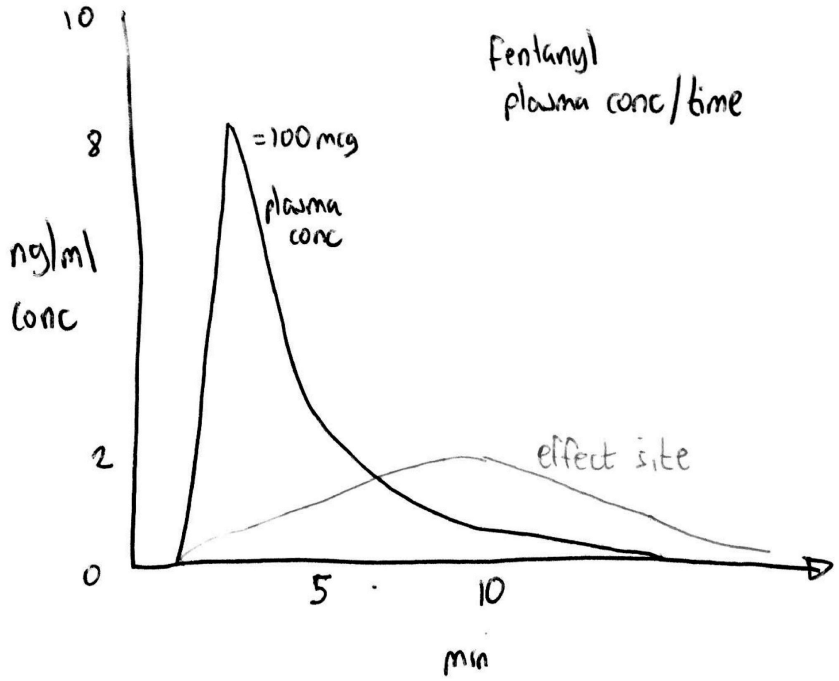
- extensive phase 1 heptaic metab
- flow dependant
- N-demethylation/dealkylation amide hydrolysis ⇒ inactive metabolites
- main metabolite = norfentanyl:
  - structurally similar to norpethidine
  - renally excreted
  - some CNS stim effects
  - (rarely) causes delirium

E

- tri-exponential decline in plasma concentrations

- t1/2 elim 3-4hrs (longer than morphine):
  ↳ due to mainly larger Vd
- dosing 6-640mcg/kg = t1/2elim, Cl, Vd independent of dose ∴ no saturation of clearance mechanisms
- Disease states/Populations variability:
  - elderly: ↑t1/2 elim – due to ↓Cl 2nd to age related ↓hepatic blood flow
    ↳ Vd relatively same as youner people
  - cirrhosis – does not significantly prolong t1/2elim (as opposed to alfentanil)
- CSHT:
  - 40mins (2hr inf)
  - 70mins (3hr inf)
  - 4hrs (6hr inf)
  - 5hrs (9hr inf)

Pharmacodynamics



- potency:
  - x100 morphine
  - x1000 pethidine
- wide dose range 1-100mcg/kg depending on intended use
- effects similar to morphine except:
  - CNS:
    - sedation:
      - low doses [1-4mcg/kg] - ↓ed sedation
      - high doses ⇒ pronounced loss consciousness
    - ↑ICP seen at 3mcg/kg – caution in head injured
    - seizure activity – has been reported but not supported by EEG changes
      ↳ 1st ß suppression > α suppression > δ activity remains
  - Resp:
    - effect site apnoeic threshold = 1.5-3ng/ml
    - ↓Vt & ↓RR: see delayed depression post op:
      - ?gastric sequestered drug ⇒ small intestine absorption although extensive 1st pass metab
      - ? washout from pulmon reservoir as V/Q relationship resetablished post op
    - antitussive – potent
    - ↓histamine release ⇒ ↓bronchospasm
    - spinal route:

- high lipid solubility & quick binding with avidiy to spinal cord/roots ⇒ ↓chance delayed resp depression

- CVS:
  - remarkably CVS stable = classic cardiac anaesthetic drug
  - no histamine release up to 100mcg/kg
  - ↑ed bradycardia (vagal) – atropine responsive
    ↳impt in neonates due to HR dependant CO
- other:
  - ↓ed constipation
  - rare allergic reactions
  - ↑sphincter tone:
    - Oddi + bilary spasm
    - urinary tract
  - no affect on ADH

Uses

- low dose (1-2ug/kg):
  - blunt intubation response (not ablate)
  - facilitate induction
  - prior to surg stimuli
  - post op analgesia
- high dose (10-100mcg/kg)
  - produces surgical anaesthesia
  - adv:
    - no direct myocardial depression
    - no histamine release
    - ↓surg stress response
  - disadv:
    - cannot assum lack of awareness
    - can fail to prevent symp response to surg stimuli
    - post op resp depression
    - chest wall rigidity
- transmucosal/transnasal:
  - effective for pre-op anxiety/facilitating induction in kids
  - ↑ed bioavailability compared to oral
  - disadvs: RR depression, PONV
- transdermal:
  - sustained plasma conc for 72hrs ∴ not easily reversed
  - heat ⇒ ↑uptake of drug from patch
  - rash & itching from site
  - after 3days patches still contain 50% activity

Alfentanil

Chemical

- =phenyl-piper-idine derivative
- analogue of fentanyl but:
  - 10-20% potency
  - 1/3 duration of action
  - shorter onset – 1-2mins vs 3-5mins

Presentation

- 500mcg/ml in 2ml clear glass vials

Pharmacokinetics

D

- 90% unionised (pKa 6.5)
- 92% PPB (AAG)
    - AAG
        - acute phase reactant ie ↑surgery, infection
        - ↑level in elderly
        - ↓ levels in neonate
- much lower lipid solubility than fentanyl but ↑ed unionised fraction (due to lower pKa) ⇒ rapid bbb crossing ⇒ rapid onset (<90secs)
    ↳eg time effect site equilibration:
        - alfentanil = 1.4mins
        - fentanyl & sufentanil = 6.5mins
- short duration of action 5-10mins:
    - rapid redistribution (mm, fat, lung)
    - rapid metabolism
    - (does not undergo 1st pass lung uptake like fentanyl/sufentanil)
- Vd 0.4 L/kg (fentanyl = x10)
    ↳cos of ↓ed lipid solubility & ↑ed PPB
- small Vd responsible for stable CSHT (compared to fentanyl)

M

- phase 1 liver metab to inactive metabolites:
    ↳ N-dealkylation ⇒ nor-alfentanil
- phase 2 glucuronide conjugation also seen
    ↳not seen in fentanyl

NB midaz is metabolised by same hepatic enzymes (CYP3A3/4) ⇒ concurrent hald lives significant ↑

- <0.5 excreted in urine unchanged

E

- 96% alfentanil cleared in 60mins
- T1/2elim = 1-2hrs (due to smaller Vd)

Special Situations

- liver cirrhosis ⇒ prolongs t1/2 elim
- cholestatic disease = no change
- renal failure: no influence on clearance or half life
- children: t1/2elim = shorter (↓fat ∴ Vd smaller)

Pharmacodynamics

- effects similar to fentanyl but:
    - small doses can unpredictably ⇒ apnoea (short duration)
        ↳ esp in elderly
    - no effect on cerebral vasculature ∴ not assoc with ↑ICP

Uses

- attenuation of catecholamine/CVS responses to brief noxious stimuli
- high dose (150-300mcg/kg) ⇒ unconsciousness in <1min
- PK's make it more suitable for infusions than fentanyl:
    - ↓Vd + short t1/2elim
    - CSHT: 40mins (2hr inf), 70min (6hr inf), 80min (9hr inf)

Remifentanyl

Chemical

- phenyl-piper-idine

- related to fentanyl (similar potency)
- pure mu agonist
- unique opioid because of ester linkage which makes it susceptible for hydrolysis by non specific tissue & plasma esterases

Presentation

- formulated in glycine (-ve neurotransmitter) ∴ not for spinal/epidural
- vial:
  - white powder (pKa 7)
  - HCL
  - glycine
- solubilised in water

Pharmacokinetics

D

- PPB 70% (AAG)
- Vd = 0.3-0.4 L/kg

M

- unique properties
- very rapid hydrolysis by non specific tissue & plasma esterases
- metab not affected by
  - atypical P-ChE
  - admin of anticholinesterases
  - isolated organ failure
- metab to inactive metabolites:
  - remifentanil acid = x300-4600 fold less potent

E

- ⇒renal excretion
- clearance 40ml/kg/min (x8 greater than alfentanil)
- t1/2elim = 6-20mins
  ↳ due to low Vd & high Cl

Pharmacodynamics

- equipotent to fentanyl
- effect & side effect profile similar to all opioids except:
  - Dosing –
    - usually given as infusion
  - obtunding symp responses:
    - dose dependant up to 1mcg/kg/min
      ↳at higher doses unpredicatbnle & unreliable ∴ must use other anaesthetic agents eg TIVA/volatile
  - no histamine release
  - opioid side effects short lived & can be rapidly antagonised if needed
  - bradycardia – more likely than fent/alfent
  - occulocardiac response during eye surg – more pronounced with remi
  - acute opioid tolerance:
    - post op analgesia requirements afer remi anaesthesia sometimes unusually high
    - ?due to acute opioid tolerance
    - also may see delayed hyperalgesia
    - mechanism is pharmacodynamic via alteration in NMDA receptors & intracell messengers
      ↳∴ NMDA antagonists eg ketamine & Mg may block opioid tolerance

Uses

- ideally suited for titration to effect during surg
- need to add longer acting opioid before cessation for post op analgesia
- ideal for intense intraop pain without post op pan eg endoscopic procedures

- PCA during labour
- induction (1mcg/kg over 1min)
  ↳modified RSI 2-3mcg/kg with small dose induction agent
- ECT: 100mcg attenuates CVS response & does not alter seizure activity

Dose

- Dose range = 0.00125-1mcg/kg/min
- TCI plasma conc 3ng/ml = 0.1mcg/kg/min

Tramadol

Chemical

- =phenyl-piper-idine analogue of codeine
- since 1977
- IV, oral, slow release preps
- 2 chiral atoms ∴ 2 pairs of enantiomers
- presented as racemic mixture of the 2 enantiomers:
  - 1R,2R tramadol
  - 1S,2S tramadol

Pharmacokinetics

A

- 68-100%
- with repetitive dosing OBA ↑s
  ↳similar to methadone

D

- PPB 20%
- Vd 3-4L/kg
- 80% crosses placenta

M

- 85% demethylation in liver
  ↳ 10% people lack CYP enzyme for this conversion ⇒ ↓analgesia
- main metabolite = O-de-methyl-tramadol (M_1) = active analgesically
- other metabolites:
  - inactive
- eliminated via kidneys
- ∴ dose reduction in:
  - liver impairment ⇒ max 300mg/day as bd
  - renal failure ⇒ max 200mg/d as bd dose

E

- Cl 6-10ml/kg/min
- t1/2 elim 4-7hrs

Pharmacodynamics

- potency & efficacy are comparable to pethidine
- compared to morphine:
  - ↓effect on resp centre compared to equipotent doses
  - ↓constipation
  - ↓potential for tolerance/dependence
- effective in Rx of post op shivering eg 25mg
- many opiate side effects exist:
  - N&V
  - sedation
  - ambulatory dizziness

- specific side effect:
    - ↓seizure threshold ⇒ avoid in epilepsy

Interactions

- carbamazepine ⇒ ↓↓plasma conc of tramadol ⇒ ↓efficacy
- warfarin ⇒ ↑warf levels
- SSRI's ⇒
    - further ↓'s seizure threshold
    - risk of serotonergic crisis

Mechanism of Action

- targets for action:
    - opioid receptors –
        - weak agonist of all types
        - affinity for mu 1/6000 than morphine
        - naloxone only removes 30% of analgesic effects
    - NA & 5-HT reuptake inhibitor (& causes ↑ed release of them)
        - via +ve effect on descending inhibitory pain pathways
        - ∴ non-opioid mechanism
    - ?GABAergic modulation
- analgesia action:
    - 40% opioid
    - 20% 5HT
    - 40% NA
- diff enantiomers have diff sites of effect:
    - 1R,2R:
        - Mu + delta effects
        - inhibit serotonin reuptake
        - ↑release of serotonin at nucleus raphe magnus (one of DIPs)
    - 1S,2S:
        - potent inhibitor of NA reuptake
        - ↑release of NA at locus ceruleus (a DIP)
        - α2 agonist

Methadone

Chemical

- synthetic opioid agonist
- = di-phenyl derivative (propionanilide)
- engineered by German scientists during WW2
- oral or IV form
- racemic mixture:
    - S = opiate agonist
    - R = NMDA antagonist
- conversion to morphine is highly variable
- initial rough guide is methadone 1mg = 7mg morphine (but be cautious)

Pharmacokinetics

A

- OBA approaches 100%
  ↳ ↑s with repeated dosing
  ie low 1st pass metab

D

- 90% PPB (aap)
- high tissue binding

M

- liver metab P450 system
- exhibits low hepatic clearance ∴ metabolism mechanisms saturated at low plasma levels ∴ plasma accumulation as dose frequency ↑s
  ↳ but x30 variation between pts (fast, medium, slow metabolisers) ⇒ t1/2 5 – 150hrs
- metab to inactive metabolites

E

- excreted in
  - bile &
  - urine – 40% as unchanged drug excreted via urine (can enhance in acidic conditons)
- T1/2 elim 5-150hrs
  ↳ ∴ accumulation with repeated dosing

Interactions

- complex interactions with other drugs metab by P450:
  - enzyme inducers ⇒ acute withdrawal of pts on long term methadone

Pharmacodynamics

- effect sites:
  - Mu agonist – compared to morphine similar properties & potency
  - NMDA antagonist – may explain ↓craving for other opioids & ↓tolerance
- compared to morphine:
  - same = resp depression, constipation, bilary tract spasm, abuse potential
  - ↓ed =
    - sedation & euphoria
    - miosis – will eventually see complete tolerance ie no miosis
- duration action up to 24hrs
- CVS: prolonged Qt interval esp >200mg/day ⇒ potential torsades/VT

Uses

- Rx of heroin + morphine dependence/addiction:
  - tolerance develops more slowly
  - efficient as orally administered drug
  - long duration ie once daily dosing
  - controlled withdrawal = milder & less acute than morphine
- long term chronic pain:
  - d1 = tds dosing
  - d2-3 = bd dosing
  - d45 = od dosing

Oxycodone

Chemical

- semi synthetic opioid derived from thebaine alkaloid of opium

Presentation

- slow release of immediate release
- also available in comb with paracetamol in USA
- IV prep also available

Pharmacokinetics

A

- OBA = 60% (better than morphine)

D

- PPB 45%

M

- mainly liver metab
- metabolites:

  - nor-oxycodone
    - =main metabolite
    - weaker analgetic than parent drug
  - oxy-morphone
    - from CYP2D6
    - some analgesic effect but mild overall contribution
  - conjugated forms of oxycodone
- 5-10% Caucasians who are poor metabolisers may have prolonged ↑ed level of parent drug
  ↳ but not thought to be of clinical significance

E

- metabs renally excereted
  ↳ but need severe renal impairement to effect oxycodone concentrations ∴ better choice than morphine
- t1/2 elim = 2-3hrs

Pharmacodynamics

- full agonist
- similar effects to morphine except:
  - ↓urticaria
  - ? ↓N&V
  - ↑abuse potential

Uses

- better OBA than morphine: 5mg oxycodone = 10mg morphine
- better choice in renal impairement compared to:
  - morphine - ↑M6G levels
  - pethidine - ↑norpethidine levels

Buprenorphine

Chemical

- synthetic derivative of naturally occurring alkaloid thebaine

Presentation

- clear colourless solution containing buprenorphine HCL
- patches
- also available in combo with naloxone for sublingual use in opioid addiction

Pharmacokinetics

A

- poor OBA due to high 1st pass metabolism
- S/L route 44-94%
- IM route 40-90%

D

- 96% PPB
- Vd 3.2 L/kg

M

- dealkylation & subsequent conjugation (glucuronide)
- polar conjugates then excreted by bile
- then hydrolysed by bacteria in GIT

E

- mostly excreted in faeces
- remainder excreted renally as conjugates
- t1/2 elim = 5hrs
- Cl 1 L/min

Pharmacodynamics

- effect site:
  - partial mu agonist
  - kappa antagonist
- at low doses [used in clinical practise] behaves like:
  - full mu agonist (in respect to analgesia)
  - partial agonist (in respect to resp depression)
- at high doses:
  - partial agonist at mu

↳∴clinically:

  - pts on low dose buprenorphine (eg patch) can continue to use other opioid analgesics for breakthrough pain
  - pt on high dose: use of another opioid will ⇒ ↑pain & withdrawal reactions
  - unable to antagonise with naloxone
- x30 analgesic potency compared to morphine

Adverse Reactions

- specific to buprenorphine:
  - CVS: minimal effects – slight ↑HR, ↓bp
  - resp: resp depression & antitussive
- otherwise similar to morphine:
  - miosis, delayed gastric emptying etc

Opiod Antagonists

- naloxone (IV/IM); naltrexone (O)
- antagonise endogenous & synthetic opiods
- drugs bind to all receptors but have greatest affinity for μ receptor

Naloxone

Chemical

- =N-allyl derivative of oxymorphine
- developed as antagonist of opiods for OD & prevention of dependence

Presentation

Pharmacokinetics

A

- OBA 20% due to 1st pass metab

D

- 50% PPB
- Vd 2.5 L/kg
- onset ~2mins, duration 30-45mins ∴ likely need infusion
- easily crosses placenta – so risk of neonatal withdrawal

M

- primarily conjugation in liver to naloxone 3 glucuronide

E

- t1/2 elim 1.5-2.5

Pharmacodynamics

- = reversible competitive antagonist:
  - no agonist activity
  - higher affinity for mu than kappa & delta
- has intrinsic stimulatory properties regardless of opiate reversal

Adverse Reactions

- N&V – related to speed of injection

- CVS - ↑SNS activity due to abrupt reversal of analgesia
  ↳ careful of arrhythmias & myocardial ischaemia
- HTN
- pulmon oedema

Uses

- Rx opioid induced resp depression
- facilitate Rx of opioid OD
- detection of suspected physical dependence
- ?role in shock: dose related ↑ myocardial contractility in animals with hypovolaemic/septic shock
  ↳ large doses >1mg/kg ?mechanism
- Rx of itch & severe N&V from opioid Rx esp neuraxial

Naltrexone

- similar to naloxone
- =pure antagonist – relatively mu selective
- has high OBA with sustained antagonism of up to 24hrs
- ∴ used in Rx of detoxified opioid dependant pts
  ↳ esp blocks euphoria of high dose opioids in relapsing cases

Opiate OD

- May start if concurrently start NSAID⇒ARF⇒accumulation of opiates
  ↳must ↓maintenance dose opiate (use same loading dose)
- Features:
  - Pin point pupils - miosis
  - Severe resp depression
  - Hypotonia – although pethidine can ⇒ ↑tone

Neuraxial Opioids

Effects of Neuraxial Opioid

- analgesia:
  - dose dependent effecrs
  - specific for visceral, not somatic pain
- unlike IV opioid or neuraxial LA they do not cause:
  - symp system denervation
  - skeletal mm weakness
  - loss of proprioception

Fate of Epidual Opioids

- include:
  - diffusion across dural membrane into CSF ⇒ onto mu receptors in spinal cord
  - systemic absorption – similar to IV but slower onset
  - can enter epidural fat
- lipid solubility major variable:
  - high lipid solubility (fentanyl, sufentanil) ⇒ most effects local
  - low lipid solubility ⇒
    - slower onset analgesia,
    - longer duration action
    - most effect due to systemic absorption

Pharmacokinetics

- penetration of opioid through dura depends on:

  - molecular weight
  - lipid solubility: compared to morphine: fentanyl x800, sufentanil x1600
- CSF conc after epidural:
  - time to peak in CSF:
    - fentanyl 20mins
    - sufentanil 6min
    - morphine 1-4hrs (only 5% of morphine enters CSF)
- plasma conc after epidural:
  - time to peak:
    - fentanyl 5-10min
    - sufentanil – sooner than fentanyl
    - morphine 10-15min
  - plasma conc similar to post IM dose
  - adding adrenaline to opioids ⇒
    - ↓systemic absorption
    - no influence on diffusion into CSF
  - adding adrenaline to intrathecal morphine ⇒ ↑ed analgesia (α2 effects)

Cephalad movement of Opioids in CSF

- depends on lipid solubility:
  - high lipid soluble:
    - faster uptake into spinal cord
    - faster offset
  - low lipid solubility:
    - more drug remains in CSF (once got there)
    - ∴ more to be transferred to more cephelad location
- bulk flow of CSF = mechanism of movement cephalad:
  - from Lx region CSF transfer time to:
    - cisterna magna = 1-2hrs
    - 4^{th} & lat ventricles = 3-6hrs
  - accelerated by coughing or straining
  - unaffected by body position

Side Effects of Neuraxial opioids

- 4 main:
  - pruritis
  - nausea & vomiting
  - resp depression
  - urinary retention
- others:
  - viral reactivation – cold sores
  - neonatal morbidity
  - sex dysfunction – sustained erection & inability to ejaculate
  - ocular dysfunction – esp with morphine
  - GIT dysfunction – delayed gastric emptying
  - thermoregulatory dysfunction – unable to shiver
  - water retention – ADH release
  - direct spinal cord damage – from toxic preservatives

Pruritis

- most mild, 1% severe
- +/- dose dependant
- more likely in obstetric patients – interaction with oestrogen receptors
- more likely localised to upper body
- may occur prior to analgesic effect

- MOA is not histamine release ⇒ ?opioid migration to CNS & interaction with receptors in trigeminal nucleus
- Rx: naloxone, ondansetron, antihistamine (sedating)

Resp Depression

- incidence 1% (same as other routes)
- biphasic presentation:
  - early (<2hrs):
    - usually with lipophilic opiates
    - due to systemic absorption
  - late (>2hrs):
    - all = morphine due to cepehald migration in CSF ⇒ ventral medulla
    - usually 6-12hrs post administration
    - not reported >24hrs
- risks:
  - coughing : ↑ITP ⇒ ↑CSF cephelad migration
  - concurrent opioids
  - high doses
  - low lipid solubility
  - old
- obstetric pts are less risk - ?due to ↑ventilatory stim 2nd to progesterone

Urinary Retention

- most common young males
- not dose dependant
- more common then with IV/IM
- epidural morphine causes marked detrusor mm relaxation:
  - onset 15mins
  - lasts upto 16hrs

  ↳ reverse with naloxone
- MOA:
  - not due to systemic absorption
  - opioid receptors in sacral spinal cord:
    - ↑ed inhibition of sacral parasymp outflow ⇒ detrusor mm relaxation & ↑bladder capacity

Others

- sedation –
  - dose dependant
- viral reactivation:
  - herpes simplex labialis reactivation 2-5days after admin
  - same dermatomes
  - due to cepehelad migration of morphine

Ketamine

(also covered in GA IV induction agent section)

- has certain benefits over other GA/analgesic agents:
  - bronchodilator
  - minimal cardiovascular depression
  - minimal resp depression
  - amnesia
- racemic mixture – S = more potent with less side effects

MOA

- non competitive NMDA receptor antagonist:
  - receptor opens in response to glutamate
  - ketamine blocks channel ⇒ analgesic effects
- at high doses: also binds to opiod μ (mu) & σ (sigma) receptors
- also effects on other receptors:
  - potent D2 partial agonist
  - dopamine reuptake inhibitor
  - NA reuptake inhibitor
  - muscarinic agonist
- produces dissociative anaesthesia
  ↳MOA of these hypnotic effects under debate

Pharmacokinetics

- onset of anaesthesia 15-30sec
- recovery time 15-30min
- metab in liver
- frequent dosing ⇒ tolerance due to induction of hepatic enzymes

Uses

- GA – induction & maintenance
- analgesia

Side Effects

- tachycardia & HT
- ↑ICP
- ↑intraocular pressure
- hypersalivation
- laryngospasm
- hallucinations – thus often also give benzodiazepines. Worse in adults
- re-emergence phenomena – disagreeable dreams, hallucination on awakening

Cautions/Contraindications

- caution in:
  - CVS disease- although tends to maintain or ↑CO
- crosses placenta:

Interactions

- additive effect with other sedatives incl benxo's, barbituates, opiates, alcohol

Dose

- induction dose 1-2mg/kg
- paeds dose for minor procedure 2-2.5mg/kg IM (0.5mg-1mg/kg IV)

Obstetric Drugs

Oxytocic Drugs

Oxytocin

Chemical

- =naturally occurring nonapeptide (9 aas) released from post lobe of pituitary gland
- synthesised in hypothalamus

Presentation

- presents as either:
  - synthetic oxytocin – 5 or 10uints/ml. no vasopressin or animal protein
  - combo with ergometrine maleate – provides more sustained effect on uterus

Mechanism of Action

- binds to specific receptors on smooth mm cells ⇒ ↑permeability of membrane to K ions ⇒ ↓rmp ⇒ ↑excitability of uterine smooth mm
- receptors are not always expressed on uterus – needs to be sensitised by pregnancy (occurs late in oreg)

Effects

Uses

- induction & acceleration of labour
- promote lactation
- management of missed & incomplete abortion
- Rx of PPH

Pharmacokinetics

- rapid metab by hydrolysis in liver & kidney by oxytocinase
- t1/2 1-7min

Adverse Reactions

- CVS:
  - ↓bp – starts witihin 30secs & lasts upto 10mins.
    - ↳ exaggerated in anaesthetised pt
    - reflex tachy ⇒ ↑CO
  - prolonged QTc
  - T wave flattening – reflect ↓coronary perfusion
  - ↑ed renal blood flow
- metabolic:
  - antidiuretic effect –
    - direct action on renal tubule
    - at high doses risk of water intoxication
  - milk ejection by contraction of mammory smooth mm
- uterine:
  - too rapid infusion ⇒ uterine spasm & rupture +/- fetal asphyxia
- anaphylactoid

Interactions

- sux: ↓fasiculations & need ↑doses of sux
- do not infuse in line with blood: will inactivate oxytocin prior to reaching body

Ergometrine

(see antimigraine section)

- 500mcg IMI or myometrial injection
- MOA – not fully understood
  - ↳ but likely 5HT3 agonist & α agonist
- ↑uterine contraction with ↑basal tone
- SEs:

- CVS:
  - ↑MAP 2nd to ↑vasoC
  - ↓coronary artery perfusion – possible angina
  - ↑PVR
- CNS:
  - N&V – 2nd to Dopamine stime of CTZ
  - blurred vision/headache – from cerebral vasoC
  - seizures

Prostaglandins

Carboprost (PGF2α)

- do not give IVI:
  - PGs metabolised in lungs ⇒
    - ↑↑PVR
    - ↑↑bronchoconstriction
    - ultimately possible death
- for myometrial injection only

Misoprostol (PGE2)

- tablets or pessaries
- used:
  - induction of labour ⇒ ↑uterine tone
  - ripening of cervix
- causes
  - ↑force of uterine contraction
  - ↑uterine basal tone
  - relexation of cervix
- SEs:
  - uterine pain
  - N&V

Tocolytics

- = anti contraction medications to supress labour
- given to:
  - ↓premature birth
  - to allow time for betamethasone to work – 24-48hrs to accelerate fetal lung maturity
- effect only partial – can only delay small amount of days
- likely need inhospital monitoring – nifedipine most used drug – need to monitor blood pressure

Contraindications to Tocolysis

- fetus >34weeks
- IUGR (<2.5g) or placental insufficiency
- lethal congenital or chromosomal abnormalities
- cervical dilation >4cm
- intrauterine infection
- medical conditions in mother:
  - eclampsia
  - active vag bleeding/placental abruption
  - cardiac disease
- any other cause of fetal distress

Choice of Agent

- no clear 1st line agent:
  - nifedipine – most commonly used
  - oxytocin antagonist

  ↳ both can delay delivery 2-7days although rarely successful >2days
  - ß agonists, oxytocin antagonist, NSAID ⇒ ↓OR of delivery:
    - 24hr = 0.54
    - 48hrs = 0.47
  - antibiotics – may delay labor in women with premature rupture of membranes (PROM)

    ↳ not usually = tocolysis

Agents

ß2 agonists

- eg terbutaline or salbutamol
- often drug given first esp if only low risk of preterm birth
- maternal effects:
  - arrhythmias
  - pulmon oedema
  - myocardial ischaemia
  - hypotension
  - death
- fetal effects:
  - fetal tachy
  - hyperinsulinaemia
  - hypoglycaemia
  - myocardial & septal hypertrophy
  - myocardial ischaemia

CCBs

- eg nifedipine
- should avoid using with Mg
- no known fetal side effects
- maternal effects:
  - see CCB section

Oxytocin Antagonist

- eg atosiban
- exhibits less side effects than ß2 receptor agonists

NSAIDs

- eg indomethacin
- fetal side effects:
    - constriction of ductus arteriosus ∴ not used after 32/40
    - pulmon HTN
    - reversible ↓renal function with oligohydraminos
    - intraventricular haemorrhage
    - hyperbilirubinaemia
    - necrotising enterocolitis (NEC)

Magnesium

- shown to be ineffective
- myosin light chain inhibitor
- contraindicated in myasthenia gravis
- foetal side effects:
    - hypotonia
    - resp depression
    - demineralisation with prolonged use
    - lethargy
- maternal effects – see anti-arrhythmic section

Nitrates

- immediate effect of uterine relaxation – can be useful if difficulty extracting fetus in C section
- no fetal side effects even with infusions >2hrs

Pre-Eclampsia Rx

- drugs of choice:
  - Magnesium
  - labetalol
  - hydralazine

Hydralazine

Presentation

- tablets
- powder for reconstitution for injection – should use 5% dex as it promotes rapid breakdown

Mechanism of Action

- exact MOA unknown but thought to be a direct vasoDilator:
  - ↑guanylate cyclase ⇒ ↑cGMP ⇒ ↓intracellular Ca ⇒ VasoD

Effects

- CVS:
  - ↓arteriolar tone ⇒ ↓SVR
  - (less effect on venous system ∴ ↓ed postural hypotension)
  - reflex tachy ⇒ ↑CO (although can antagonise with ßB
- CNS:
  - ↑cerebral artery vasoD ⇒ cerebral artery blood flow
- renal:
  - ↑renal blood flow but still see:
    - fluid retention, oedema, ↓UO
      ↳ can counteract with diuretic
- GIT – N&V common
- misc:
  - periph neuropathy
  - blood dyscrasias
  - SLE type syndrome– after long term use – more common in women

Uses

- orally:
  - chronic HTN
  - chronic heart failure in conjunction with other agents
- IV:
  - acute HTN assoc with pre-eclampsia
  - 10-20mg
  - takes 20mins to work
  - rpt doses likely necessary

Pharmacokinetics

- OBA 25-50% depending on acetylator status of individual
- plasma t1/2 2-3hrs
  ↳rapid acetylators ⇒ shorten to 45mins
- 90% PPB
- urinary excretion:
  - 15% unchanged
  - 85% as acetylated & hydroxylated metabolites

crosses placenta ⇒ may cause fetal tachycardia

By Adam Hollingworth

IV Fluid Replacement

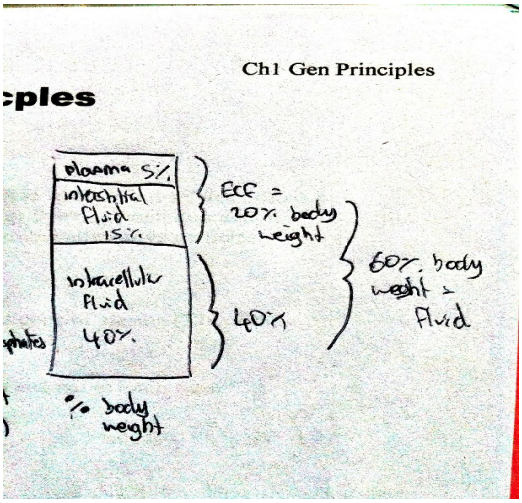
Body Fluid Distribution

(revision from physiology – gen priniciples)

- TBW = total body fluid
- weights in adult:
  - 60% fluid
    - intracellular - 40%
    - extracellular - 20%
  - 17% protein
  - 15% fat
  - 7% mineral

  ↳ in neonate = 80% Total body fluid
- total body fluid ~60% weight
  - 2/3 in ICF (actually 55%)
  - 1/3 in ECF

  ↳ ∴ ICF:ECF 2:1
- ECF = IVF (1/4) + ISF (3/4)
- ∴ 70kg person:
  - Total body fluid = 42litres
  - ICF = 28litres
  - ECF = 14 litres:
    - 3.5 litres plasma (+haematocrit)
    - 10.5 litres interstitial fluid
- ECF = majority Na & Cl
- ICF = majority:
  - K (most ~150mmol/L)
  - Misc phosphates
  - Protein
  - (small amount Na)



Process of Distribution

- IVF contain:
  - water
  - electrolytes (mostly Na)
  - large molecules (gelatins, starches, albumin)
- water:
  - no charge
  - will distribute rapidly across all compartments ⇒ minor ↑in plasma volume
- solution with a high Na content will have greater effect on plasma volume than water (D5W)
  - Na: has a charge ∴ ⇒ rapid distribution to ECF
  - K: charge ∴ ⇒ rapid into ICF
- fluid with larger molecules more likely to have greater impact on plasma volume
- additional factors governing fluid shifts between compartments:
  - shape & size of molecules
  - hydrostatic pressure gradients oncotic pressure gradients
  - time over which fluid given
  - endothelial barrier

  ↳ all linked in Starlings equation as below

***from chp32 dynamics of blood flow CVS physiology ***

- Depends on balance:

  - Hydrostatic pressure gradient
    - = Pressure in capillary (P_c) – pressure in interstitial fluid (P_i)
  - Osmotic pressure gradient:
    - = osmotic pressure in capillary (π_c) – osmotic pressure of interstitial fluid (π_I)
- pressures vary:
  - by tissue
  - along length of capillary - NET movement:
    - outward - arterial end
    - inward – venous end

Net driving pressure = α [$(P_c - P_i)$ - $(\pi_c - \pi_I)$]

- 2 more additional factors added:
  - reflection coefficient (σ) = leakiness for proteins
  - filtration coefficient (K) = leakiness for water

= K x [$(P_c - P_i) - \sigma(\pi_c - \pi_I)$]

****

- decision on what fluids to use complicated by pts premorbind state:
  - simple starvation ⇒ water & electrolytes
  - bowel prep ⇒ ↑↑water & electrolytes
  - pyloric stenosis ⇒ careful fluid titration
  - burns/trauma/sepsis ⇒ ↑risk of loss of albumin from intravascular space ⇒ ?colloid (but don't!)

Crystalloids vs Colloids

(traditional argument: colloids now entirely debunked!)

	Crystalloid	Colloid
IV persistence	poor	good
Haemodynamic stabilization	transient	prolonged
Inf vol needed	large	moderate
Plasma COP	reduced	maintained
Risk of oedema *	obvious	less risk
Enhancement of cap perfusion	poor	good
Risk of allergic reactions	non-existant	low-mod
Cost	cheap	expensive

Crystalloids

- sub-classification:
  - balanced ie plasmalyte, hartmans
  - unbalanced ie norm saline, D5W
- Norm Saline given rapidly can ⇒ hyperchloraemic metabolic acidosis:
  - usually transient & clinically insignificant unless frail/elderly/kids
  - mechansism:
    - NormS has equal amounts of Na + Cl
    - As Cl is in higher conc than in serum ⇒ ↑ed serum Cl
    - ↑ed serum Cl ⇒ dissociation of water ⇒ ↑free H ions ⇒ ↓pH
      ↳ occurs to preserve electrical neutrality

- Hartmans
  - = slightly hypo-osmolar ie lower border of norm
    ↳ ∴ not best choice in head injured/↑ed ICP/TURP
  - only fluid with lactate ie not good choice in DKA
    ↳ lactate was added to ↓chloride load
- Plasmalyte
  - = replaced lactate with acetate
  - acetate has added benefit that is metabolised in all tissues ie better in MODS
    ↳ lactate only metabolised by liver & kidney
    ↳lactate & acetate both metabolised to bicarbonate

	Normal Saline (0.9%)	Dextrose 4% /Saline (0.18%)	Plasmalyte 148 pH 7.4	Gelofusine	Pentastarch	Ringers Lactate/ Hartmans
Na (mM/l)	150	30	140	154	154	130 Na
K (mM /l)			5			4 K
Ca (mM /l)						4 Ca
Mg (mM /l)			1.6			
Cl (mM /l)	150	30	98	120	154	107 CL
Acetate (mM /l)			27			
Gluconate (mM/l)			23			
Glucose (mM /l)		222				29 lactate
Osmolality (mOsm/kg)	300	282	294	274	320	274
Energy (Kilojoules/l)	0	638	66			37.8
Molecular Wt (Daltons)				30 K	250 K	
PH	5.0	4 -5	7.4	7.4	5	6.7

Colloids

Gelatins

- short t1/2 life of 1-2hrs
- contain solution of gelatins of varying large MW proteins
- proteins commonly suspended in saline like solutions
- manufactured from bovine gelatin:
  - gelatin heated ⇒ protein denature ⇒ cool ⇒ new interchain bonds to form
  - new bonds = urea cross linked or succinylated
- used for plasma replacement & transiently ↑colloid osmotic pressure
  ↳ but not long lasting ∴ not considered as serious volume expanders
  ↳ modern gelatins have smaller MW and do not draw fluid into vasculature ie only expand volume the amount infused
- 2 major types:
  - gelofusin
    - 4% solution
    - COP 35mmHg
  - haemaccel
    - 3.5% solution
    - cross linked with urea – which issue in renal failure

Kinetics
- 95% of gelatins are excreted unchanged in urine
- t1/2 2-4hrs
- not stored in reticuloendothelial system (unlike HES)
- very wide range of Vd depending on nature of capillaries

Side Effects/Benefits
- side effects:
  - anaphylactic & anaphylactoid – 1:10,000 administrations
  - ?coagulation disturbance
- advs:
  - no infection risk compared to albumin
  - long shelf life
  - only limit to transfusion is HCT

Hydroxyethyl Starches (HES)
- = derivative of amylopectin which = highly branched starch compound
- to create: anhydroglucose residues are substituted with hydroxyethyl gps ⇒
  - ↑solubility
  - ↓ed metabolism ⇒ ↑t1/2

Formulation
- many diff preparations of HES compared to gelatins
- defined by:
  - conc - %grams/100mls
  - MWs – wide variation in weights. definied by variation from mean
    ↳ 130-200 KPa
  - degree of molar substitution = proportion of glucose units on starch molecule which have been replaced with hydroxyethyls

  ↳ ∴ voluven = 6%|130|0.4
- examples incl:
  - pentastach = 10%
  - hexastarch = 6% (voluven)

Kinetics
- high MW HES solutions provide longest plasma volume expanding effect & low MW the least
  ↳ but also assoc with unwanted effects ∴ balance needed
- metabolised by serum amylase ⇒ renal or RES
- elimination depends on molecular weights
  - 60-70KDa excreted by kindey quickly
  - higher weights difficult to excrete
- t1/2 life:
  - ~50% excreted within 24hrs
  - rest can be found in body for months

Side Effects
- coagulation:
  - balanced HES may have no effect
  - high MW ⇒ type I vWD like effect
- renal:
  - may be involved in renal tubular swelling due to reabsorption of macromolecules ⇒ tubular obstruction, ischaemia & failure
    ↳ esp likely in people receiving large amounts
  - issues with ↑renal failure now means HES been withdrawn worldwide
- accumulation:
  - RES takes up the HES and stores it
  - possibility of pruritis/pyrexia/headache developing weeks later

- analphylaxis: 1:20,000

Adv

- does nto interfere with x matching
- long lasting plasma volume expanding effects

Dose

- max 20ml/kg

Dextran 40 +70

- = polysaccharides made from sucrose by bacterial action
- D40 = 10% sol, MW 40K with normal saline (300mosm/l)
- D70 = 6% sol, MW 70K with norm saline (300mosm/l)

Kinetics

- plasma expansion with rapid infusion:
  - 500ml D40 ⇒ x2 (transfused volume) ↑ in plasma vol
  - 500ml D70 ⇒ 750ml plasma exp
- metab in lung/kidney/liver/spleen ⇒ glucose
- t1/2:
  - D40 = 4-9hrs
  - d70 = 23hrs

Side Effects

- severe allergic – 1:3000
- risk of volume overload
- coagulopathy: antithrombotic effects

Advs

- do not interefer with Xmatching
- D70 could be used in eg burns with large loss of protein

Albumin 5%/20%

Endogenous Albumin

- albumin = ~50% of 5 available plasma proteins
  ↳ α1, α2, ß globulin & γ globulin
- synthesised in liver
- t1/2 20days
- 50% is intravascular with rest in skin/mm
  ↳ less in gut, liver, s/c

Chemical

- sourced from pooled donors ie expensive (unless Australia where cheap byproduct)
- heat treated, then added to norm saline ⇒ 330mosm/l
- albumin exerts greater colloid osmotic effecr than mW alone due to highly negative charge

Interactions

- note albumin highly involved in PPB ∴ infusion may ↓ free fraction of some drugs
  ↳ clinically impt in drugs highly PPB ie eg warf, aspirin, furosemide
- albumin also carries bilirubin, fatty acids, calcium, Mg
  ↳ ∴ albumin transfusion may ↓active levels of these

Kinetics

- distribute only in plasma space ⇒ transcapillary leak ~5%/hr
- 25% albumin ⇒ x5 (transfused volume) ↑in plasma volume
- t1/2 16hrs, clinical duration >14hrs

Side Effects

- expensive
- limited availability
- anaphylactoid/anaphylaxis

- risk of other transfusion reactions

Advs

- ?↓platelet aggregation
- O2 free radical scavenger
- SAFE study ⇒ shows safe

Uses

- 5% resuscitation fluid or loss of protein
- 25% when plasma volume diminished/ECF expanded but bp acceptable

Miscellaneous Toxicology

Metabolic Acidosis

- use gaps classify:
  - anion gap
  - SID

Anion Gap

- Calculated from (Na + K) – (Cl + HCO3)
- causes of ↑gap met acidosis (8-16mmol): (MUDPILES)
  - Methanol/metformin
  - Uraemia
  - DKA
  - Paraldehyde
  - Infection
  - Lactic acids
  - Ethylene glycol
  - Saliicylates
- causes of normal gap met acidosis: (USEDCARP)
  - Ureto-enteric fistula
  - Saline
  - Endocrine eg Addisons, spironolactone
  - Diarrhoea
  - Carbonic anhydrase inhibitors
  - Ammonium chloride
  - Renal tubular acidosis
  - Pancreatitis

Strong Ion Difference (SID)

- ions in plasma classified into 3 gps:
  - resp gp (HCO_3 + CO_2)
    ↳ lungs
  - weak acids (albumin + phosphate) = not completely dissociated
    ↳ liver/kidney
  - strong ions (Na, K, Ca, Mg & Cl, Lactate) = complete dissociated
    ↳ kidney
- SID = diff between
  - cations (Na, K, Ca, Mg) &
  - anions (Cl, lactate)
- Normal SID = ~42-46mEq/l in healthy
  - ↓SID ⇒ ↓HCO_3 because of ↑Cl ⇒ ↑H^+
  - ↑SID ⇒ ↓dissociation of water ⇒ ↓H^+
- clinical examples:
  - prolonged vomiting: loss of Cl ⇒ ↑SID ⇒ ↓H^+
  - IV bicarb ⇒ ↑Na ⇒ ↑SID ⇒ ↓H^+

Osmolal Gap

- Measured plasma osmolality – calculated osmolality
- Calculated = 2x (Na + K) + urea + glucose
- If >10 ≈
  - DM – ketones
  - Ethanol

    - Methanol
    - Mannitol
    - Ethylene glycol
- If do osmolal gap 1-2hr after ingestion may be >25

Pupils & Diagnosis

- Constricted pupils (miosis)
    - Opioids
    - Trichlorethanol
    - Organophosphates
- Dilated puplils (mydriasis)
    - TCA poisoning
    - Belladonna alkaloid poisoning
    - Phenothiazine
    - Cocaine/amphetamines
    - Cyanide toxicity

Antidotes

- Ethylene glycol – ethanol/fomepizole
- Cyanide – cobalt edentate/sodium nitrite/sodium thiosulphate
- Methanol – ethanol / fomepizole

Ethylene Glycol Poisoning

- Aka antifreeze
- Has clinical appearance of alcohol intoxication
- No definitive lab test to confirm
  ↳can send someone home to check of collateral Hx
- Features:
    - Cerebellar signs & symptoms
    - No smell of alcohol
    - Raised anion gap – ethylene glycol breaks down to oxalate to cause acidosis
    - Raised osmolal gap
    - ↓Ca – give Ca
    - renal failure – caused by ATN 2nd to Ca oxalate crystals
- Rx:
    - Na bicarbonate to ↓acidosis & limit penetration
    - IV ethanol - inhibit ethylene glycol metabolism
    - IV fomepizole –
        - inhibitor of alcohol dehydrogenase
        - better than IV ethanol
    - Ca IV
    - Folic acid & thiamine
    - Haemodialysis

Methanol Poisoning

- ?60ml of methanol can be fatal
- toxic effects 2nd to metabolites formaldehyde & formic acid
- methylated spirits = mixture of methanol (5%) & ethanol
- Features:
    - ↑serum amylase
    - hyperglycaemia
    - optic nerve damage ⇒ sudden blindness

Cyanide Poisioning

- May occur from:
  - Infusions of nitroprusside
  - Inhalation of smoke from burning plastics in closed space
  - Ingestion of nail remover & cosmetic solvents
- High cyanide assoc with ↑CO
- MOA: disrupts ATP production in aerobic metabolism by binding to cytochrome AA3 complex

Ecstasy OD

- Assoc with ↑ADH & polydipsia to avoid hyperthermia ⇒ hypervolaemia & hyponatraemia
- Hyponatraemia:
  - Rx with fluid restriction
  - If develop focal neurology: give 3% saline
    ↳ok to rapidly correct and acute hyponatraemia
    ↳NOT ok to correct chronic hyponatraemia
- SE's:
  - Bruxism – common (=grinding of teeth)
  - Pneumomediastinum – MOA ?vomit, whistle blowing, valsalva
  - Myalgia
  - Seizures – don't use phenytoin
  - Hyperthermia

(0.9% norm saline = 154mmol Na/L)

Cocaine

- Taken nasally
  - peak effect 30min
  - duration 1 – 3hr
- features:
  - causes QRS widening & QTc Prolongation
  - mydriasis
  - toxic to myocardium & negative inotropy – in large doses

Haemodialysis

- Works for
  - Lithium
  - Barbituates
  - Alcohol
  - Methanol
  - Ethylene glycol
  - salicylate
- Not work for:
  - Amiodarone – large volume distribution
  - Paraquat --------- "
  - Digoxin "
  - Phenytoin -high protein bound "

Charcoal

- dosing 1gram/kg (adults norm get 50-100g)
- MOA:

- binds toxin to prevent absorbtion
  ↳binding is reversible ∴ cathartic eg sorbitol often added
  ↳accelerates defecation (Not a laxative, which eases pooing)
- interrupts enterohepatic & enteroenteric circulations of some drugs & metabolites

- Useful Rx in:
  - Ca channel blockers
  - B blockers
- Contraindications:
  - Poorly binding substances
    - Metals & salts eg iron, lead, lithium, potassium
    - Alcohols: ethanol, ethylene, glycol, methanol
    - Corrosives: acids, alkali, hydrocarbons (petrols)
  - Pt to undergo endoscopy eg corrosive ingestion
- major risks of use = pulmonary aspiration which can be fatal if immed med Rx not initiated

Sodium Bicarbonate

Uses

- orally:
  - antacid
  - Rx chronic metabolic acidosis eg CRF or renal tubular acidosis
- IV:
  - Rx acute metabolic acidosis:
    - aspirin overdoe
    - TCA overdose
  - uric acid stones
  - ↑K

MOA

- used in acidosis when there is insufficient sodium or bicarbonate ions in blood
- infused sodium bicarb drives carbonic acid/bicarbonate buffer to Left ∴ ⇒ ↑pH
- bicarb only indicated if pH <7.0
- 2000mosm/Kg osmolality

Adverse Reactions

- met alkalosis
- Na overload ⇒
  - oedema
  - heart failure
  - hypervolaemic hypernatraemia
  - HTN

Miscellaneous

Drug Induced hepatitis

- Can occur with:
    - Isoniazid
    - Methyldopa
    - Valproate
    - Statins
    - Pyrazinamid
    - Phenytoin
    - Amiodarone

Pancreatitis:

- Drug causes:
    - Azathioprine
    - Thiazides & loops
    - Oestrogen & OCPs
    - Cortisone
    - Warfarin
    - Calcium
    - Salicylates
    - Tetracyclines
    - Statins
    - ACEIs

SIADH

- Drugs causes:
    - TCAs
    - Carbamazepine
    - Opiates
    - SSRIs
    - Cytotoxics
- Other:
    - Malignancy
    - CNS disorders – HI, infection, bleeds, vascultitis
    - Chest disease eg TB, pneumonia
    - Met disease – porphyria, trauma
- Rx:
    - Fluid restrict & Rx cause
    - Can try demeclocycline

[lithium – causes DI]

Prolonged QT Interval

- TCAs – prolonged QT predisposes to torsades
- Sleep
- Sotalol
- Hypothermia
- Hypocalcaemia