1995b(13): Give a brief account of drug protein binding and outline its significance

General: Drug protein binding refers to the interaction a drug has with proteins.
- Can be intravascular, interstitial, or intracellular proteins
  - Plasma proteins binding is most significant
- Interaction is usually reversible
- Ionic or electrostatic
- Obeys the law of mass action
  \[ \text{[drug]} + \text{[protein]} \rightleftharpoons \text{[drug.protein]} \]

Plasma Protein Binding

Albumin
- Present in high conc (40g/L)
- Binds neutral/acidic drugs (eg barbiturates)
- 2 important binding sites → (I) warfarin and (II) BZ
- Drugs compete for these sites
  - Binding readily reversible, therefore can affect active unbound fraction of drug
- Binding at other sites on the molecule can change conformation of molecule and affect binding at the warfarin and BZ binding sites

α1-acid glycoprotein
- Low conc, low capacity
- Most important of the plasma globulins
- Binds basic drugs (LAs, morphine)
- Acute phase reactant

Lipoproteins
- Not true binding
- Function to partition highly lipophilic drugs (eg fentanyl)

Extent of protein binding determined by:

Drug characteristics
- Affinity for protein
- Conc of drug
- pKa relative to pH of plasma: ↑ionised → ↑protein binding, ↑unionised → ↑partitioning of drug
- Presence of other drugs competing for same site

Protein characteristics
- Conc
- Number of available binding sites → Altered by conformational changes

Significance
- Vd: ↑protein binding → ↓Vd as remains in vascular compartment
- Clearance: ↑protein binding → ↓renal/hepatic clearance
  - BUT propofol 98% protein bound AND rapidly metabolised HER1.0
    - 2° rapid equilibrium of bound/unbound drug
- Drug action: only unbound fraction of drug pharmacologically active

Altered states of protein binding
- Pathological states: end-stage liver failure, burns → ↓protein binding
- Inflammation: ↑protein binding as proteins are acute phase reactants

By Amanda Diaz
1996a(13): Describe briefly the factors determining transdermal uptake of drugs and give examples. Outline the advantages and disadvantages of transdermal administration of drugs

General: Transdermal application of drugs can be achieved through use of
- Patch eg fentanyl, GTN, oestrogen, nicotine

All applications require the drug to diffuse through epidermis to access target site, dermal vessels for systemic absorption
- Behave in accordance with Fick’s Law of Diffusion

\[ F = \frac{A \times \text{sol} \times P_{1-2}}{T \sqrt{MW}} \]

where \( F \) = rate of diffusion, \( A \) = surface area for diffusion, \( T \) = thickness of Barrier, \( P_{1-2} \) = conc gradient of drug across barrier

\( \text{sol} \) = solubility of drug, \( MW \) = MW of drug

Factors affecting uptake
A: surface area of diffusion
- ↑surface area (by ↑size of patch) will ↑rate of diffusion

T: Barrier thickness
- Thicker barrier (eg back) will ↓rate of diffusion
- Inner thigh/mucosal, relatively thin barrier have ↑rate of diffusion

Sol: Drug solubility
- ↑lipid solubility will ↑uptake (↑unionised portion of drug)
- ↑hydration of skin will ↑penetration of horny layer
- Electrical current will ↑solubility

MW: <1,000 Da → ↑uptake

\( P_{1-2} \): ↑conc applied will ↑conc gradient across skin barrier → ↑diffusion
- Vascularity of site → ↑systemic absorption → maintain gradient for ↑uptake
- ↑CO → ↑systemic absorption

Advantages/Disadvantages of Transdermal application

Advantages:
- Avoid 1st pass metabolism
  - Only other route injectable
- Avoid use of needles/invasive administration
  - ↓risk blood-borne disease
  - ↓discomfort
- Slow release application
  - Controlled dose over long period → prevents peak-trough phenomenon with po/Intermittent injection
  - Patches worn for 12-18hours
  - GTN patch suitable for stable angina
- Abuse potential low
  - Sustained release formulations of fentanyl/buprenorphine

Disadvantages:
- Allergy
  - To adhesive component
  - Preservatives/buffers in formulation → skin irritant
  - Anaphylaxis rare
- Continued absorption after removal of patch

By Amanda Diaz
- Latent effect
  - Acts as a depot
- Tachyphylaxis
  - Especially a problem with GTN → requires o/night break (on 12hrs, off 12hrs) or loses effectiveness
- Slow SoO
  - GTN patch unsuitable for Rx during AMI
  - Delayed onset → 4hrs for effect with patch v almost immediate
- Risk of inadvertent overdose
  - Forgotten patch → >1 patch on at a time
  - Application heat → deaths 2° heat pack over fentanyl/buprenorphine patch → ↑rate of diffusion → opioid OD
  - Electricity → GTN patch and external defibrillator → ↑diffusion (explosion potential)
1996a(16): Define therapeutic index and briefly outline its significance. Briefly describe also therapeutic ration & use of cardiac/CNS toxicity ratio

**Therapeutic Index (TI)** = Derived from quantal dose-response curves.
- The margin of safety of a drug measured as the ratio of the median effective dose (ED$_{50}$) and the median lethal dose (LD$_{50}$)

Mathematically expressed as:
\[
TI = \frac{LD_{50}}{ED_{50}}
\]

**Uses**: Provides a crude indication of the margin of safety of a drug (i.e. the larger the TI, the larger the gap between an effective dose and a harmful dose)
- High TI drug: Paracetamol, BZ
  - Can safely give large bolus doses with low frequency
  - Nil plasma monitoring required
- Low TI drug: Theophylline, digoxin
  - In general, need lower doses, ↑freq administration (to limit peak toxicity) (Exception, gentamicin which has toxicity not conc-related)
  - Need to monitor plasma levels of drug (eg phenytoin, digoxin)

**Limitations**:
- LD$_{50}$ not good guide to toxicity in humans (measured in animals) → adverse effects limiting use in clinical practice may be overlooked in animal models
- ED$_{50}$ is not definable i.e. it depends on the measure of effectiveness being applied (eg differences in dosage of aspirin to treat a headache vs Rx of RA)
- As it is a ratio based on median doses, it does not take into account *interindividual variability* with respect to effective or lethal doses or idiosyncratic reactions
- Median values taken from healthy subjects (ED$_{50}$) or animals (LD$_{50}$) therefore may overlook ‘vulnerable’ populations eg paeds, elderly, chronic disease, co-morbidities
- Alterations in dose-response curve characteristics can give a high (safe) TI despite differences in the curves leading to significant overlap in ED and LD (eg ED$_{70}$ = LD$_{20}$)

**Therapeutic Ratio (TR)** = Comparison of any 2 parameters (eg CVS vs CNS toxicity).
- Commonly used with LA to describe the relationship b/n the drug dose required to produce CNS and CVS toxicity in experimental subjects.
- The higher the number, the larger the gap b/n the doses and the ‘safer’ the LA is (as CNS Sx are 1) easier to manage, 2) less lethal, and 3) precede CVS Sx

The CC/CNS ratio lignocaine = 7
The CC/CNS ration bupivocaine = 3.7, i.e. only 3.7 x the convulsive dose is required to produce a high risk of CVS collapse
**Pharmacodynamics/Pharmacokinetics**

By Amanda Diaz

**2000a(14): Discuss the roles of plasma esterases on drugs used in anaesthesia**

General: Esterases are a heterogenous group of enzymes which hydrolyse esters through the oxygen bridge to form alcohol and alkanoic acid → inactivates ester drugs

- Found in plasma, NMJ, RBC, hepatic sinusoids
- High capacity pathway with high clearance
- Non-organ dependent metabolic pathway (except in severe hepatic disease → ↓production plasma cholinesterases)
- Metabolites are usually inactive
  - Except laudanosine (atracurium/cisatracurium) and salicylic acid → which can be active at high doses

**Red Cell Esterases**

Drugs metabolised:
- Esmolol
- Remifentanil (small proportion)

High capacity/high clearance

**Plasma Esterases**

Drugs metabolised:
- Remifentanil → predictable t½β fixed and context-independent
- Atracurium/Cisatracurium
- Etomidate → plasma and hepatic microenzymes

Independent of liver function

High capacity/high clearance

**Pseudocholinesterase (plasma cholinesterase)**

Drugs metabolised:
- Suxamethonium
- Mivacurium
- Ester LA (eg amethacaine)

Affected by altered physiology/co-morbidities → acquired/inherited
- Pregnancy
- Liver disease
- Inherited disorder (pseudocholinesterase deficiency) → autosomal dominant with variable penetrance → atypical 1:3000 homozygotes, 1:500 heterozygote

↓by drugs
- Anti-cholinesterases → neostigmine
- LAs → dibucaine
- Metaclopramide

**NMJ acetylcholinesterase (AChE)**

- Nil significant direct metabolism of drugs used in anaesthesia
- Pseudocholinesterase deficiency (↓metabolism of sux) will result in recruitment of AChE to cease effect

By Amanda Diaz
2002b(2): Briefly describe the factors affecting the uptake of an orally administered drug

General: Uptake of an orally administered drug will be dependent on:
  1. Drug characteristics
  2. Pt characteristics

Drug Characteristics:
Uptake from GIT is dependent on rate of diffusion, which follows Fick’s law of diffusion
\[
F = A \times \frac{\text{sol}}{\sqrt[2]{\text{MW}}} \times P_{1-2}
\]
where F=flux, A=surface area, sol=drug solubility, \(\sqrt[2]{\text{MW}}\)=barrier thickness, \(P_{1-2}\)=conc gradient

Passive diffusion is most common method of drug absorption.
Dependent on:
  - MW: Rate of diffusion inversely proportional to MW Graham’s law
    - MW<1,000 Da ↑diffusion
  - pKa (sol): the degree of ionisation determines solubility across the membrane.
    - Only unionised pass readily.
    - Acidic drugs (eg aspirin) are unionised in the acid stomach, are absorbed rapidly
    - Weak bases (eg propranolol) are ionised in the stomach (↓uptake), relatively unionised in the duodenum (↑uptake).
  - Formulation:
    - delay absorption → ↑size of molecule, binding agents (eg enteric coated), granulated
    - rapid absorption → liquids
  - Physicochemical interaction (↓\(P_{1-2}\)):
    - gut contents/food/other drugs → bind/inactivate drug
      - eg tetracycline bound with Ca\(^{2+}\) from milk
      - eg bile salts, bacterial degradation
  - Pharmacokinetics: metabolism at the gut wall (eg GTN) (↓\(P_{1-2}\))

Patient characteristics
  - Compliance with medication
  - Mucosal blood flow (↓\(P_{1-2}\))
  - Vomiting (↓A)
    - Insufficient/inadequate exposure to GIT to allow absorption
  - Malabsorption syndrome/↑transit time (↓A)
    - Acquired (eg tropical sprue) or congenital (Coeliac disease)
      ↓effective area of absorption
  - Gastric stasis (↓A)
    - Illness, trauma, drugs
    - Most drugs → ↓absorption (except aspirin, which is unionised in the stomach, and will continue to be absorbed from there in event of gastric stasis)
2003a(4): Outline the potential problems associated with additives used to make medications suitable for IV injection

General: IV medications are a common part of anaesthetic practice
- Enables rapidly available mode of administration
- Faster onset of action than other modes
- Can be administered whilst patient is unconscious

Additives are included in preparations in order to:

\[ \text{\textit{solubility of drug}} \rightarrow \text{Easy storage} \]

- Emulsifiers → soybean oil / lipids (Propofol / Etomidate)
  - Allergy / anaphylaxis
  - ↑calories
  - Pain on injection
- Propylene glycol (Etomidate / digoxin / phenytoin)
  - Thrombophlebitis
  - Pain
  - ↓BP 2° vasodilation
  - Blood: ↑osmolarity / ↓pH (↑lactate production)
- Benzyl alcohol (diazepam, phenobarbitalone)
  - CVS S/E if given too rapidly
- Cremaphor EL *no longer used → previously propofol, Vit K, pregnelone*
  - Anaphylaxis

\textbf{Stabilising Agent} → prevent hydrolysis / oxidation whilst stored → predictable dose / effect

- Sulfites (metabisulfite) → adrenaline / TIVA propofol
  - Trigger asthma (bronchospasm)
  - Allergy / anaphylactoid reactions → Itch
- Lecithin → Propofol →?allergy in those with egg allergy

\textbf{Maintains optimal pH / Osmolarity} → soluble

- HCl maintains pH < 4 → closes ring in \textit{midazolam} ↑ water solubility / easy storage
- Na\textsubscript{2}CO\textsubscript{3}
  - Acidic / alkaline solutions can be \textit{irritant} to veins → minimised by use of \textit{large / central veins}
  - Pain on injection
  - Thrombophlebitis

\textbf{Preservatives} → prevent contamination

- Benzalkonium Cl (BAC) → Bronchodilators, some ketamine preparations
  - Bronchoconstriction
  - Anaphylactoid reactions
- Chlorbutol → *not used → previously in ketamine*
  - Hypersensitivity
- \textit{Parabens} → Na Benzoate / benzoic acid / Methyl paraben
  - Multiple agents
  - Very low allergenicity
  - ?vasodilation effect
  - Prevents yeast / funghi growth > bacteria

By Amanda Diaz
2004b(1)/01a(9)/96b(12): Briefly describe how drugs may produce their pharmacological effects. Illustrate each mechanism with examples

General: effect can be separated into receptor mediated and non-receptor mediated effects.

1. Receptor-mediated
   - Receptors are **proteins/glycoproteins**, and can be present in the cell **membrane**, within the **cytosol** or associated with **intracellular** organelles/nucleus
   - Receptors can i) alter ion permeability (ionotropic), ii) produce intermediate messengers (metabotropic) or iii) regulate gene transcription

**Ionotropic Receptors**
- Membrane spanning complexes made up of multiple subunits.
- Are associated with an ion channel, either intrinsic or extrinsic to the receptor structure.
  - Activation by a ligand produces a conformational change which opens the channel
    - Allows movement of ions down electrochemical gradients
- Drugs can act by:
  - Activating channel by binding to the ligand site (e.g., ACh → nAChR → activation → rapid Na⁺ influx → propagation of action potential)
  - Enhance opening time of channel (e.g., STP → α_1-subunit of the activated GABA<sub>A</sub>R → ↑Cl⁻ ion opening time).
- Now largely accepted that volatiles work directly on the GABA<sub>A</sub>R

**Metabotropic Receptors**
- Receptors are 7-transmembrane spanning proteins with ligand-binding moiety on the extracellular side and cytosolic side associated with intracellular intermediate messengers
  a) **G-protein coupled receptor (GPCR)**
    - Most common type of metabotropic receptor. Receptor is associated with α-GDPβγ protein complex.
    - 100:1 G-protein: GPCR therefore, effective signal amplification with relatively small [ligand]
    - Ligand binding to the GPCR → α-GDPβγ is converted to α-GTPβγ → α-GTP dissociates from βγ and activates 2<sup>nd</sup> messengers (adenylyl cyclase, phospholipase C).
      - Some systems, βγ activate intermediaries (e.g., opioid receptor activation leads to βγ inhibiting N-type Ca<sup>2+</sup> channels)
    - α-GTP → α-GDP and reassociates with βγ to form inactive α-GDPβγ
    - e.g., β adrenoceptor agonists activate GPCR which activates G<sub>s</sub> protein → activation of adenylyl cyclase and formation of cAMP. Effect = + inotropy
    - e.g., α adrenoceptor agonists activate GPCR with associated G<sub>q</sub> protein → activation of phospholipase C → breakdown of PIP<sub>2</sub> into IP<sub>3</sub> and DAG.
    - IP<sub>3</sub> = ↑Ca<sup>2+</sup> release from ER, DAG = activation of protein kinase C
  b) **Tyrosine kinase**
    - Membrane bound receptor system
      - Eg activation of insulin receptor (2α and 2β subunits)
Ligand binds \( \alpha \) subunit → phosphorylation of intracellular tyrosine residues on the \( \beta \) subunits to tyrosine kinase → tyrosine kinase catalyses target protein phosphorylation. Effects = glycogenesis, activate glucose transporters, regulate gene transcription.

**Regulation of gene transcription**

- Steroids and thyroid hormones alter DNA and RNA expression
- Effects are slow
- Cytosolic receptor proteins (lipid soluble ligands). Receptor-steroid complex transported into nucleus to exert effect.

**2. Non-receptor mediated**

**Enzymes**

- most drugs are inhibitors (eg ACE-I)
- Action is 2-fold i) ↑[substrate] normally metabolised, and ii) ↓[product(s)] of reaction
  - Eg ACE-I - ↑[angiotensin-I], with a concomitant ↓[angiotensin-II] to ↓BP. Also ↑[bradykinin] and ↓[inactive metabolites] → intractable cough.
  - Eg acetylcholinesterase inhibitors (eg neostigmine) prevents the breakdown of ACh → ↑[ACh] at NMJ and continued activation of nAChR

**Direct Ion channel action**

- Prevent action potential by stopping changes in the RMP.
- Eg LAs block fast Na\(^+\) channels preventing influx of Na\(^+\)

**Carrier molecules**

- Prevention of transport against a concentration gradient
- Eg digoxin inhibits Na\(^+\)/K\(^+\) ATPase thus preventing Na\(^+\) removal from ICF, which ↑[Ca\(^{2+}\)] and ↑inotropic activity of heart mm
- Eg diuretics

**Structural analogue/counterfeiting**

- Competes with endogenous molecules in chemical reactions
- Eg \( \alpha \)-methyldopa decarboxylates to \( \alpha \)-methylnoradrenaline which has limited \( \alpha_1 \) activity its \( \alpha_2 \) effects prevent noradrenaline release and ↓SNS tone
- Eg acyclovir, MTX

**Structural**

- eg colchicine inhibits microtubular formation

**Colligative properties**

- eg mannitol ↑plasma/ECF osmolality → ICF depletion & osmotic diuresis

**Physicochemical activity**

- Eg. Antacids → neutralise gastric acid. Chelating agents (resonium) bind metals in the gut to prevent reabsorption

**Unknown**

- ? physicochemical (Myer-Overton theory)
- Placebo effect
Graded log-dose response curve
Eg. Response = receptor occupancy

**Full agonist:** Curve (a)
- Achieve maximal response from the receptor
- eg Morphine is full μ-agonist

**Potency:** ED50 on graph → dose of drug required to produce 50% effect from receptor activation
- mid-point of straight portion of log-dose response curve
- more potent drug (eg sufentanyl) [curve (a)] will have lower ED50 than less potent drug (eg fentanyl) [curve (b)]

**Efficacy:** Effectiveness at which a drug binds to a receptor
- Represented on graph as maximal response (flat upper portion of sigmoid curve)
- Full agonists will have maximal efficacy (response 100%)

**Partial agonist:** Curve (c)
- Drug which has a lower efficacy than a full agonist
- ↓maximal response (less than 100%)
- Eg buprenorphine is a partial agonist of μ-receptor (maximal response less than for morphine)

**Competitive antagonist:** Reversible blockade of the receptor
- Addition of antagonist causes ↑ED50 of full agonist (right shift of curve)
- Effect of antagonist can be overcome by ↑dose of agonist
- Eg naloxone shifts the morphine log₁₀ dose-response curve (a) to the right (b)

**Therapeutic Index:** Ratio of LD50 (or TD50):ED50, i.e. ratio b/n effective and lethal (toxic) dose
- lethal/toxic dose for 50% of subjects v effective dose for 50% of subjects
- Enables comparison b/n different drugs
- Provides a measure of margin of safety
- Cannot be determined on a graded log-dose response curve, but needs to be calculated using a quantal curve (needs > 1 subject)
2006a(2)/00b(9): What is an isomer? Briefly write an account of types of isomers and significance to drugs in anaesthesia

General: An isomer is the phenomenon by which molecules with the same atomic formulae have different structural arrangements. 2 different types exist: structural and optical isomers.

Structural isomers:
- Identical atomic formulae, the order of the atomic bonds differ.
- Depending on the degree of similarity, the molecules may behave similarly (enflurane and isoflurane) or differently (dobutamine and dihydrocodeine)
  1. Tautomerism
    - Refers to the dynamic interchange b/n 2 forms of a molecular structure 2° to change in the physical environment.
    - Eg. Keto-enol transformation of both morphine and thiopentone (changing the lipid solubility)
  2. Stereoisomerism
    - Refers to the differences in 3-D arrangement of the side-groups around the same bond structure. Same formula.
    - 2 forms: Geometric and Optical

Geometric
- Exists when a molecule has dissimilar groups attached to 2 atoms (usually C) linked by a double-bond or ring structure.
- Rotation of the side groups is restricted to either lying on the same side (cis-) or opposite sides (trans-)
- Eg. Mivacurium has 3 geometric isomers: cis-cis-mivacurium, cis-trans-mivacurium, and trans-trans-mivacurium, which affects potency, and kinetics

Optical Isomers
- Optical isomers have 1 or more chiral centres. These are usually C (or quaternary N), 4 different groups attached.
- Used to be named L or D depending on which direction the molecule polarized light
- Now named by the smallest atomic number being placed at the back and the direction determined in descending order based on atomic no. R rotates clockwise in descending order, S rotates anti-clockwise.
  a) Enantiomers
    - x1 chiral centre
    - R or S depending on the “handedness” of the molecule
  b) Diastereoisomers
    - >1 chiral centre
    - n chiral centres = 2^n stereoisomers are possible (although if there is internal symmetry, some of these may be duplicated).
- Eg. Atracurium has 4 chiral centres (2C, 2N) and is a symmetrical molecule, therefore instead of the expected 16 stereoisomers, there is only 10.

**Atracurium v cisatracurium**
- Atracurium is 15% by weight cis-atracurium
- Cis-atracurium is
  - More potent
  - Results in no histamine release
  - Degradation mainly 1° through Hofmann degradation (atracurium is 60:40 Esterase:Hofmann)
2006b(3)/2005a(3): Describe factors which contribute to the inter-individual variability in drug response seen with IV anaesthetic induction agents

**Pharmacodynamic**

Physiological differences
- Age: young need > amount agent than elderly
- Pregnancy
- Body habitus → larger people need >doses

Pathology
- Acute co-morbidities: eg low CO states (LVF, dehydration) will prolong onset
  - Arm-brain circulation time increased → ↑effect-site eq time
- Chronic illness: eg chronic liver failure → ↓albumin production, ↑free drug conc.
- pH changes: acidosis changing unionized proportion based on drugs pKₐ
  - ↑keto-transformation of STP as is weakly acidic (pKa 7.6)

CVS:
- CO
  - ↑CO → faster effect site equilibration, but shorter time to redistribution to peripheral compartments (fast offset of drug) → requiring ↑dose
  - ↓CO → slower time to effect site equilibration, but longer redistribution time (slow offset of drug) → requires ↓dose
- Regional blood flow → ↓blood flow peripheral compartments → longer time to redistribution

CNS:
- Tolerance → previous regular exposure may also change effect (eg methadone, phenytoin, BZ → ↓GABAₐR density (tolerance). → requires ↑dose
- Illicit drugs (marijuana, methamphetamine) usually ↑IV induction agent requirements

Concurrent drug administration
- Drug interaction may potentiate the effect of the agent, add to its effect, act synergistically, produce idiosyncratic response or antagonise
  - Drugs used in the conduction of anaesthesia: eg opioid administration will ↓induction agent requirements (synergistic).

Idiosyncratic
- Allergy/Anaphylaxis
  - >risk with STP than propofol

**Pharmacokinetic**

Absorption: little effect to IV induction agents
Distribution: changes to Vd alter the amount of agent remaining in the central compartment to reach brain
- Changes to central compartment volume
  - Pregnancy ↑blood vol → requires ↑amount agent
  - Dehydration ↓plasma vol → ↓amount agent req
- Changes protein-binding

By Amanda Diaz
Pharmacodynamics/Pharmacokinetics

- ↑protein (↓free fraction): pregnancy, infection/inflammation (acute phase reactants)
- ↓protein (↑free fraction): Liver disease ↓albumin prod0, protein losing nephropathy, burns
  - ↑competition for protein binding → 1° other drugs (BZ, warfarin, LA, morphine)
  - ↑fat stores → ↑capacity of peripheral compartment
  - Rate of distribution dependent on blood flow (eg ↓ in septic shock, ↓CO, dehydration
  - ↑Vd in 3rd spacing…

Metabolism: usually hepatic via the cyt P450 system
- ↓hepatic blood flow (↓metabolism): cirrhosis
- ↑enzyme activity (↑metabolism of agent): phenytoin
- ↓enzyme activity (↓metabolism): Cimetidine
- Time of exposure to agent
  - STP → elimination half-life = ~24hrs → accumulation if multiple closely timed surgeries

Elimination: Changes to elimination pathways will effect excretion of drug
- Renal failure: may prolong the t½ of active metabolites (eg of barbituric acid (thio metabolite)
2007a(3): Discuss factors contributing to inter-individual variability in therapeutic response to opioid analgesic medications
Classed according to effects on:
- Pharmacodynamics
- Pharmacokinetics

Pharmacodynamic Effects
- Age: Extremes (elderly, neonates) → ↓dose required
- Pregnancy: ↓dose 2° summation by progesterone
- Tolerance: ↑dose required for therapeutic effect (2° change in receptor affinity / up regulation of receptor number)
- Drug Interactions:
  o Direct interaction: naloxone competes for binding at μ receptor → ↑dose opioid required; buprenorphine is partial agonist which ↓availability of μ receptor for activation by opioid
  o Indirect interaction:
    ▪ Summation - α2 agonists ↓cAMP → ↓excitatory NT release as does opioids → therefore, ↓dose required
  o Synergism: NSAID use → ↓opioid required

Pharmacogenetics
- 10% popn non-metabolisers of codeine / tramadol (required for therapeutic effect) due to absence of CYTP450 2D6

Pharmacokinetic effects
Absorption: Route dependent → affect time to reach effect site
- Oral: ↓w/gastric stasis
- SC / IM: blood flow dependent
- IV: CO dependent
Distribution:
- Vd → ↓Vd (hypovolaemia) → ↓dose
- Protein binding
  o Competition for binding sites (AAG) by other drugs (LA) → ↓dose req
  o Inflammation → ↑AAG (acute phase reactant) → ↓free fraction → ↑dose req
  o ↓synthesis → severe liver disease → ↑free fraction → ↑dose
  o ↑loss → protein losing nephropathy / burns → ↑free fraction → ↓dose
- Degree ionisation: opioids weak bases pKa ~8 (9% unionised fent, 23% unionised morph) → acidosis → ↓unionised portion → ↑dose req
Metabolism:
- Enzyme induction (CYTp45) → Cimetidine → ↑metabolism → ↑dose req
- Enzyme inhibition (phenytoin) → ↓metabolism → ↓dose req
- Active metabolites?
Elimination:
- Removal of active metabolites → morphine-6-glucuronide active (analgesic) → ↓dose
- Morphine-3-glucuronide antanalgesic → ↑req
MAKEUP: Discuss the possible interactions that can occur between agents

General: In anaesthesia, drugs are often given concurrently
- Risk of interactions between agents ↑with:
  - ↑no agents
  - Coexisting disease
  - ↑age
  - pregnancy

Physicochemical

Precipitation
- STP / Suxamethonium
- Propofol / atracurium
- Ca²⁺ / HCO₃⁻

Denaturation
- Insulin / dextrose

Adsorption
- Diazepam → plastic tubing
- GTN → plastic tubing
- Insulin → plastic tubing

Bind
- Insulin → Zn / protamine (desirable effect)

Pharmacodynamic

Direct Interaction → same receptor / pathway
- Flumazenil / benzodiazepines

Indirect Interaction → different receptor / pathway
**Isobologram describes interaction between 2 drugs**

Summation → each drug has an independent action
- Adrenaline / milronone → positive inotropy via different mechanisms
  - Adrenaline: GPCR → ↑adylyl cyclase → ↑cAMP
  - Milronone: PDE inhibitor → ↓cAMP breakdown
- BZ / Propofol

Potentiation → one drug with no independent action on its own
- Probenicid / Penicillin
  - Probenecid ↓renal excretion penicillin

Synergism → action of both > expected by summation alone
- Penicillin / gentamycin

Antagonism
- Neostigmine → ↑ACh → ↑offset NMBD

Idiosyncratic → unexpected / unusual reaction

Pharmacokinetic

Absorption:
- ↑absorption: metoclopramide → ↑gastric motility → ↑opioid absorption
- ↓absorption: charcoal (physicochemical)

Distribution:
- Competition for protein binding → warfarin displaced by macrolides / phenytoin / amiodarone
- ↓CO → β blocker → ↓SO suxamethonium
- ↓hepatic blood flow → propranolol / lignocaine

Metabolism:
- Induction of hepatic enzymes esp cytP450 (↑metabolism) → induced by phenytoin → ↑metabolism warfarin, pethidine, BZ
- Inhibition of cytP450 (↓metabolism) → inhibited by Cimetidine → ↓metabolism warfarin, phenytoin, BZ, lignocaine

Elimination:
- Change urinary pH
  - NaHCO₃ → ↑pH → ↑excretion aspirin / barbiturates
- Prevent elimination:
  - Probenecid prevents renal excretion penicillin