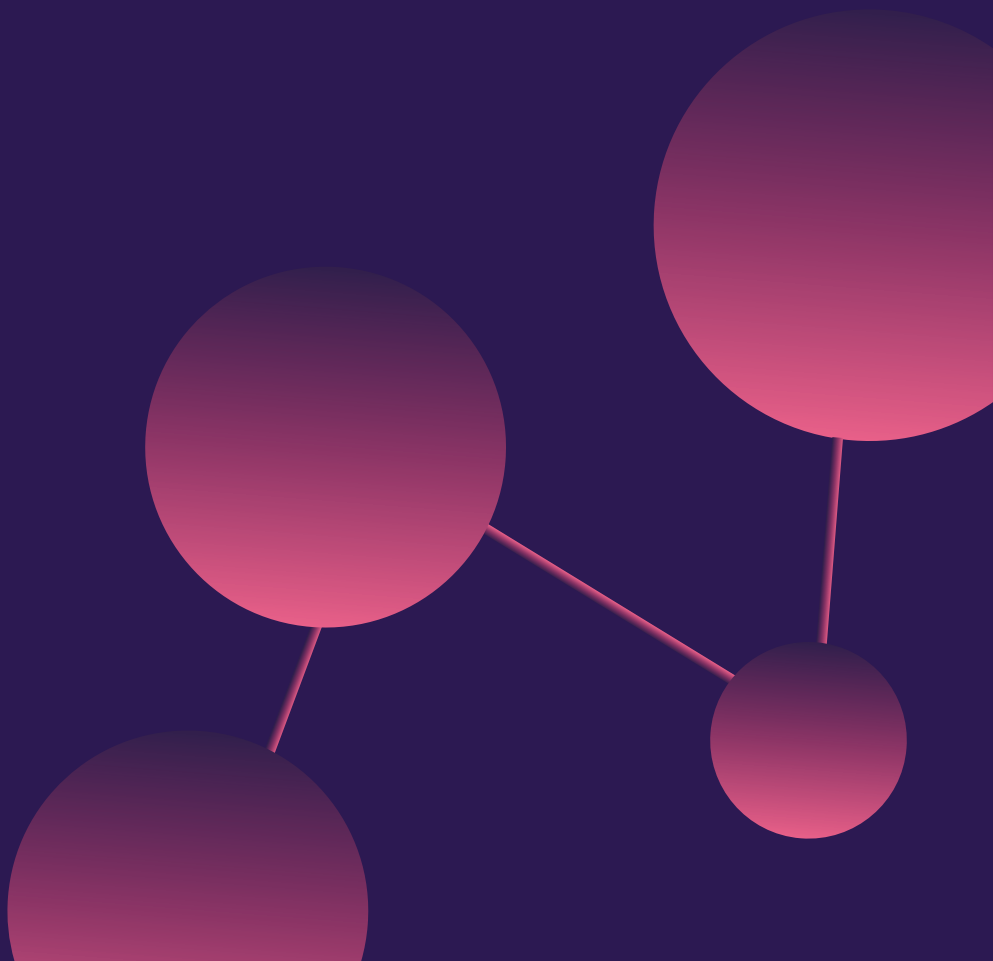
Royal College of Anaesthetists

e-LA
e-Learning Anaesthesia

e-LA Revision Guide:
Pharmacology

Version 1.00 July 2020



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These revision notes have been compiled from sessions in the Pharmacology module of e-Learning Anaesthesia to support your preparation for the Primary Exam. They cover the basic principles of applied chemistry, pharmacodynamics and pharmacokinetics. The section of systemic pharmacology is not included and you should continue to access those sessions through e-LA.

The notes are presented as an interactive pdf document which can be downloaded to your smart phone, tablet or desktop computer for offline access

The Table of Contents contains active hyperlinks which allow you to jump straight to a section or topic.

Each topic also contains links to the relevant e-Learning sessions which you can access by clicking on the session id below the title of the topic e.g 07c_03_01. This will take you to the session information page on the e-LfH Hub from which you can log in and access the session.

Dr Ed Hammond
Dr Andrew McIndoe
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Clinical Leads e-Learning Anaesthesia

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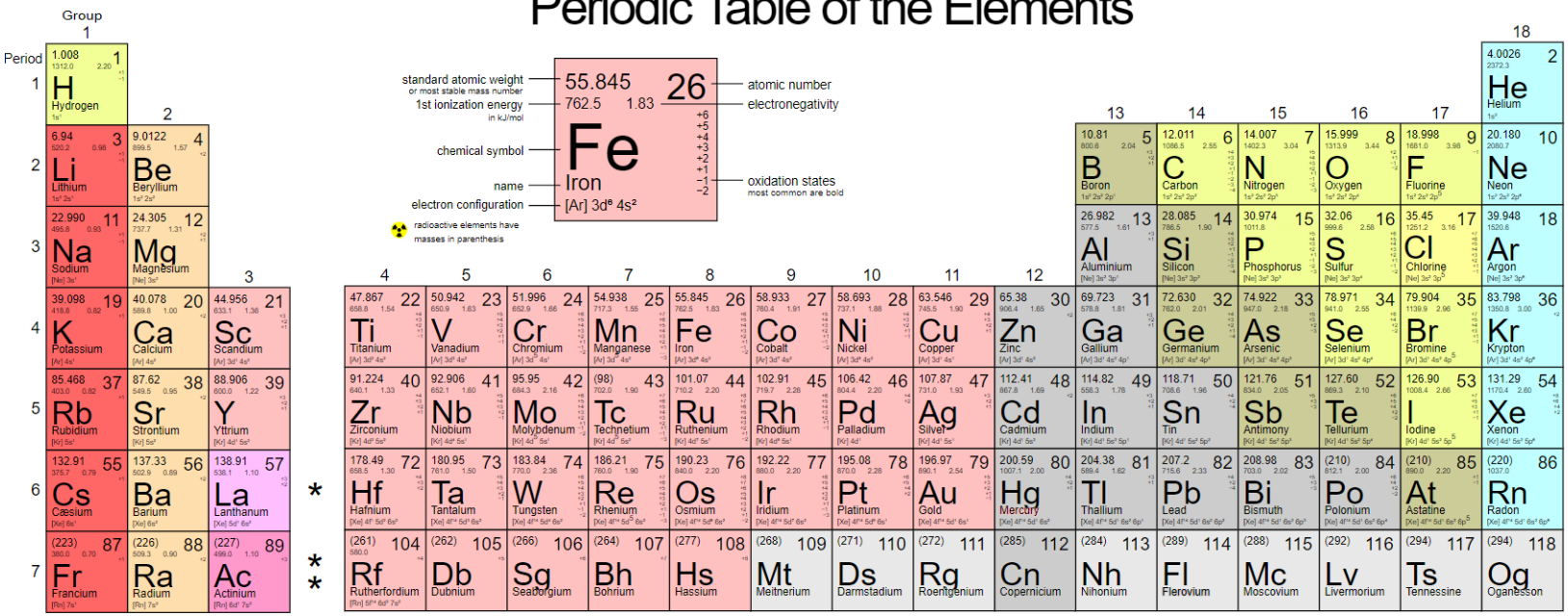
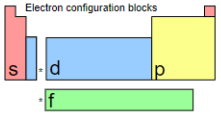
APPLIED CHEMISTRY

Periodic Table of the Elements

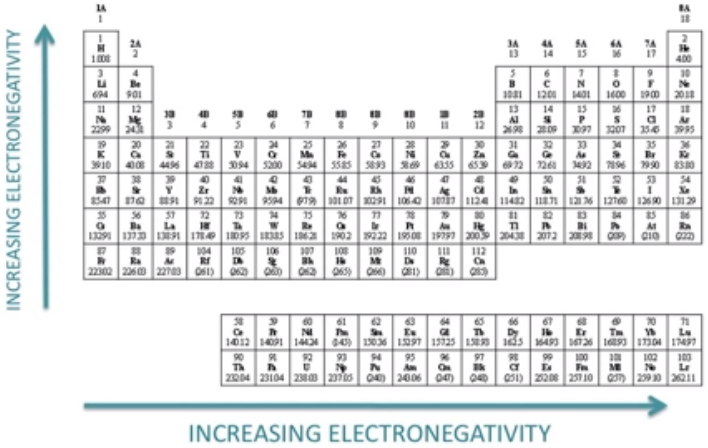




Notes

- 1 kJ/mol ≈ 96.485 eV
- all elements are implied to have an oxidation state of zero.

by Robert Campion / updated 2016, 2018



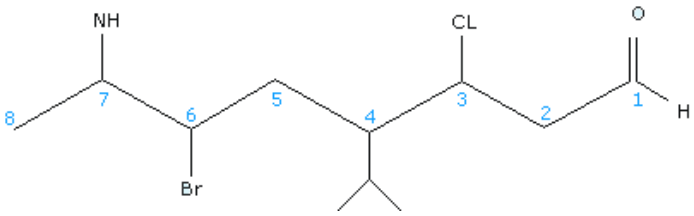
Drugs as Organic Molecules

(07c_01_01)

Organic molecules are based on a **carbon skeleton** and each carbon can form 4 bonds. They are classified as either **aliphatic** or **aromatic:**

Aliphatic Compounds

Describes a carbon chain (root) with functional groups attached to it. The **carbon is numbered starting from the carbon starting at the functional group** which defines the molecule type:



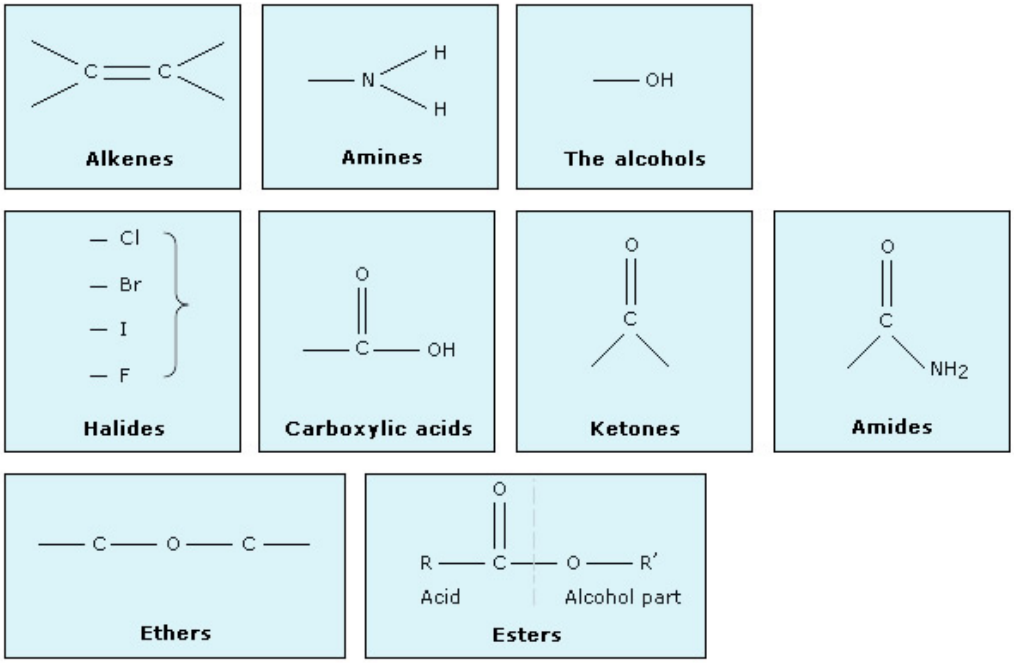
The number of carbons in the longest root determines the parent molecule.

Alkanes all contain no functional groups and are named as follows:

- Methane (1C)
- Ethane
- Propane
- Butane
- Pentane (5C)
- Hexane
- Heptane
- Octane
- Nonane
- Decane (10C)

Depending on the functional group, the nomenclature changes accordingly:

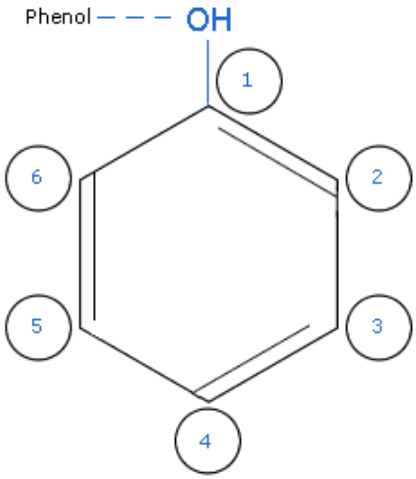
This determines the characteristic pharmacokinetics of a drug.



Aromatic Compounds

All aromatic compounds have a **benzene ring** which consists of a 6-C ring with alternate single and double bonds. It is named a **phenol** with an -OH group.

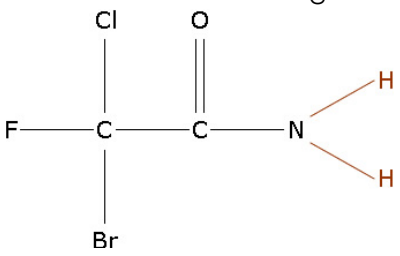
Carbons are numbered from the atom in which the principle functional group is attached.



Valency

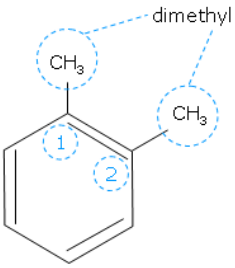
This is the number of bonds an atom has in its uncharged state.
For example in this molecule, one can see the following valencies of each atom:

- F = 1
- Br = 1
- O = 2
- C = 4
- N = 3



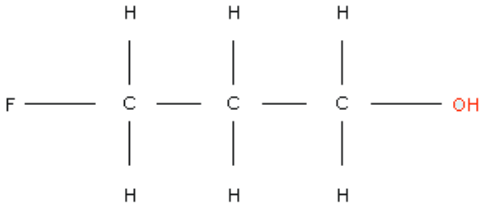
Nomenclature

The number of carbons in the longest chain provides the stem of the name (**prop**). The side chain is named according to the carbon number it is attached to **(3-fluoro)**. A **prefix** is added with >1 identical side chain (**di, tri** etc). The **suffix** is determined by the main functional group (**ol)**.



← 1,2 - dimethyl benzene.

3-fluoropropanol→

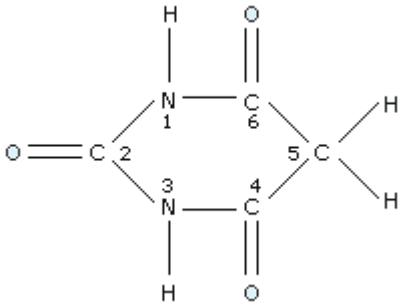


Structure Activity Relationships

Describes the change in pharmacological activity of a molecule when changing different groups. For example,

Barbituric acid is not active but with a phenyl group on C5 will be an anticonvulsant and an alkyl will be hypnotic. Increasing the alkyl group number of carbons will result in hypnotic activity but will result in convulsant properties if >5 carbons.

Oxybarbiturate→thiobarbiturate at C2 (sulphur bond) increases solubility to cross BBB.

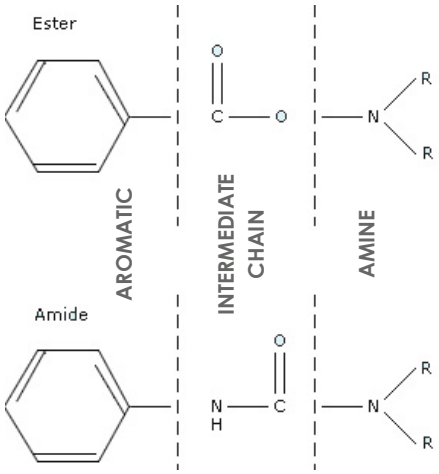


Volatile anaesthetic agents are either ethers or halogenated hydrocarbons. The addition of chloride or bromide increase potency whereas fluoride increases stability of the molecule. The presence of the **ether group** increases stability.

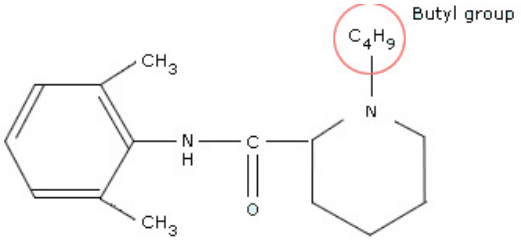
Local anaesthetics have 3 different components:

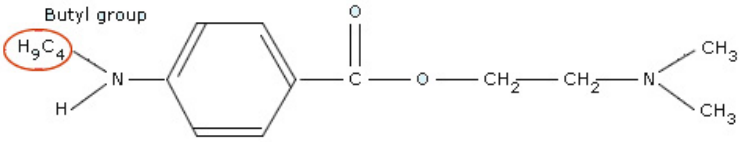
- Aromatic group
- Intermediate chain
- Amine group

They are split into esters (i.e. procaine, tetracaine) and amides dependent on the intermediate chain.



These linkage types determine the speed of metabolism.



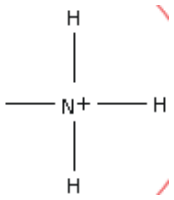


Potency and duration of action is determined by increased lipid solubility. This is achieved through increasing the bulk at the amine side chains i.e. butyl group and addition of groups to the aromatic portion of the drug i.e. aminobutyl group:

Drugs as Acids/Bases

Proton donor = **acid** Proton acceptor = **base**

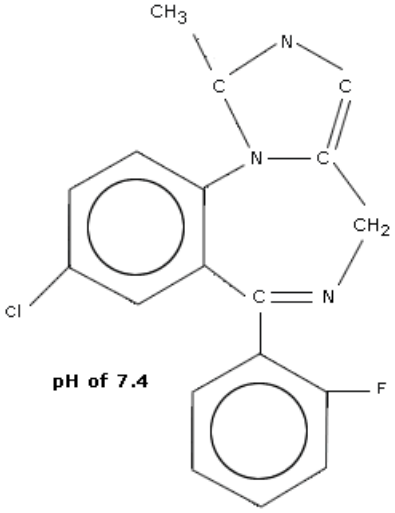
i.e. amine groups have a lone pair of electrons on the nitrogen so can accept a proton → ammonium group.



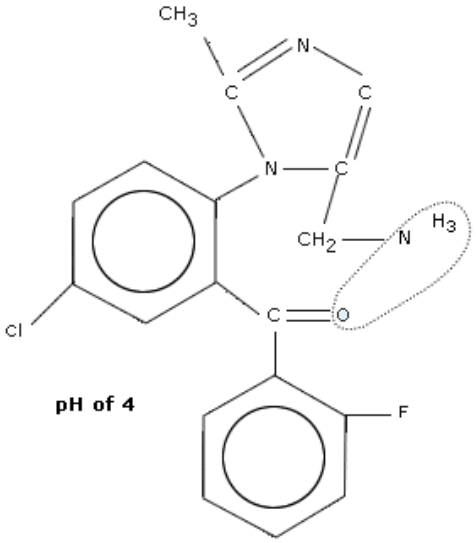
Phenols are weak acids.

Influence of pH on structure

Midazolam has an amine group → weak base and can form an ammonium ion. In acidic environments, it is buffered and is ionised to become water soluble.

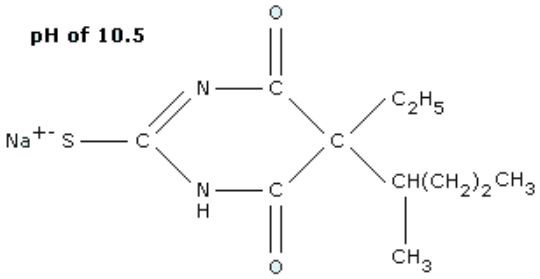


At physiological pH, the amine group is incorporated into a benzodiazepine ring and the ring becomes closed making it non-ionised, lipid soluble and can cross the BBB. This is a **pH dependent ring closure**.



pH of 4

pH of 10.5

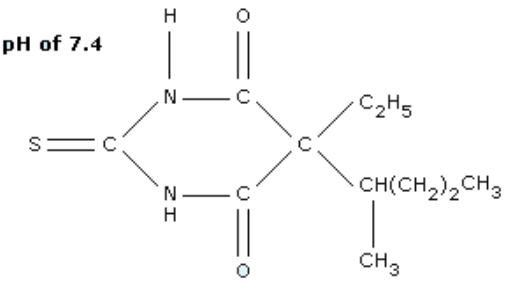


Thiopental is a weak acid and can exist in 2 different structural forms dependent on pH. It is prepared in an alkaline environment to make it ionised and water soluble as an **enol** by substituting a proton for a sodium (left)

At physiological pH, it undergoes **tautomerization** (transforms) to a lipid soluble molecule by dissociating the sodium to bind to the proton and therefore once again form the unionised molecule as a **ketone** (right)

Known as **keto-enol tautomerization.**

pH of 7.4



Interactions Between Molecules

(07c_01_02)

Bonding may be **intramolecular** (within molecules) or **intermolecular** (between molecules). The most common intramolecular bonds are ionic and covalent bonds.

INTRAMOLECULAR

Ionic Bonds

Performed via electrostatic attraction between oppositely charged ions which are produced from **electron transfer** between atoms.

- **Cations** (+ve) – removal of electrons. Mainly metals
- **Anions** (-ve) – gain of electrons. Mainly non-metallic elements.

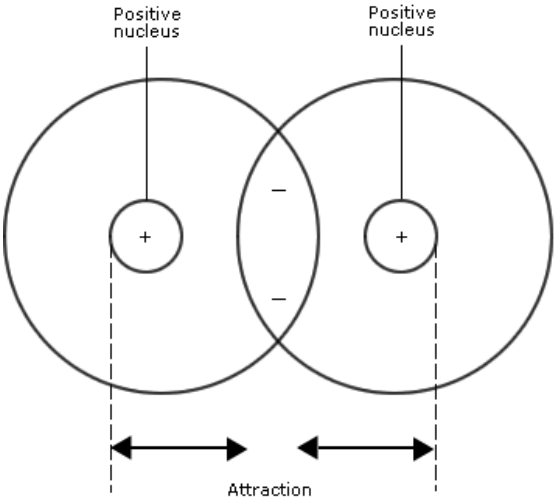
Characteristics:

- Strong forces – tend to have high boiling and melting points
- Soluble in water
- Conduct electricity

Covalent Bonds

Atoms **share electrons** – one donated from each atom and they are held together by forces of attraction between the +ve nuclei and -ve charged electrons.

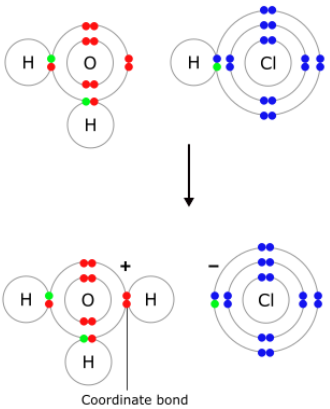
- Usually non-metallic elements
- Often liquids or gases with low boiling points.



Co-ordinate Bonding

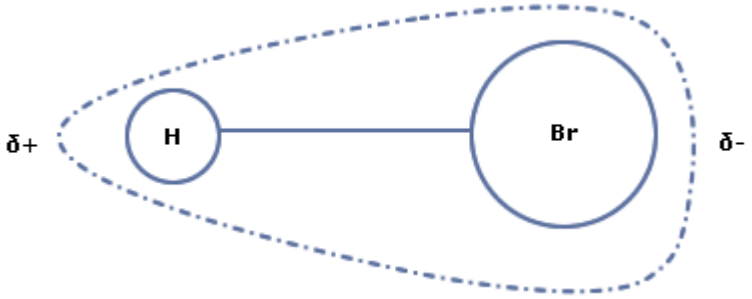
This is when 1 atom supplies both their electrons to form a bond shared with another atom. These atoms usually have a **lone pair of electrons** not involved in a covalent bond. In the following example, H_2O has 2 lone pairs of electrons, one of which can form a co-ordinate bond with a H^+ ion forming an **oxonium ion**.

Similarly, NH_3 has 1 lone pair and can form an ammonium ion with a co-ordinate bond.



Intermediate bonds

Some atoms may form a bond between that of a covalent and an ionic nature. The bond in this case is **polar** where one atom has a larger share of the electrons and creates a slight (but not full) charge.



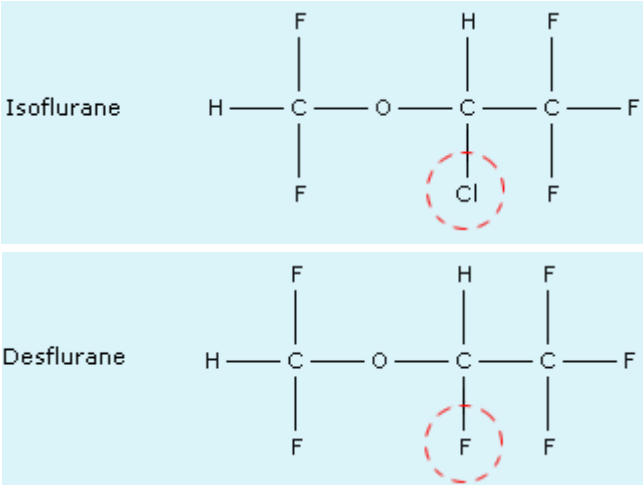
The degree of polarity depends on the **electronegativity of the bond** which describes the proportion of how much each atom attracts the electron. This depends on the **position in the periodic table**.

Example: Halogenated volatiles:

Isoflurane: Has a C-Cl bond

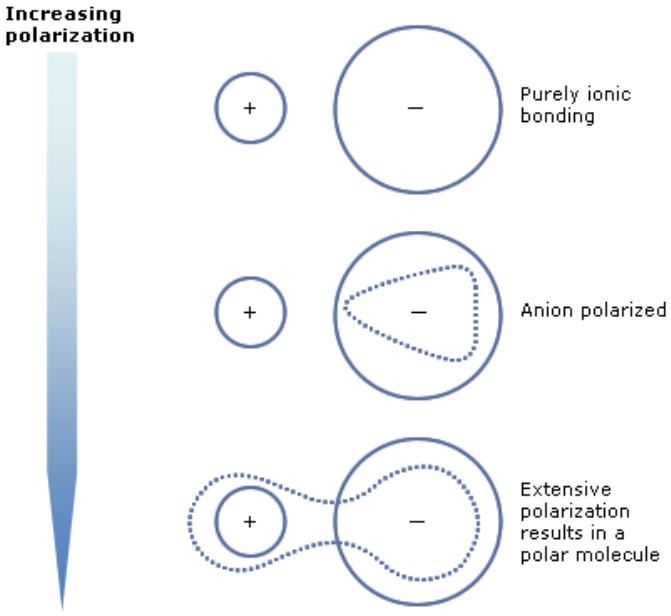
Desflurane: Has a C-F bond

F has higher electronegativity than Cl, creating a stronger polar bond with Carbon than Cl. Therefore, desflurane has a higher bond strength explaining its increased resistance to metabolism compared to that of isoflurane.



Polarisation

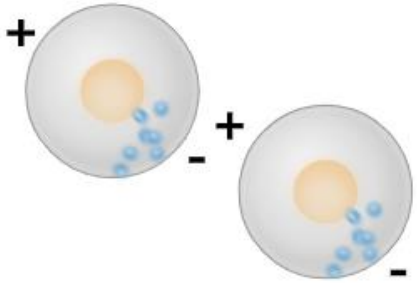
This occurs due to the cation distorting the negative charge of the electron cloud on the anion. There is more electron charge influence on the nuclei of the 2 and hence produces a degree of covalent binding.



INTERMOLECULAR

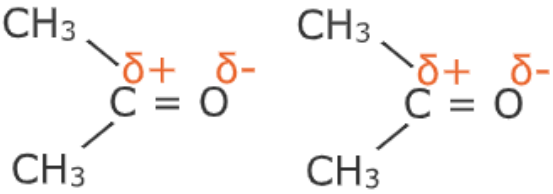
This enables a change of state of a substance. There are 3 types of attractions between molecules:

1. Van der Waals' forces



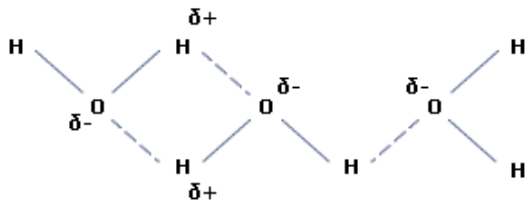
These are the weakest type of attractive force. Formed from the **orbit of electrons** round an atom at high speeds creating spontaneous dipole charges influencing the neighbouring dipole:

1. Dipole-dipole attractions

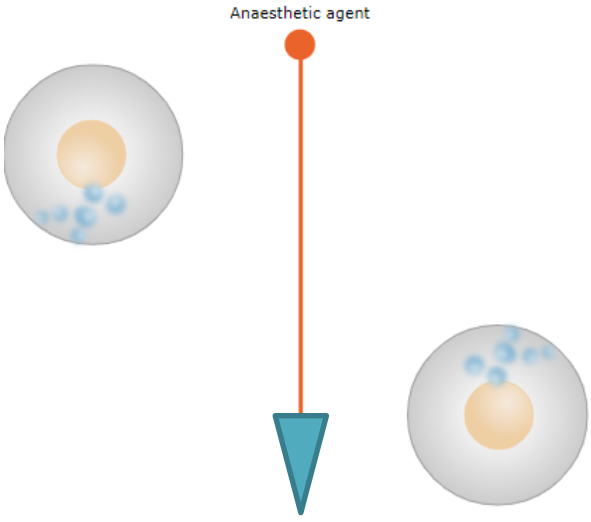


Permanent dipoles exist in polar molecules from the difference in electronegativity (see intermediate bonds above)

2. Hydrogen Bonding



These are the strongest type of intermolecular attractive force. Occurs as a result of hydrogen bonding to a strongly electronegative atom i.e. Oxygen, fluorine, nitrogen. The polarity is much increased and is therefore a form of dipole-dipole attraction.



It is thought that **general anaesthetics disrupt** the Van der Waals or hydrogen bond **molecular associations within lipid membranes**. This also includes the bonds that neurotransmitters form with their receptors (i.e. OH and NH group hydrogen bonds).

They can also act by **formation of hydrogen bonds** with other molecules i.e. volatile anaesthetics can donate protons to form hydrogen bonds with i.e. aromatic rings in amino acids.

Strength of Bonds

Strongest	Ionic Bonds ✓
Second strongest	Covalent Bonds ✓
Third strongest	Hydrogen bonds ✓
Fourth strongest	Dipole-dipole attractions ✓
Least Strongest	Van der Waals' forces ✓

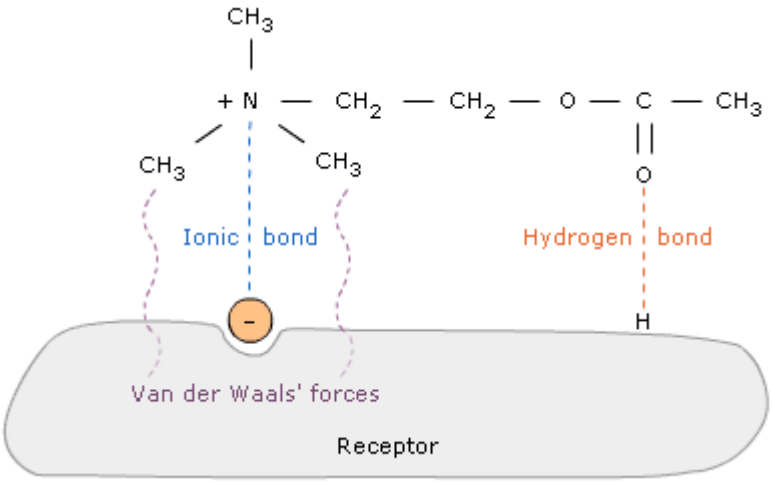
Drug-Receptor Interactions

To **exert a response** to a receptor, the drug needs to bind to its receptor and hold it there long enough to exert its effect. The primary attraction needs to:

1. **Form rapidly**
2. Be strong enough to **hold the interaction together**
3. **Exert its attraction at a distance** from the receptor

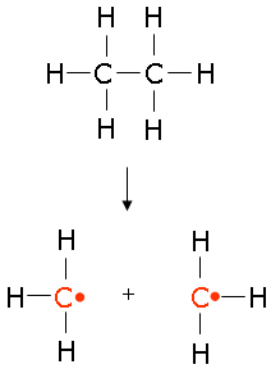
An **ionic bond** can fulfil these criteria (1 and 3) but needs extra hydrogen bonds or Van der Waal forces to hold the drug-receptor complex together for long enough to exert its effect.

Acetylcholine binds with an ionic bond via the quaternary ammonium ion and Van der Waals forces and hydrogen bonds form to improve stability and specificity of the drug-receptor complex.



Breaking Bonds

Covalent bonds can be broken by either:

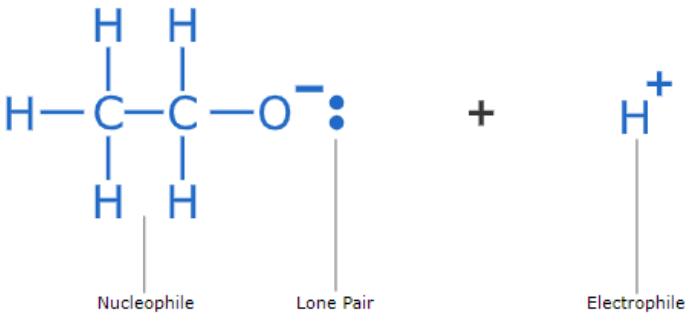


1. Homolytic fission

The bond breaks and each element take one of the electrons so now each element has a single electron → **free radicals**. This requires UV light or high temperatures for this reaction.

2. Heterolytic fission

The more electronegative element takes both electrons and forms 2 **oppositely charged ions**. The ions are now known as:



- **Positive ion**: **Electrophile** – attracted to an electron rich molecule to form a new covalent bond by accepting electrons
- **Negative ion**: **Nucleophile** – attracted to a positively charged atom to form a new covalent bond. They must possess a lone pair of electrons to create this new bond.

Ionisation

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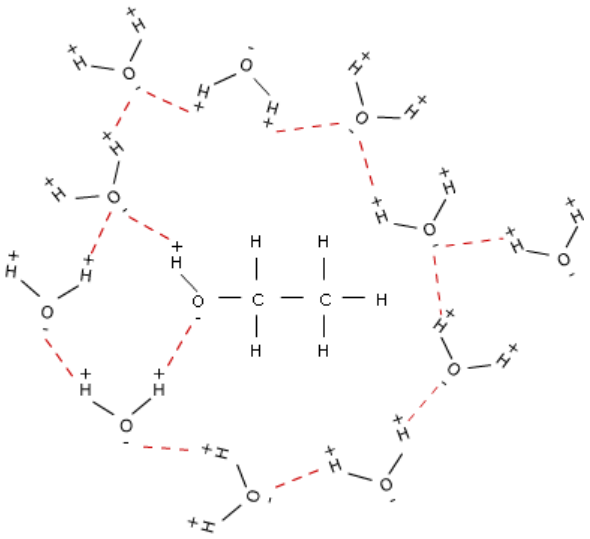
Hydrophilic Properties

Requires a molecule with polarity to disrupt the hydrogen bonds of water. This means that hydrocarbons require **functional groups** (particularly nitrogen and oxygen) to dissolve. Note that the solubility is affected by the size of the hydrocarbon i.e. ethanol is soluble but dodecanol is not.



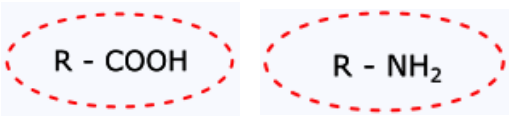
Ionisation

In water, some molecules dissociate into ions. This varies according to the strength of the dissociation:

- **Strong electrolytes** – Fully dissociates in solution i.e. NaCl
- **Weak electrolytes** – Fraction of the molecule dissociates into ions i.e. acetic acid. The proportions are dependent on pH.

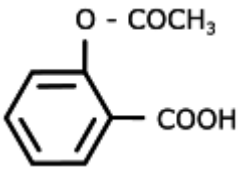
Functional Groups

The 2 most important functional groups to allow partial dissociation are the **carboxyl** and the **amine groups**:

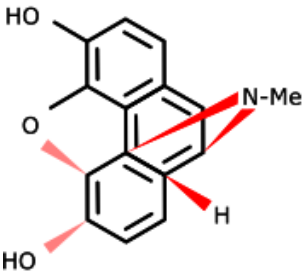


For example:

ASPIRIN:



MORPHINE:



proton donor ⇔ proton acceptor + H^+

With both morphine and aspirin (acetylsalicylic acid), the carboxyl group dissociates dependent on the pH of the environment and the dissociation constant: **pK_a** (the pH at which 50% dissociation is maintained).

NOTE, that the pK_a value is not related to whether the drug is an acid or a base: a base can have a high or low pK_a as can an acid.

The **forward rate constant is depicted as K_1** and the **backward rate constant is depicted as K_2.**

Therefore, at equilibrium:

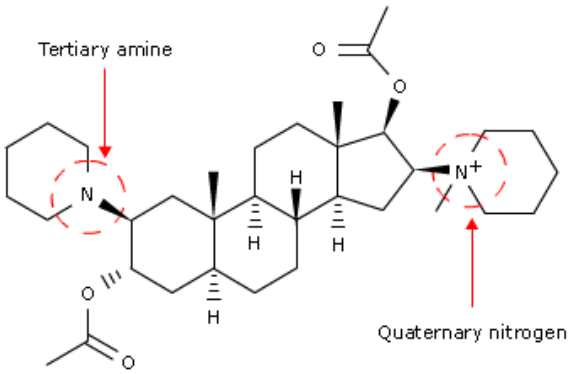
$$k_1[\text{proton donor}] = k_2[\text{proton acceptor}][H^+]$$

$$[H^+] = (k_1/k_2)([\text{proton donor}]/[\text{proton acceptor}])$$

k_1/k_2 is now the acid dissociation constant, K_a. The negative logarithm of which is the pK_a.

Anaesthetic Drugs

Induction agents and analgesic agents are all weak acids or bases **apart from volatiles**. The majority of NMBs have at least 2 permanently charged quaternary nitrogen atoms. Vecuronium (right) however, has only 1 and a tertiary amine group which can ionise at body pH.



Once a pK_a value is more than 2 pH units away from 7.4, then the drug is either 99% or 1% ionised.

Induction agent	Weak acid or base	Functional group 1	Functional group 2	Functional group 3	pK_a functional group 1
Thiopental	Weak acid	S=O	C=O	-NH-	7.6
Propofol	Weak acid	-OH			11.0
Etomidate	Weak base	-N-	=N-		4.2
Ketamine	Weak base	-NH-	C=O		7.5

Analgesic	Functional group 1	Functional group 2	Functional group 3	pK_a of functional group 1
Paracetamol	-OH	-NH-		9.4
Ibuprofen	-COOH			4.9
Tramadol	$-NR_3$	-OH		9.4
Fentanyl	-N-	$N-(CH_2)_2$	C=O	8.4

Henderson-Hasselbalch Equation

The Henderson-Hasselbalch equation describes how the pH of the environment influences the equilibrium between weak acids/bases

$$[H^+] = K_a([\text{proton donor}]/[\text{proton acceptor}])$$

$$\log[H^+] = \log(K_a) + \log([\text{proton donor}]/[\text{proton acceptor}])$$

$$-\log[H^+] = -\log(K_a) - \log([\text{proton donor}]/[\text{proton acceptor}])$$

$$pH = pKa + \log([\text{proton acceptor}]/[\text{proton donor}])$$

Log1 = 0. Therefore, pKa is the pH at which the concentrations of the above are equal.

For a weak base: **$pH = pK_a + \log([B]/[BH^+])$**

For a weak acid: **$pH = pK_a + \log([A^-]/[AH])$**

Ionised forms are on different sides of the equation

Bicarbonate

The Henderson-Hasselbalch equation describes how the pH of the environment influences the equilibrium between carbonic acid and bicarbonate. The **pK_a** of this system is **6.1**:

$$pH = pK_a + \log\left(\frac{[HCO_3^-]}{[H_2CO_3]}\right)$$

If $\log([HCO_3^-]/[H_2CO_3]) = pH - pK_a$

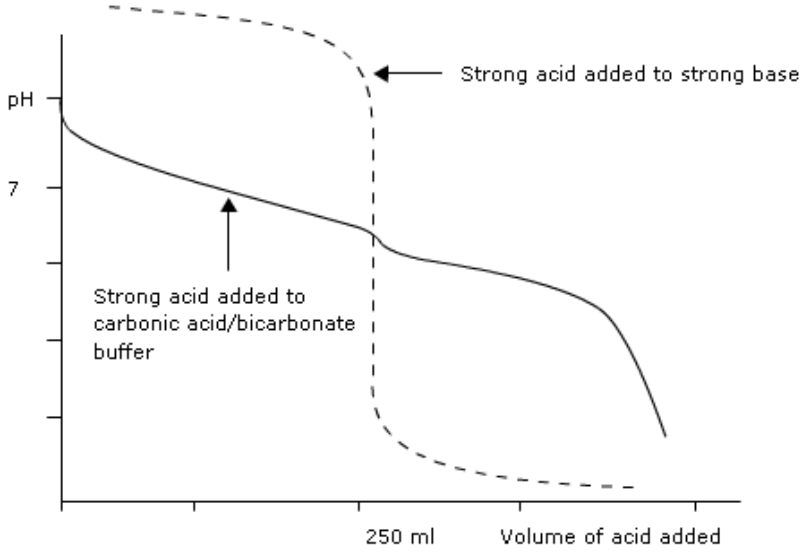
Then… if pH is 7.1, then $\log([HCO_3^-]/[H_2CO_3]) = 1$

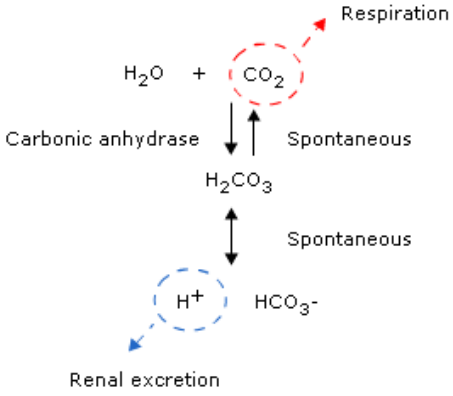
If… $\log_{10} 10 = 1$ then $HCO_3^-:H_2CO_3 = 10:1$

pH	Ratio of ionised:unionised
7.1	10
8.1	100
9.1	1000

Buffering

Due to the movement of equilibrium secondary to a change in pH, bicarbonate acts as a buffer to **limit changes of pH in solution**. This is most effective when existing at equal ratios i.e. pH 6.1, bicarbonate is most effective at buffering.





Open system as the products can be excreted i.e. H^+ by the kidney and CO_2 by the lungs. 80% of HCO_3^- is reabsorbed by the proximal tubule.

Deoxyhaemoglobin buffers tissue production of carbon dioxide for transport to the lungs (this is a 2nd buffer system).

For more information about buffers, see physiology notes (phosphate and ammonia buffers in urinary elimination of protons.

Remember that bases are ionized below their pKa and acids are ionized above their pKa.

Pharmacokinetic Behaviour of Ionisable drugs

For an anaesthetic agent to reach the brain depends on 2 properties:

- **Lipid solubility**
- **pKa of a drug.**

The issue: for it to be directly injected, needs to exist in a soluble ionised form but this can be very irritant to veins if high or low pH. There needs other methods of solubility and includes the following:

1. **Propofol** – lipid emulsion through egg phosphatide
2. **Etomidate** – solubilised with polyethylene glycol or intralipid
3. **Na Thiopental** – Powder held under nitrogen dissolves into alkaline form with water.

Oral preparations will absorb according to the environmental pH.

Stomach = pH 3 **Small intestines = pH 8**

Drug	pK_a
Aspirin (weak acid)	3.5
Ibuprofen (weak acid)	5.9
Paracetamol (weak acid)	9.4
Morphine (weak base)	7.9

Now you can work out the order of ionisation of the following drugs in the stomach and small intestines… *Take care with paracetamol*

Onset of Action

As mentioned earlier, to cross the BBB in greater amounts means a faster onset of action dependent on:

1. pKa
2. Lipid solubility
3. Proportion of unbound drug (>protein binding means unfavourable conc. gradient)

Morphine has a pK_a of 7.9 **40% protein bound**

Alfentanil has a pK_a of 6.4. **90% protein bound**

Due to Alfentanil being 100x less ionised in the bloodstream than morphine, it has a much faster onset of action.

Duration of Action

Ionisation impacts the duration of action. With greater ionisation, there is a **greater effective concentration** in the plasma away from lipid stores and hence there is greater duration of action. When comparing the following:

Fentanyl has a pK_a of 8.5

Propofol has a pK_a of 11

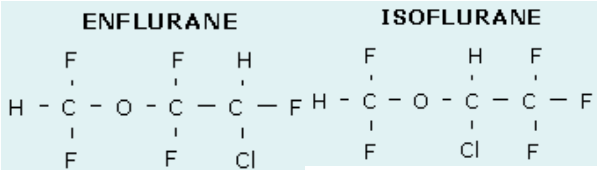
Propofol is more unionised and therefore has a reduced duration of action as is **redistributed**.

Isomers
(07c_01_04)

Isomers are molecules that have the **same molecular formula** but have atoms arranged in a different way.

Structural Isomers

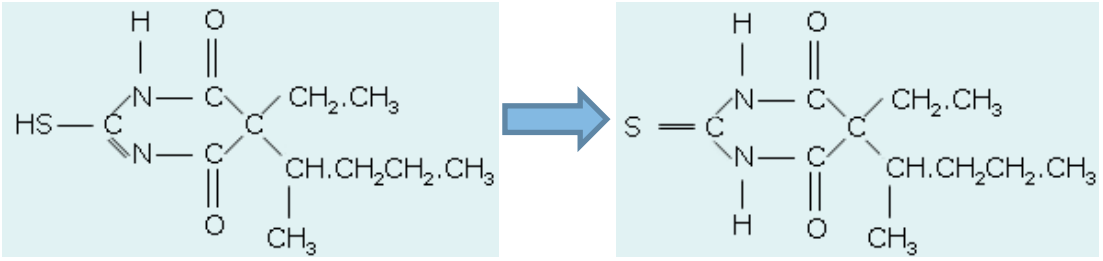
These are isomers that have **different chemical structures** (***different arrangement of the atoms***). For example, with **isoflurane** **and** **enflurane**. They have **different physical and pharmacological properties.**



Tautomerization

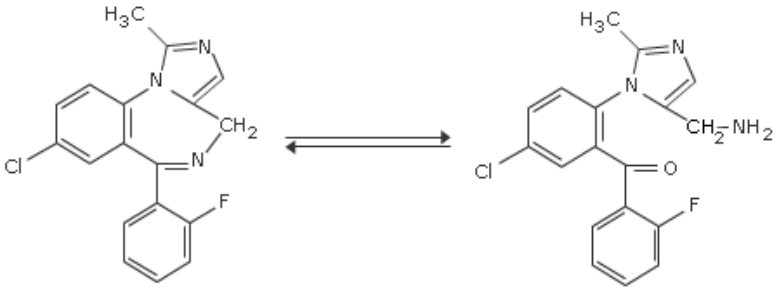
This is a form of ***dynamic structural isomerism*** where 2 structural isomers exist in equilibrium with each other.

For example, with **thiopental**, the -SH (thiol) group displaces the sodium (-SNa) following exposure to an acidic environment. The thiol then undergoes tautomerization to thione (-C=S) which is lipid soluble.



Unionized **Ionized**

Midazolam also may be referred to as undergoing tautomerization. However, this is not true isomerism as H_2O is eliminated upon ring closure.



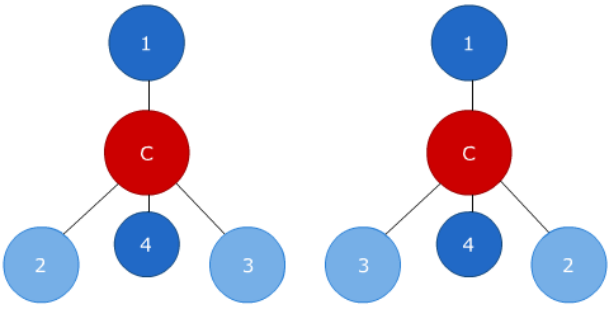
pH>4.0 **pH<4.0**

+ H_2O

Stereoisomerism

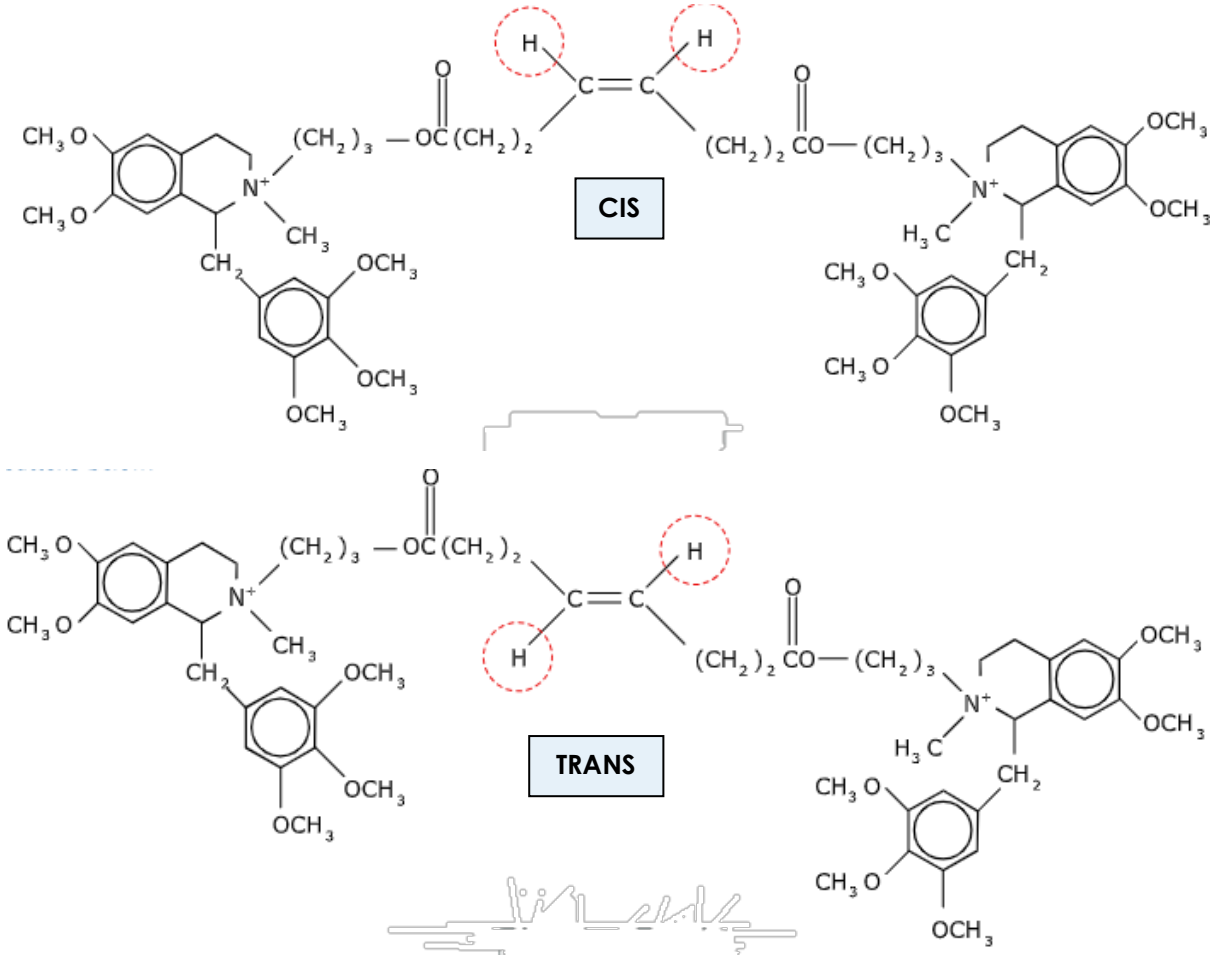
Isomers with the **same chemical structure** but has **different special configurations**. There are 2 types:

1. Geometric
2. Optical



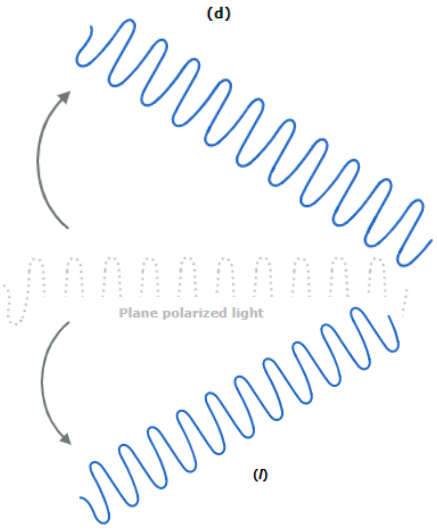
Geometric Isomers

These occur in compounds with an **alkene group** (**C=C**) as there is no free rotation around a double bond. These may either be **cis** or **trans** isomers. **Mivacurium** is an example:



Optical Isomers

This is when **4 different groups are attached to the same atom**. They are mirror images but are non-superimposable. A Pair of optical isomers are known as **enantiomers** which have **identical chemical and physical properties** but rotate plane polarised light (light where vibrations are all in one plane) in opposite directions.



Dextrorotatory enantiomer rotates it to the Right:

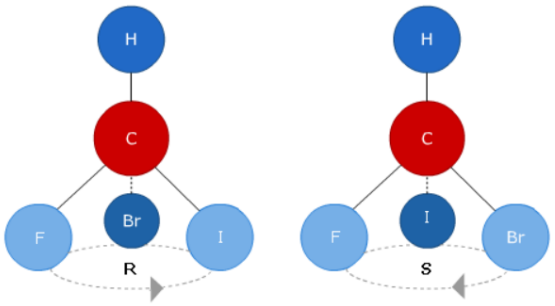
Levorotatory enantiomer rotates it to the Left:

An **equal mixture** is known as a **Racaemic mixture** and has no overall effect on the plane of polarised light.

R and S naming system

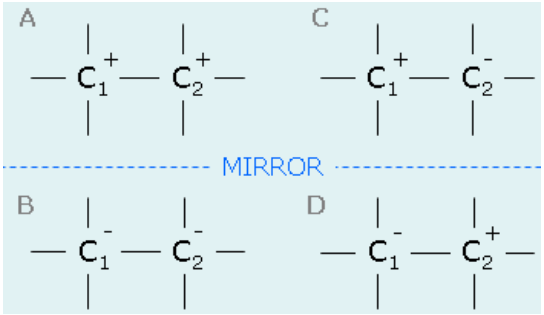
Each group is given a priority according to the **atomic number** (number of protons in the nucleus) of each atom and the lowest (hydrogen usually) will be placed at the top. The order of the other 3 atoms around the chiral centre in descending order will be in a:

- Clockwise (R) orientation
- Anticlockwise (S) orientation



Diastereoisomers

When a drug has **more than 1 chiral centre** and hence do not form a mirror image of each other (A with C or D). **Atracurium, tramadol** and **methohexital** are all Diastereoisomers as well as enantiomers.



Clinical Implications

2 isomers may produce different responses due to different conformational relationships with a chiral receptor causing differing:

- Potencies
- Intrinsic activity
- Pharmacological responses

Single isomers therefore produce a more predictable and often more desirable response to minimise unwanted effects.

DRUG	ENANTIOMER
Ketamine	S (+) enantiomer is the useful intravenous anaesthetic agent. R (-) enantiomer causes agitation, postoperative pain and emergence reactions.
Bupivacaine	S (+) enantiomer produces prolonged local anaesthesia. R (-) enantiomer is responsible for convulsant and cardiotoxic side effects.

With **muscle relaxants**. Atracurium contains a mix of 10 different isomers. One isomer, cisatracurium, has various clinical advantages, including:

- Three times increase in potency
- Minimal autonomic effects
- Minimal histamine release
- Reduced laudanosine levels
- It is produced as a single enantiomer and available commercially

With **local anaesthetics:** Mepivacaine, prilocaine, bupivacaine and ropivacaine all exist as pairs of optical isomers. The S-isomer is favourable as:

- Increased vasoconstriction → prolonged duration of action and less systemic absorption
- Reduced cardiotoxicity
- Reduced motor blockade

PHARMACODYNAMICS

In general, the mechanism of drug action can be divided into:

- Direct physical and chemical reactions
- Pharmacokinetic actions including mechanisms involving enzymes
- Actions mediated through receptors, including those involving secondary messengers that activate or inhibit enzyme systems

Agonists and Receptors

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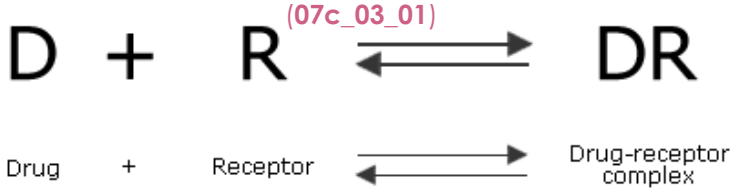


This equation only applies to reversible reactions which are prevalent.

Mass Action

The law of mass action states the rate of a chemical reaction is proportional to the concentrations of the reacting components.

In the above equation, the **forward reaction** is proportional to [D] and [R] and is therefore **proportional to the product of k1[D][R].**

Abbreviation	Definition
D	Drug
R	Receptor
[D]	Concentration of drug
[R]	Concentration of receptor
[DR]	Concentration of drug receptor complex
k1	A constant that defines the rate of the forward (association reaction)
k2	A constant that defines the rate of the backward (dissociation reaction)
KD	The dissociation constant - this defines the equilibrium point of whole reaction

The **backward reaction** is **proportional only to k2[DR].**

$$k_1\,[D][R] = k_2\,[DR]$$

At Equilibrium:

Note, k2 must have different units to k1 as the units must equal either side of the equation.

K_D is the **dissociation constant** and allows comparison for different drug receptor combinations.

K_A is the **affinity constant** and is the reciprocal of K_D i.e. $1/K_D$. This describes the affinity of the drug to its receptor. Known as the **POTENCY**

If the K_A is doubled, then the K_D will be halved.

$$k_1\,[D][R] = k_2\,[DR]$$

Rearrange

$$\frac{k_2}{k_1} = \frac{[D][R]}{[DR]}$$

Substitute one constant for two

$$K_D = \frac{[D][R]}{[DR]}$$

Drug Concentration to Occupancy

$[R_T]$ = Total number of receptors (bound and free ([R] + [DR]))

r = fractional occupancy (i.e. the proportion of drug attached to the receptors)

$$r = \frac{[DR]}{[R_T]}$$

If the K_D is equal to the drug concentration, then the fractional occupancy is 0.5.

Therefore, the Dissociation constant K_D describes the drug concentration at which half of the receptors are occupied i.e. r = 0.5.

This is important as the fractional occupancy determines the response of a drug. We need to relate the fractional occupancy (and hence response) to the drug concentration. The following substitutions allow this specific equation:

$$r = \frac{[DR]}{[R_T]}$$

Substitute for [RT]
[RT] = [R] + [DR]

$$r = \frac{[DR]}{[R] + [DR]}$$

Substitute for [DR] from the relationship
$[DR] = [D][R]/K_D$

$$r = \frac{[DR][R]/K_D}{[R] + [D][R]/K_D}$$

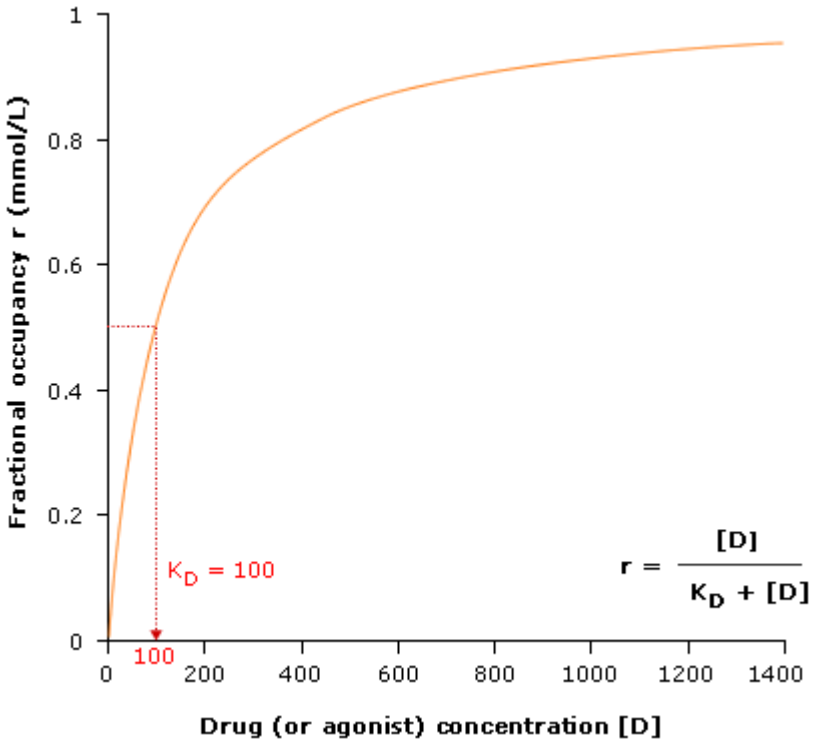
Divide top and bottom elements by [R] and multiply them by K_D

$$r = \frac{[D]}{Kd + [D]}$$

Graphical Representation of affinity

This equation can be plotted graphically as a **hyperbolic curve** and demonstrates how fractional occupancy and hence response varies with concentration of drug.

As the K_D increases, the curve is shifted to the right – i.e. has less affinity.

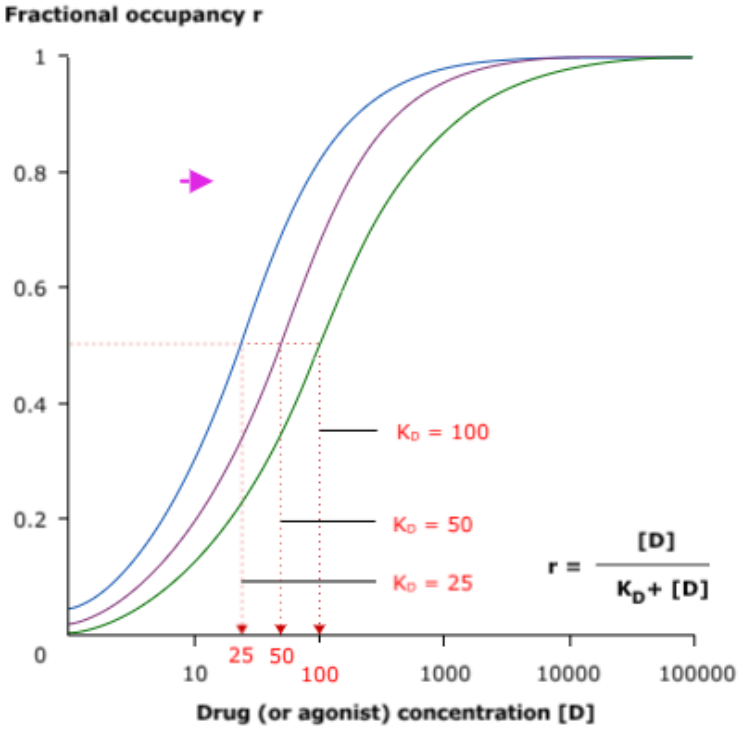


Semi-Logarithmic Plot

The graph above is difficult to compare drugs with different dissociation constants which is represented by the point of r=0.5. Using a logarithmic scale for drug concentration allows improved interpretation of this point. This point is also known as **ED50.**

$$ED50 = K_D$$

Changing K_D shifts the curve to the right if higher and to the left if lower.



Response and Efficacy

The 1st part of this lecture does not consider the effect a drug has once bound to its receptor. The following describes a simple 1:1 drug:receptor relationship.

The **observed response** (**E**) is proportional to the **fractional occupancy** (**r**) and the **intrinsic activity** (or efficacy) (**e**) a drug has to its receptor.

$$E = e\,r$$

Full agonists: Those that provide a maximum response (E) – an intrinsic activity of 1.

Partial agonists: Those that provide a response (E) but not a maximum one i.e. an intrinsic activity between 0 and 1.

If $r = \frac{[D]}{K_D + [D]}$, then

$$E = \frac{e[D]}{K_D + [D]}$$

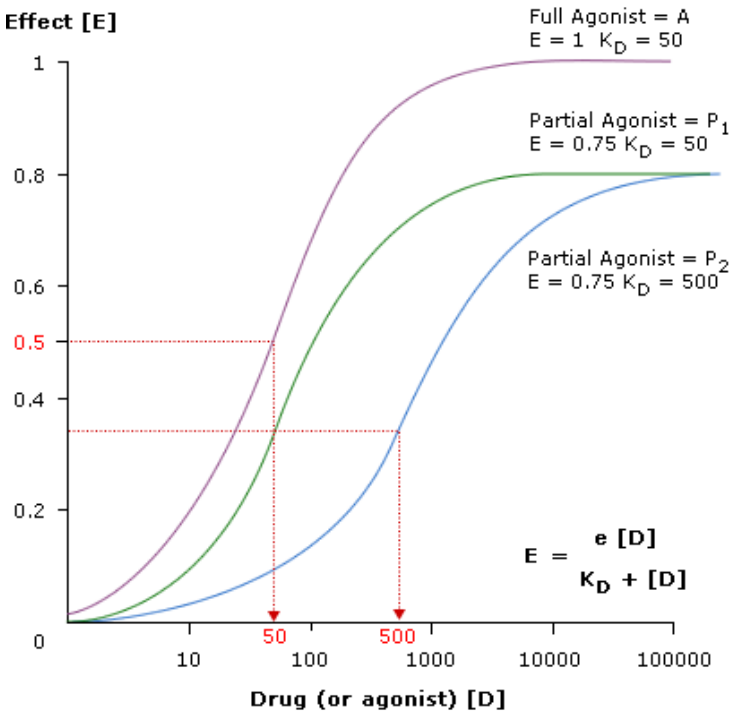
NOTE: This equation can be used in all drug receptor relationships.

The dissociation constant is the concentration of full agonist producing a half-maximal response. (substitute in the above equation).

Partial Agonists

0 < e < 1. The E will therefore be reduced <1 and cause a downward shift of the curve.

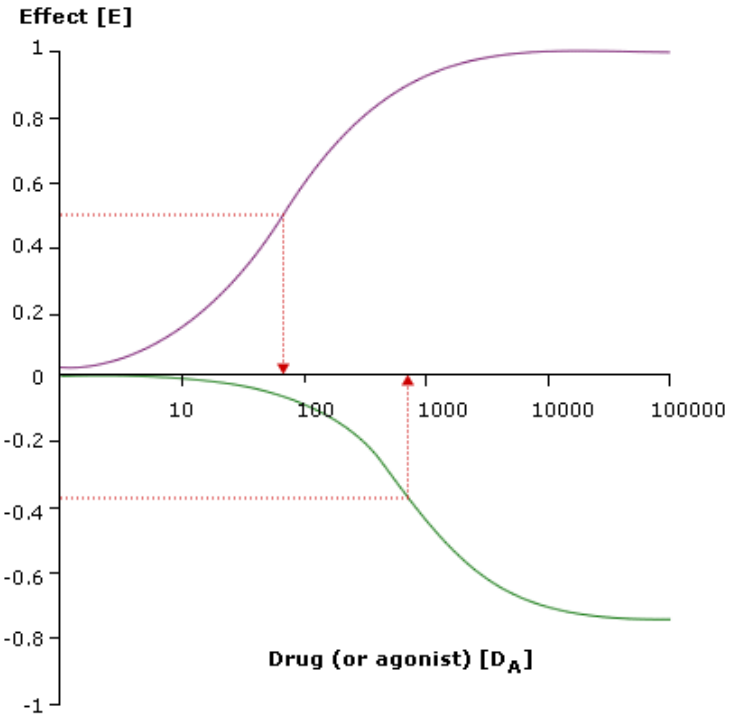
The affinity or the K_A may be lower but not always. If it is, the there will be an additional rightward shift of the curve



Inverse Agonists

0 > e > -1

These exert an **opposite** effect on the receptor. The graph represents a response seen with a full agonist and an inverse agonist with an intrinsic activity of -0.75.



Enzyme Induction and Inhibition

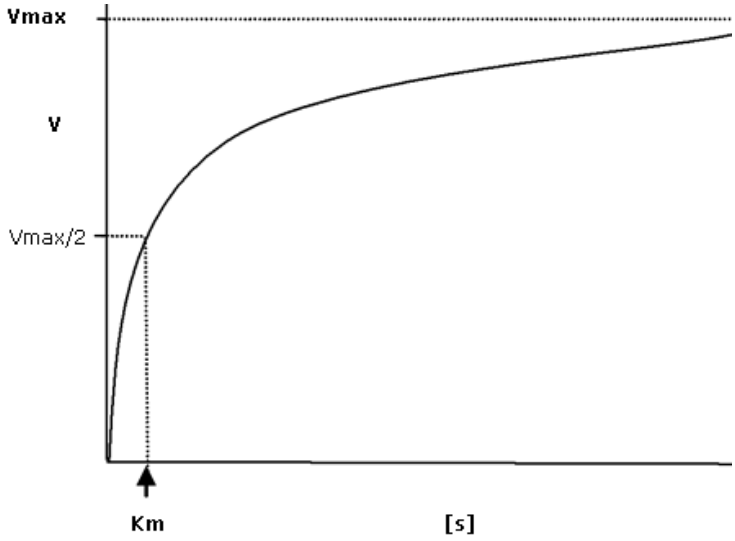
(07c_05_02)

This lecture only deals with drugs that alter enzyme activity.

Enzyme Stimulation

The rate of reaction between an enzyme and substrate depends on the substrate concentration and like the above graphs, it is **hyperbolic**.

Km is the **Michaelis constant** which is the concentration of substrate at which the velocity of the reaction is ½ the Vmax.



Enzyme activity can be altered by either changing substrate and/or enzyme concentration or changing the V_{MAX} and/or Km. The **Michaelis-Menten equation**:

$$V = Vmax\ [S] / (Km + [S])$$

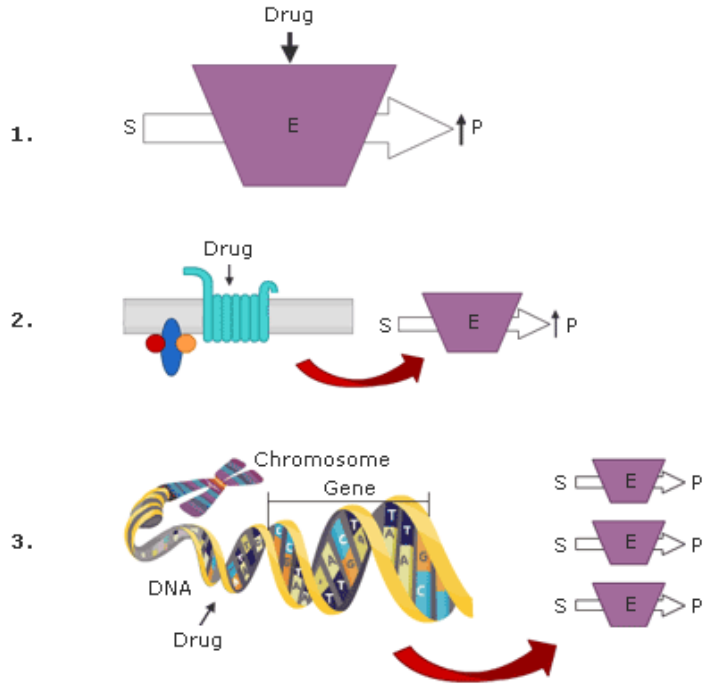
Drugs Increasing Enzyme Activity

Drugs can increase enzyme activity in 3 gross ways:

1. **Direct positive allosteric modulation** (increases Vmax or Km)
    a. i.e. Insulin on Tyrosine Kinase

2. **Indirect increase via intermediate messengers** i.e. G-protein coupled receptors agonists coupled with adenylate cyclase i.e. H2, D1 & b-receptors.

3. Increase in the enzyme concentration (**enzyme induction**). The **CYP450** enzymes are responsible for the metabolism of many drugs and their chronic exposure to their drug substrate will result in increased concentrations and hence more effective clearing of that drug. Some **isoforms** metabolise many different drugs so each drug of that isoform will be affected as a result.



LEARN THIS TABLE of **enzyme inductors**:

CYP1A2	CYP2B6/2C9	CYP2C19	CYP2E1	CYP3A4
Omeprazole	Barbiturates	Rifampicin	Ethanol	Phenytoin
Tobacco	Rifampicin	Prednisolone	Isoniazid	Carbamazepine
		Carbamazepine		Barbiturates
				Rifampicin
				Glucocorticoids

Drug Interactions

Due to enzyme induction, there are a number of important interactions one must know. If the enzyme inducing drug is suddenly stopped, then the effect of the other drug would increase…

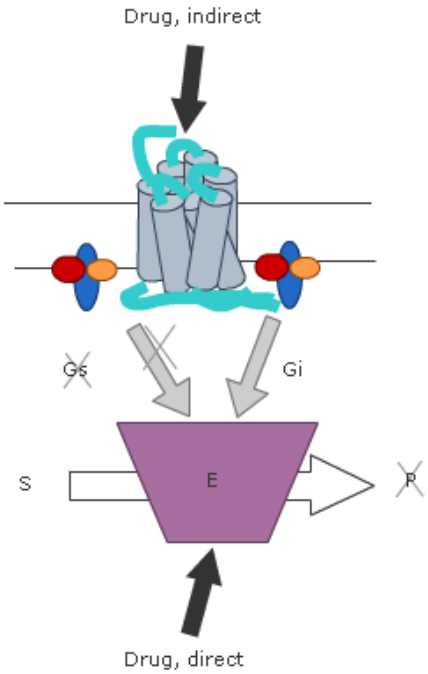
Drug A	Drug B	Effect
Phenytoin	Vecuronium	Reduced duration of neuromuscular blockade
Carbamazepine	Vecuronium	Reduced duration of neuromuscular blockade
Rifampicin	Warfarin	Reduced efficacy of warfarin
Carbamazepine	Warfarin	Reduced efficacy of warfarin
Rifampicin	Ciclosporin	Reduced efficacy of ciclosporin
Barbiturates	Corticosteroids	Reduced efficacy of corticosteroids

Drugs Reducing Enzyme Activity

Drugs can reduce enzyme activity in 2 ways:

1. **Direct inhibition** of the enzyme via reduction in Km or Vmax.
2. **Indirect** decrease in enzyme activity via **intermediary messengers.**

Enzyme inhibition can be classified as either **reversible** or **irreversible**.



Reversible

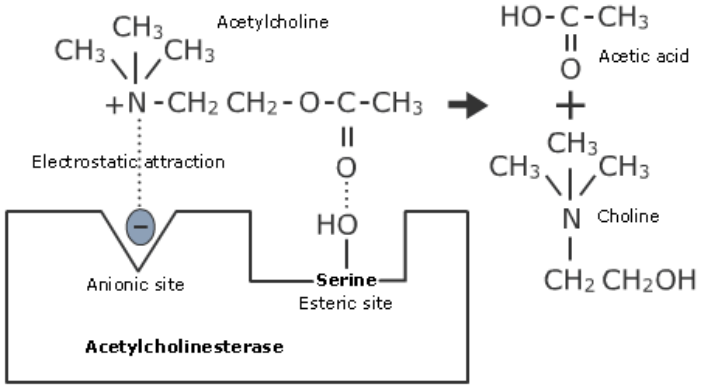
Aka **competitive antagonism**. The degree of enzyme inhibition depends upon plasma concentration of inhibitor compared to the natural agonist.

- Neostigmine – acetylcholinesterase inhibitor
- Ramipril – ACE inhibitor
- Milrinone – phosphodiesterase 3 inhibitor
- NSAIDs – COX inhibitor

Acetylcholinesterase Inhibitors

AChE is responsible for the ester hydrolysis of acetylcholine at the NMJ. It contains an:

- **Anionic site** i.e. negatively charged attracting a positive quaternary ammonium ion
- **Esteric site** involved in ester hydrolysis to form choline and acetic acid.



There are 3 different examples of inhibitors. These include:

1. **Pyridostigmine** and **Neostigmine**: These are substrates that bind to both sites of AChE
2. **Edrophonium:** Binds only to the anionic site i.e. not a normal substrate.
3. **Organophosphates:** Irreversible inhibitors of AChE

Reversible Inhibitors

The reversible inhibitors (1 and 2) are further divided into 2 groups:

1. Enzyme CARBAMYLATORS

a. **Neostigmine**
b. **Pyridostigmine**
c. **Physostigmine**

> The carbamylated enzyme (rather than the acetylated enzyme) reacts with water more slowly reducing the rate of ACh breakdown allowing its build up in the cleft.

These therefore allow an increase in the concentration of ACh and subsequent reversal of the competitive non-depolarising nAChR antagonists.

2. Anionic site competitive inhibitors

a. **Edrophonium**

Short acting competitive inhibitors and are used for diagnostic purposes.

NOTE: Those with myasthenia gravis will be taking pyridostigmine and will be relatively insensitive to succinylcholine but will be very sensitive to non-depolarising muscular blockers.

Irreversible Inhibitors

Organophosphates i.e. parathion interact with the esteratic site to phosphorylate AChE. The drug-enzyme complex becomes '**aged**' with time and inhibition becomes irreversible.

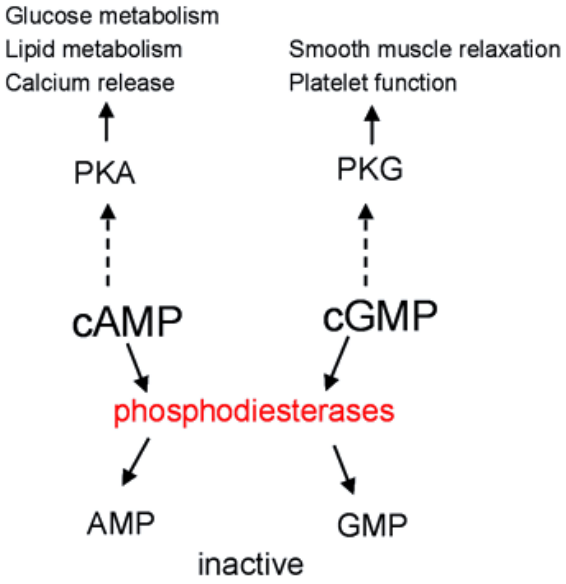
The **phosphorylated AChE** reacts extremely slowly with water allowing ACh concentrations to rise in all sites centrally and peripherally. This is characterised by a cholinergic crisis involving salivation, abdominal pain, weakness and bradycardia.

Pralidoxime can be used before 'ageing' occurs within 36-48 hours to reverse the complex more rapidly. It does this by **displacing phosphate** from the esteratic site and remains bound for a time until the poison can be eliminated. **Oximes** are then given to allow the enzyme to recover.

Without any treatment, recovery depends on the synthesis of new AChE.

Phosphodiesterase Inhibitors

Phosphodiesterases (PDE) are responsible for **degradation of the phosphodiester bond** in second messenger molecules **cGMP** and **cAMP** rendering them inactive.



Non-Selective i.e. **Aminophylline** and **theophylline**

Inhibition of PDE in many tissues. Mainly **bronchial smooth muscle**. It may also cause:

- Vasodilation
- Inhibition of platelet aggregation
- Positive inotropy

Selective

Enoximone and **milrinone** selectively inhibit **PDE-III** and are structurally similar to cAMP. PDE-III is predominantly located in the heart producing a **positive inotropic effect**.

Dipyridamole and **sildenafil** both inhibit **PDE-V** which **inhibits platelet aggregation** and treats (**pulmonary HTN** and **erectile dysfunction**) respectively.

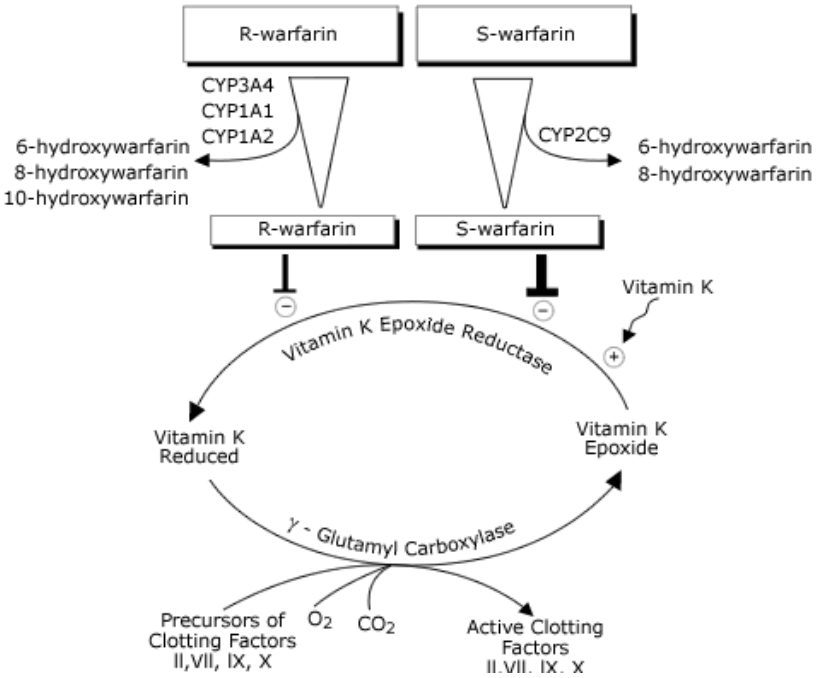
Warfarin

This is a **racaemic** mixture.

II, VII, IX and X require vitamin K as a co-factor. **Vitamin K** is usually recycled through the actions of **Vitamin K epoxide Reductase (VKOR)**. Warfarin inhibits VKOR to prevent the regeneration of active vitamin K.

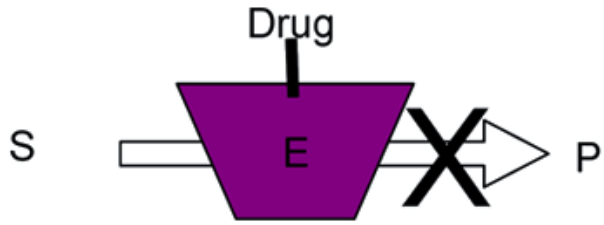
S-enantiomer is more potent at VKOR inhibition and **CYP2C9** is responsible for S-warfarin metabolism which is subject to genetic variation.

VKOR genetic variants exist also.



Irreversible

These drugs have a long duration of action as they require the re-synthesis of an enzyme before normal activity can be retained i.e. organophosphates. Other examples include:



- **Aspirin** acetylation of COX in platelets. Duration of a platelet life-span = 5-10 days
- **Phenelzine** and **tranylcypromine** are both non-selective MAO inhibitors.

SUMMARY OF DRUGS WORKING BY ENZYME INHIBITION

Name of drug /drugs	Inhibited enzyme/enzymes
Allopurinol	Xanthine oxidase
Aminophylline, enoximone and milrinone	Phosphodiesterases
Aspirin and NSAIDs	Cyclooxygenase
Captopril, enalapril and lisinopril	Angiotensin converting enzyme
Methyldopa	Dopa decarboxylase
Edrophonium, neostigmine, pyridostigmine, organophosphates	Acetylcholinesterase and plasma cholinesterase
Benzyl penicillin	Bacterial wall peptidase
Moclobemide, phenelzine, tranylcypromine and selegiline	Monoamine oxidase

CYP450 Enzyme Inhibition

CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Fluvoxamine	Fluconazole	Lansoprazole	Fluoxetine	Clarithromycin
	Amiodarone	Omeprazole	Paroxetine	Grapefruit juice
			Quinidine	Ketoconazole
			Ketoconazole	Verapamil

Unlike induction, inhibition does not involve DNA transcription.

Examples of interaction include the following:

Drug A	Drug B	Effect
Verapamil	Beta-blockers	Severe bradycardia, asystole, hypotension
Amiodarone	Warfarin	Risk of haemorrhagic complications
Diltiazem	Beta-blockers	Risk of AV block and bradycardia
Grapefruit juice	Ciclosporin	Risk of toxicity with ciclosporin
Paroxetine	NSAIDs	Increased risk of bleeding
Clarithromycin	Terfenidine	Torsades-de-points
Ketoconazole	Buprenorphine	Increased plasma levels of buprenorphine

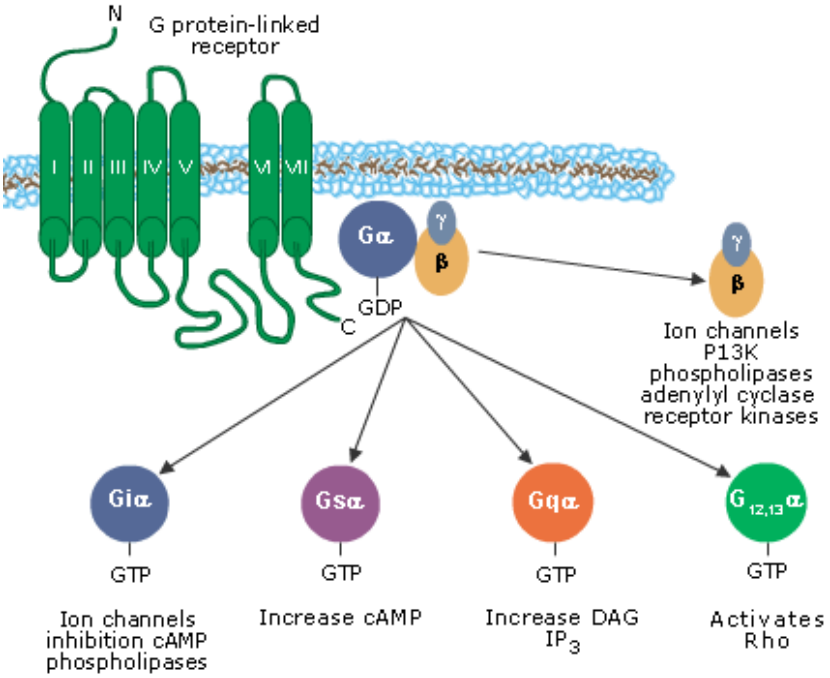
If one adds amiodarone to a patient on warfarin, there is a risk of increasing haemorrhagic complications. This is because warfarin (as mentioned above) is metabolised by CYP2C9.

INDIRECT ENZYME INHIBITION

Indirect inhibition of enzymes can arise through a reduction in Km, Vmax or both through the actions of intermediary messengers. These may act as **agonists through Gi coupled receptors** to increase cAMP; as an example:

- α2 agonism with clonidine
- mu receptors with opioids.

Inhibition of Gs receptors will also reduce the cAMP concentrations i.e. beta blockers.



Enzymes as Drugs

Streptokinase, urokinase and **alteplase** may be used as a fibrinolytics to convert plasminogen to plasmin which degrades fibrin.

Hyaluronidase breaks down hyaluronic acid which is involved in structure of tissues and is added to LA to promote diffusion in ophthalmic regional blocks.

Unwanted Drug Effects

(07c_06_01)

Defined as ***"Any noxious or unintended reaction to a drug that has been given at a standard dose by an approved route for the prevention, treatment or diagnosis of a condition"***

These adverse drug reactions (ADRs) can be divided in the following 3 ways:

1. Reactions that can occur in ANYONE

Drug Overdose: Excess dosing, impaired excretion or both i.e. gentamicin use in renal failure or prescription error with insulin.

Drug Side-effect: An undesirable pharmacological effect that happens at recommended doses i.e. constipation with codeine

Drug Interaction: See the following module for further details.

2. Reactions that occur only in SUSCEPTIBLE individuals

Drug Intolerance: Low threshold to the normal pharmacological action of a drug

Drug Idiosyncrasy: Genetically determined, qualitatively abnormal reaction to a drug related to a metabolic or enzyme deficiency i.e. suxamethonium apnoea, CYP2D6 deficiency, G6PD deficiency etc

3. Reactions due to ALLERGIES

Drug allergy: Immunologically mediated reaction to a drug. **Pseudoallergies** have similar clinical manifestations to a true allergy due to histaminic release but is not immunologically mediated i.e. NSAIDs and Aspirin.

Classification of ADRs

The classical method of classification is the following:

Extended Type A and B Classification

	Mnemonic	Example	Type
A	*Augmented*	Propofol and hypotension	**DOSE-RELATED**
B	*Bizarre*	Anaphylaxis	**DOSE-UNRELATED**
C	*Chronic*	Propofol Infusion Syndrome	**DOSE & TIME**
D	*Delayed*	Fluoride Nephrotoicity	**TIME RELATED**
E	*End-of-use*	On withdrawal i.e. rebound HTN with clonidine	**WITHDRAWAL**
F	*Failure*	Oral contraceptive pill	**UNEXPECTED FAILURE**

This is a simple classification but sometimes ADRs fall into more than one type i.e. erythromycin and nausea and vomiting is both type A and B as is not pharmacologically predictable.

DoTS Classification

This is based on 3 types of reactions and overcomes barriers of the Type A→F classification:

1. **Dose Relatedness**
    a. ADRs at subtherapeutic doses i.e. toxic effects
    b. ADRs at therapeutic doses i.e. collateral effects
    c. ADRs at subtherapeutic doses in susceptible patients
2. **Time Relatedness**
    a. ***Rapid reactions*** (administered too quickly)
    b. ***First dose reactions*** that don't necessarily recur i.e. hypotension with ACEi
    c. ***Early reactions*** that abate due to tolerance i.e. nitrate induced headache
    d. ***Intermediate reactions*** occurring after some delay (Coombs type II→IV)
    e. ***Late reactions*** where risk increases with continued or repeated exposure. Withdrawal reactions are also classified as late reactions
    f. ***Delayed reactions*** sometime after exposure i.e. carcinogenesis.
3. **Susceptibility** including genetic variation, age, sex, physiological variation, exogenous factors and disease. These can all co-exist. i.e. anaphylaxis due to penicillin.

There is also an immunological classification by Coombs types I→IV which is covered in the '*Allergy and Inflammatory Response'* module in the physiology notes.

Drug Interactions

(07c_06_03)

These can be broadly characterised into:

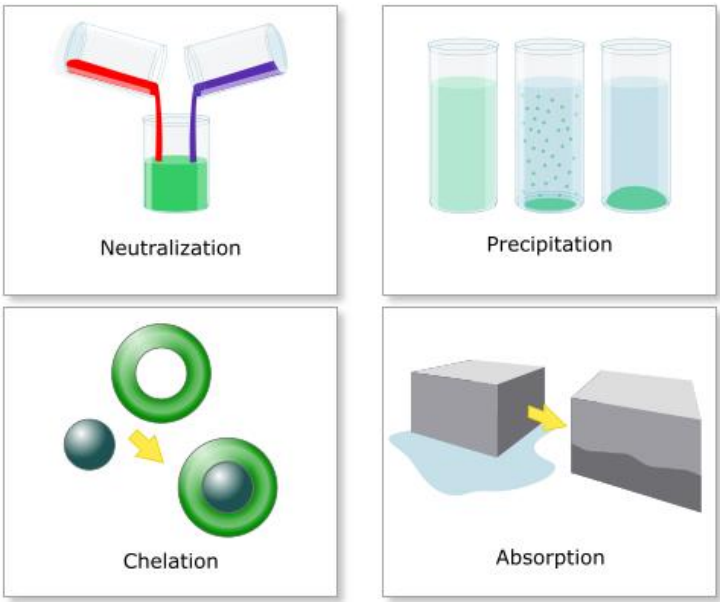
1. **Pharmacodynamic interactions**
2. **Pharmacokinetic interactions**
3. **Pharmaceutical incompatibility**

There are also type 1 or type 2 reactions.

Pharmaceutical Incompatibility

This is the situation where 2 drugs are physically or chemically incompatible and can occur inside or outside the body.

- **Neutralisation**
  - Heparin and protamine
- **Precipitation**
  - Thiopentone and suxamethonium
- **Chelation**
  - Sugammadex and rocuronium
  - Penicillamine and copper
  - Citrate and Calcium
- **Absorption**
  - Halothane into rubber



Pharmacokinetic Interactions

Absorption: i.e. charcoal and poisoning; prokinetics (metoclopramide); muscarinic antagonists (reduced kinetics); LA with adrenaline; second gas effect

Distribution: With any drug that alters cardiac output i.e. b-blockers slow the onset of action of succinylcholine. Competition with binding sites i.e. amiodarone and warfarin in protein binding

Metabolism: Many examples. One includes: those with a high hepatic extraction ratio will be flow dependent and an increased flow will increase clearance i.e. with lidocaine.

Elimination: e.g. doxapram increases minute ventilation and elimination of volatile agents

Pharmacodynamic Interactions

Pharmacodynamic interactions can be described as interactions where one drug alters the sensitivity of tissues to another drug, either by having an agonistic (same) effect or an antagonistic (blocking) effect.

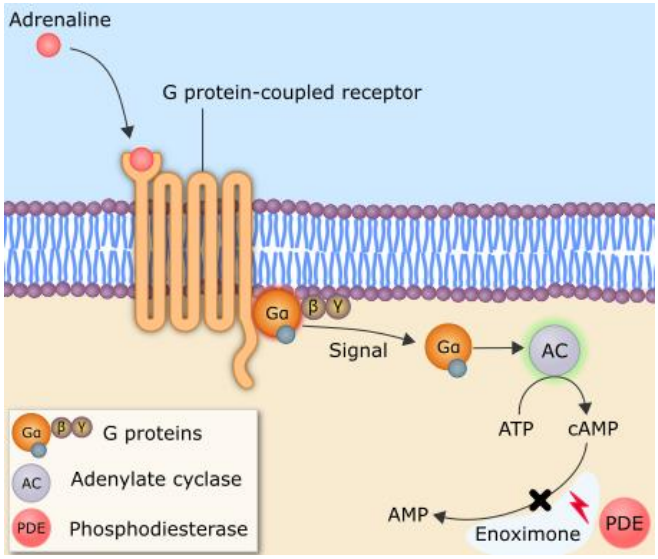
- **Summation** – drugs are additive in effect
  - Benzodiazepines and propofol
  - N_2O and volatile agents
- **Synergism –** the effect of 2 drugs together is greater than what would expect if only additive
  - Clonidine and opioids
  - Remifentanil and propofol
- **Potentiation –** One drug increases the effect of another
  - Potentiation of Non-Depolarising NMBs with magnesium
  - Probenacid prevents renal excretion of penicillin
- **Antagonism –** Opposing effects of drugs
  - Flumazenil with benzodiazepines
  - Neostigmine and non-depolarising NMBs.

Pharmacodynamic interactions can be **direct** or **indirect.** For example:

Direct interaction	Indirect interaction
Flumazenil reversing the effect of benzodiazepines	Neostigmine for reversal of nondepolarizing muscle relaxants
Morphine and naloxone	Adrenaline and enoximone

Enoximone inhibits PDE III which (as well as adrenaline) increases the levels of cAMP.

Adrenaline achieves this by binding to G-protein receptors.



Electrolyte Interactions

- **Hypokalaemia:** Increases cardiac excitability and lowers the arrhythmia threshold. Diuretics, corticosteroids and insulin.
- **Hyperkalaemia:** Reduced cardiac automaticity, suxamethonium, potassium sparing diuretics, ACEi.
- **Hyponatraemia:** Potentiates local anaesthetics. Diuretics and sulphonylureas
- **Hypernatraemia:** Mannitol, sodium bicarbonate, hypertonic saline
- **Hypomagnesaemia:** Cardiac arrhythmias – diuretics and laxatives
- **Hypermagnesaemia:** prolonged NMB, hypotension and other effects.

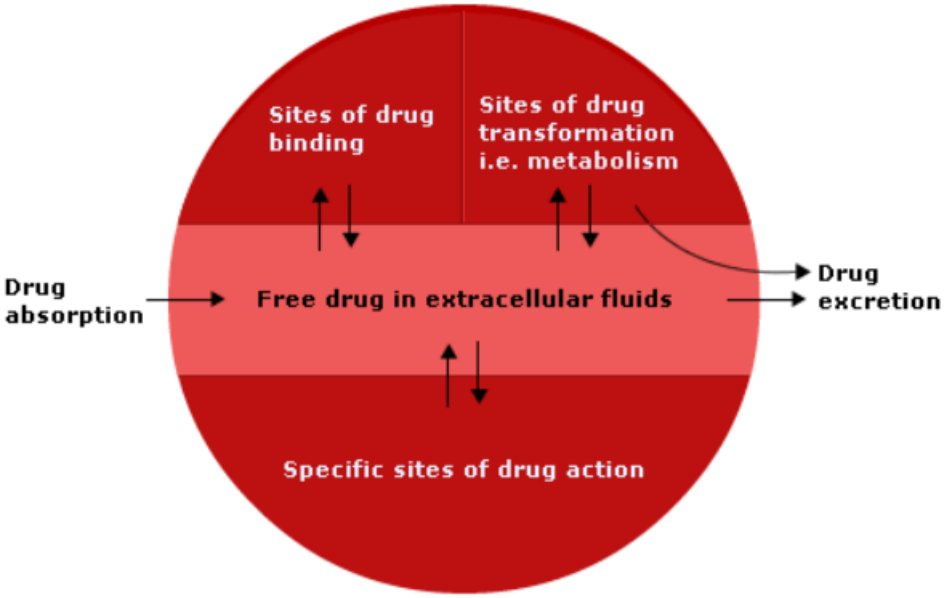
Herbal Medications

There are a number of herbal medications that can do many things. These include:

Substance	Proposed benefits	Pharmacological effects	Periop considerations
Echinacea	Improve immune system	Modulates cytokines Stimulates macrophages and NK cells	Avoid known hepatotoxic drugs i.e. amiodarone, methotrexate, halothane
Ephedra	CNS stimulant Weight loss Asthma treatment	Sympathomimetic	Caution with other sympathomimetics. LT use may deplete catecholamine stores causing tachyphylaxis to other sympathomimetic drugs. Arrhythmia with halothane
Garlic	Treatment of hypertension, hyperlipidaemia, atherosclerosis	Antiplatelet effects	Risk of bleeding Caution with aspirin and NSAIDs.
Ginger	Anti inflammatory and antiemetic	Inhibit serotonergic pathways Stimulate GI tract	Risk of bleeding Caution with NSAIDs and warfarin
Ginkgo biloba	Neuroprotective Improved blood flow	Free radical scavenger Antiplatelet effects	Risk of bleeding Avoided with NSAIDs, aspirin and warfarin
Ginseng	Mood enhancer Aphrodisiac	Sympathomimetic	Risk of bleeding (NSAIDs and warfarin) Hypoglycaemic effect Action with other sympathomimetic
St. John's Wort	Antidepressant	Inhibits MAOIs Induces **CYP3A4 and CYP2C9**	Serotonergic crisis Sedative effect Reduces the effect of midazolam, alfentanil, lidocaine, warfarin and NSAIDs.
Valerian	Anxiolytics Hypnotic	Potentate GABA-ergic system	Reduced anaesthetic requirements

PHARMACOKINETICS

What does the body do to the drug?



Absorption and Bioavailability

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Absorption

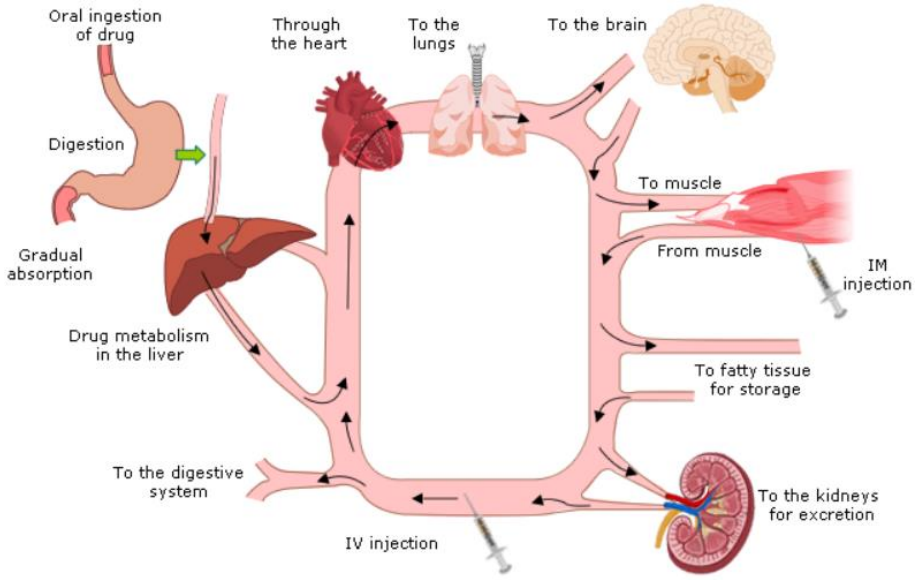
"The movement of a drug from its site of administration into the plasma". Note that this is not necessary for all drugs to work i.e. topical emollients for dermatological conditions, bronchodilators for asthma etc. **Factors** that determine absorption includes:

1. **Drug Formulation** – how is it presented?
2. **Route of Administration**
3. **Physiochemical properties** i.e. solubility, ionisation (pKa) and partition coefficients.
4. **Local blood flow**

Routes of Administration

The main routes of administration include:

- Oral
- Sublingual
- Rectal
- Topical
- Inhalation
- Parenteral:
  - Intravenous
  - Intramuscular
  - Subcutaneous
  - Neuraxial

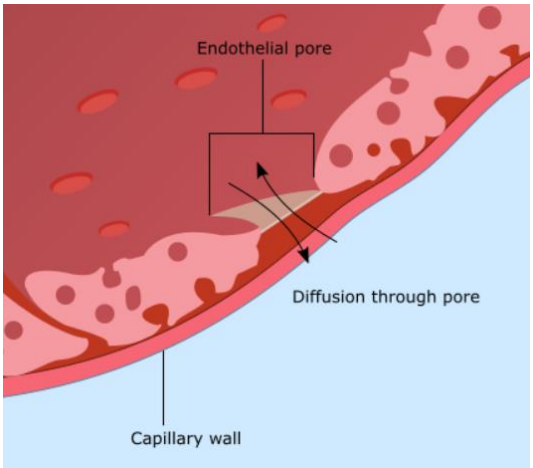


Note that with the ***IV*** Route, by definition, absorption is complete and none is lost (100% bioavailability). This will pass through the lungs prior to reaching the systemic arterial circulation.

Movement Across Barriers

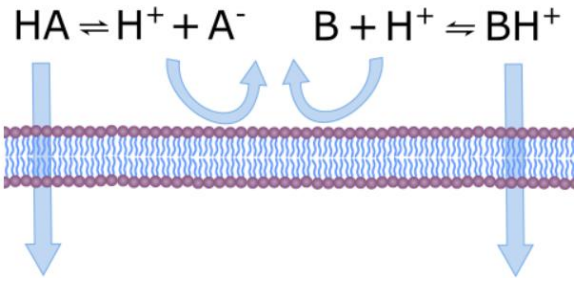
Cell membranes from the barrier between aqueous compartments in the body. The basic structure of the cell membrane and mechanisms of transport across membranes is covered in the general physiology, "*Cell Membrane Characteristics and Receptors*" module.

In order to be absorbed, drugs need to pass through the cell membranes from its route of administration i.e. the GIT. Certain membranes are generally more permeable than others i.e. glomerulus>BBB capillaries and have pores to allow free passage of molecules:



*Effect of **pK_a** and **pH***

These, as well as whether the drug is an **acid or a base**, determine the **degree of ionisation** of a molecule.



The **ionised** component has **hydrophilic** characteristics and hence is **virtually unable to cross membranes**.

The **unionised** component is **lipophilic** and therefore is **able to cross cell membranes**.

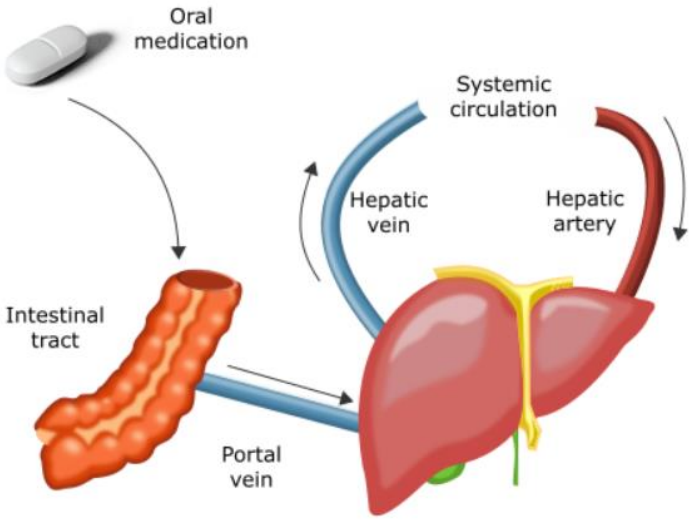
See the ionisation module in this note-set for further information

GIT Absorption

The factors contributing to GIT absorption includes:

- Gut motility
- Local pH
- Size of the drug molecule
- Physicochemical interactions with GIT contents
- The process of first-pass metabolism

First-pass Metabolism is also known as 'pre-systemic metabolism. This is where an orally administered drug is metabolised by the liver via the **portal system** prior to reaching the systemic circulation.



Other routes i.e. IM can avoid first-pass metabolism as they allow direct absorption into the systemic circulation.

Drugs with high first-pass metabolism include:

- Morphine
- Midazolam
- Lidocaine
- Aspirin
- GTN

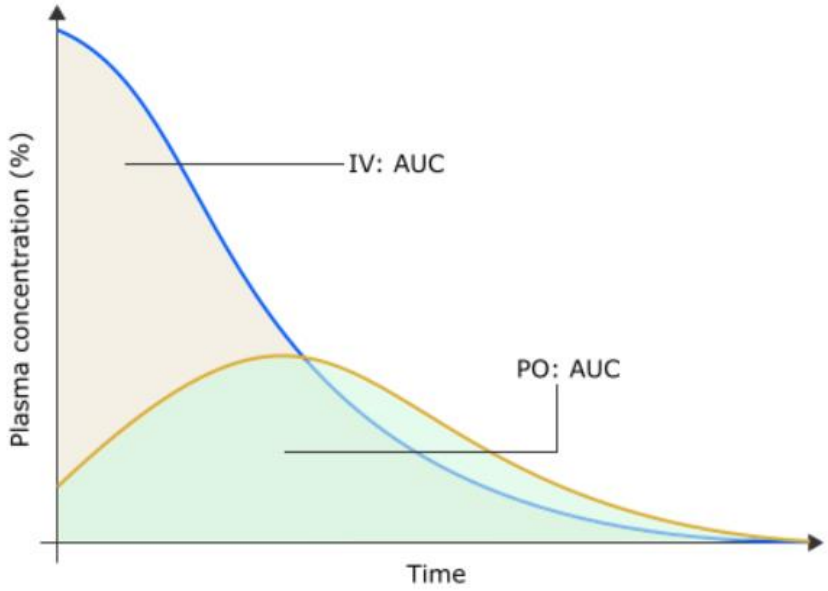
Bioavailability (BA)

"The fraction (F) of an administered drug that reaches the systemic circulation intact and is therefore available to act at the site of action"

By definition, BA following an IV dose is 100%. Any other route, the BA will reduce due to factors affecting the absorption process.

Assessing BA requires calculation of the area under a curve (AUC) which describes blood drug concentration versus time following administration via a defined route and comparing this to the AUC of the same drug given IV.

BA (F) = AUC (PO) / AUC (IV)



Absolute vs Relative

ABSOLUTE BA is what is usually understood by the term bioavailability as shown in the equation above (comparison with an intravenously administered version of the same drug)

RELATIVE BA is calculated for drugs that are **unable to be administered IV**. It refers to the amount of a drug of a specific formulation which reaches the systemic circulation, compared to that of the same drug given by the same route but in a different formulation (the reference standard). For example, capsule vs tablet.

Inhalational Drug Administration

(07c_07_03)

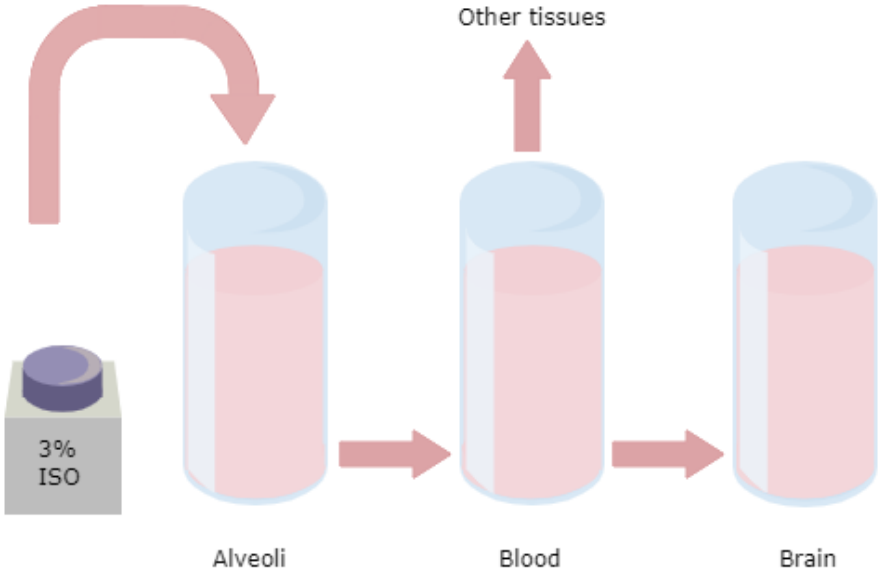
Inhalational agents exist in 3 compartments:

- Alveoli - P_A
- Blood - P_a
- Brain - P_B

Partial pressure is the pressure exerted by a gas in a mixture of gases if it occupied the container alone (Dalton's law of partial

Initially on inhalation, the **PA > Pa > PB** down the pressure gradient. After a period of time, the gradients equalise in the 3 compartments where PA = Pa = PB. This may take many hours to achieve in practice.

For an effect, the drug must exert its partial pressure in the CNS. The driving pressure therefore depends on the PA and **if the concentration is reduced, then the transfer of agent into the brain will also be reduced.**



Initial Maintenance

When initially turning on a gas agent, there will be an end tidal measurement (P_A) of a gas that will not reflect the Pa or the PB and therefore, the MAC will be inaccurate. To overcome this, the way to rapidly increase the amount of anaesthetic in the CNS is through **overpressure**.

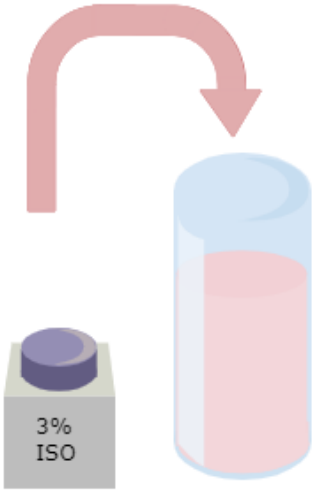
Overpressure

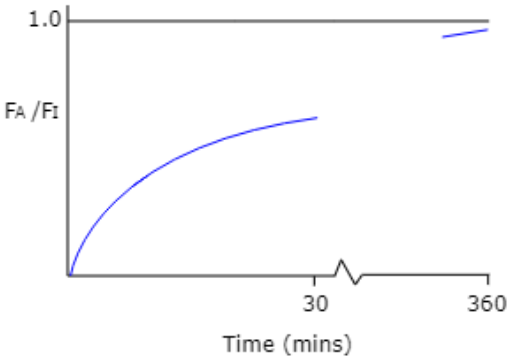
A high inspired concentration of agent is delivered more than what is required for anaesthesia in order to increase the partial pressure gradient driving the agent to the brain and reach the desired PB more quickly.

Onset-Time

The rate of rise at which the alveolar concentration is reached is represented by the **WASH-IN CURVE.** This is the F_A/F_I ratio where 1 is equal to equilibrium.

This is a **negative exponential function** because the rate at which equilibrium is reached decreases with time.



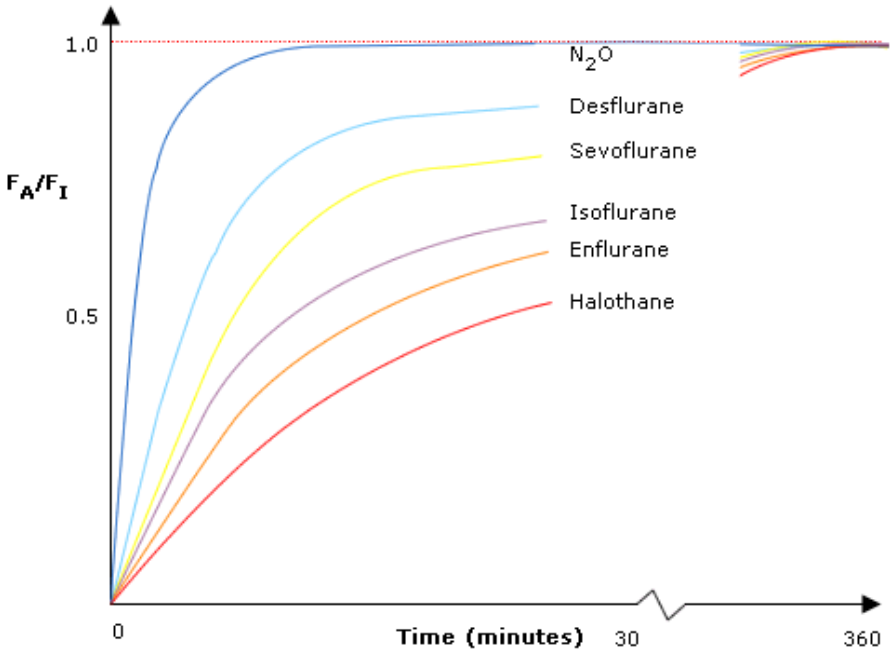


These are the wash in curves of the agents:

The most important factor for this is the

BLOOD: GAS PARTITION COEFFICIENT (B:GPC)

There are also many other factors which will all be discussed now:

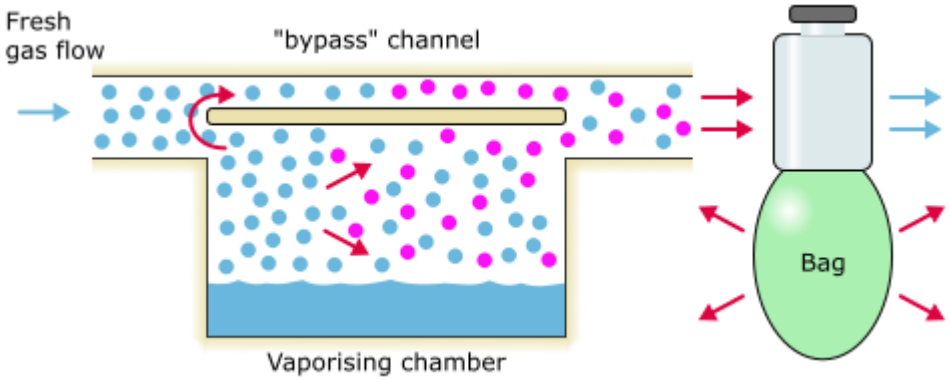


Equipment

The **higher the dialled-up concentration** the higher the concentration will be delivered. This may not actually match the actual concentration delivered because of:

1. **Dilution** with other gases in the circuit – especially in circle systems
2. Volatile **absorption** by CO_2 absorbers, plastic and rubber components.

The **pumping effect** is a method in IPPV which can increase the volatile agent delivered through a reduction in dilution due to back pressure:



- Pressure increases (insp) → gas in back bar moves back into the vaporiser via the **bypass channel**
- Pressure falls → gas in vaporiser moves into the back bar to mix with the gases in the circuit
- Increased concentration in the fresh gas to be delivered. This is much more effective in low gas flows (less dilution).

Its effect can be minimised by:

1. Placing a **non-return valve** downstream of the bypass channel,
2. **Increasing resistance** to flow in the vaporiser and bypass channel
3. **Minimising the volume** of the **vaporiser chamber** or increasing the length of the gas conduit leaving the vaporiser

Patient Physiology

Minute ventilation (Vm): The **higher the minute ventilation** is, the more rapidly equilibrium will be reached (faster wash in curve).

Cardiac output: The **LOWER** it is, the **FASTER the F_A/F_I ratio will be reached**. This is because:

1. There is a **slower transfer of anaesthetic agent into the blood** from the alveoli resulting in a higher alveolar concentration. In contrast, high cardiac output states result in a faster delivery of agent to the tissues and hence increases the speed of blood:compartment equilibration but also increases the uptake from the alveoli and prevents the increase in P_A. Remember, it is the higher pressures that results in faster onset.
2. In low cardiac output states, a higher proportion of the effective blood circulation volume will travel to the brain with the anaesthetic agent.

Functional Residual Capacity (FRC): A high FRC results in greater **dilution** of the agent. Therefore, there is an **increased P_A with a smaller FRC**.

Cerebral blood flow: The higher it is, the more agent is delivered over unit time. Hypercapnia increases CBF (as well as causing hyperventilation). Volatile agents also increase CBF and hence ICP. A concentration of 1 MAC is usually safe. N_2O is best avoided.

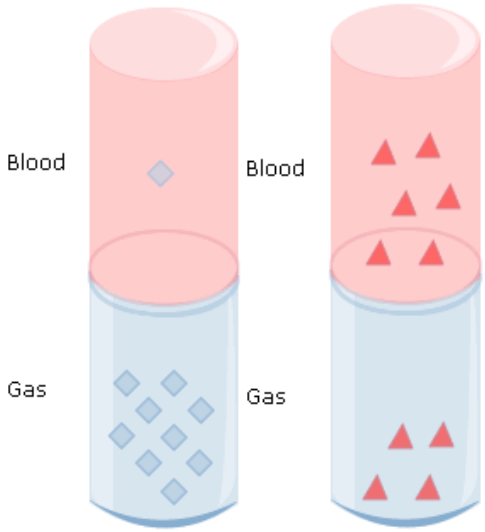
Physiochemical properties of the Volatile Agents

POTENCY: This is the pharmacodynamic property of a drug that reflects how much drug is required to produce an effect. In volatiles, potency is reflected by MAC and dependent on oil:gas partition coefficient (lipid solubility).

Those factors that affect speed of onset (not reflected by higher potency) are solubility in the blood and hence blood:gas partition coefficient.

Partition Coefficients

These reflect the **relative solubility** of a substance in 2 separate compartments of the same volume, temperature and at equilibrium.

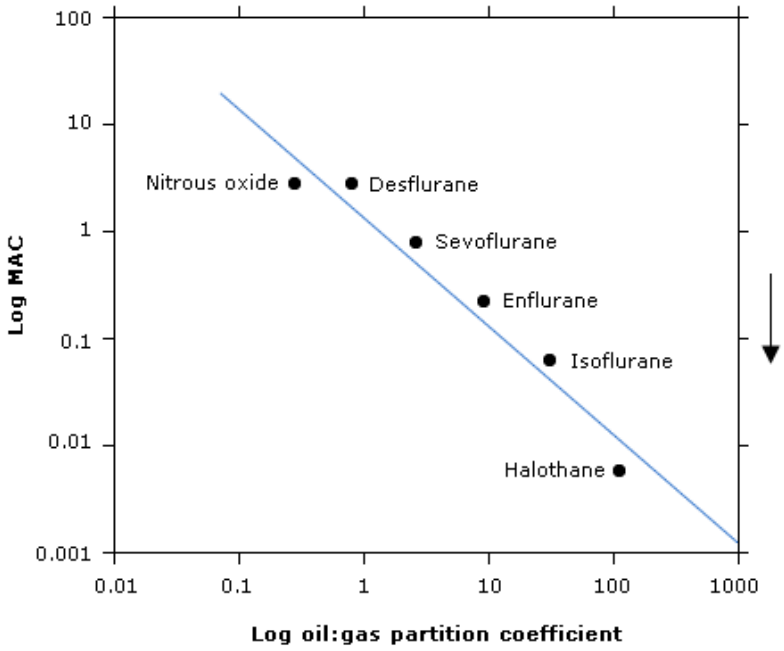


Blood:gas partition coefficient

Is the solubility of an agent in blood relative to the partial pressure it exerts in its gaseous phase. The **lower the B:G PC, the lower the relative solubility in the blood** and the **faster onset and offset time** it will have. The agent on the left diagram has the lower B:G PC.

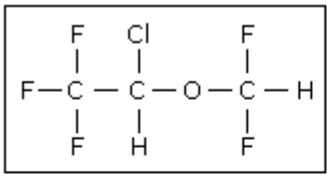
Oil:Gas Partition Coefficient

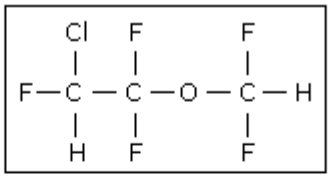
Aka the **Meyer-Overton hypothesis** which reflects the fact that anaesthetic agents must cross the BBB.

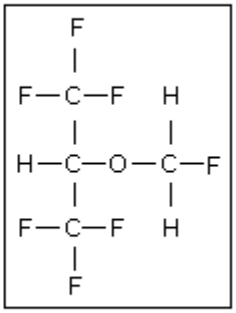


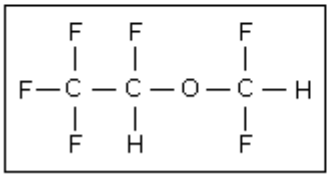
Chemistry

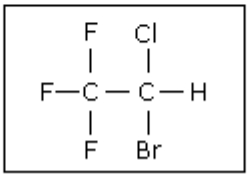
It is the chemical structures of agents that determine their physicochemical properties such as partition coefficients and SVP and boiling points.


Isoflurane


Enflurane


Sevoflurane


Desflurane


Halothane

All are ethers EXCEPT halothane. Ethers are larger molecules and **less lipid soluble**, hence halothane has the highest oil:gas partition coefficient.

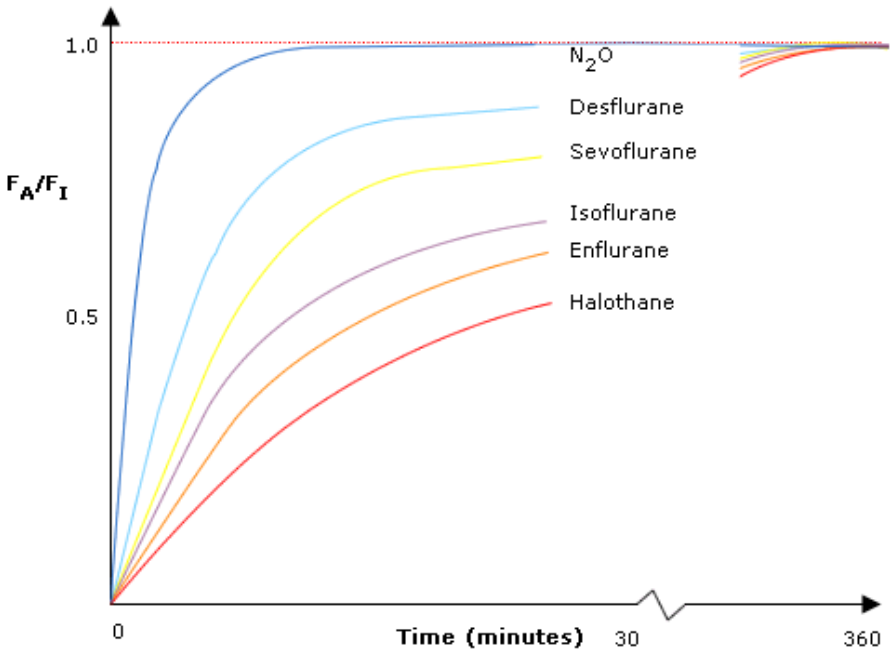
Ethers are also **less water soluble** as they do not polarise. As the C-F bond has a higher difference in electronegativity than i.e. C-Cl, (see 2nd module), desflurane is the most resistant to metabolism.

Although isoflurane and enflurane are structural isomers, the position of the C-F bond in isoflurane makes it less water soluble and more resistant to metabolism than enflurane

Physicochemical property	Halothane	Enflurane	Isoflurane	Sevoflurane	N_2O	Desflurane
B:G PC @ 37°C	2.4	1.9	1.4	0.69	0.47	0.42
O:G PC	224	98	91	53	1.4	19
SVP (20°C)	32.5	23	32	21.3		88.5
BP	50	56.5	48.5	59	-89	23
MAC	0.75	1.68	1.15	2.0	104	6.0

Nitrous Oxide

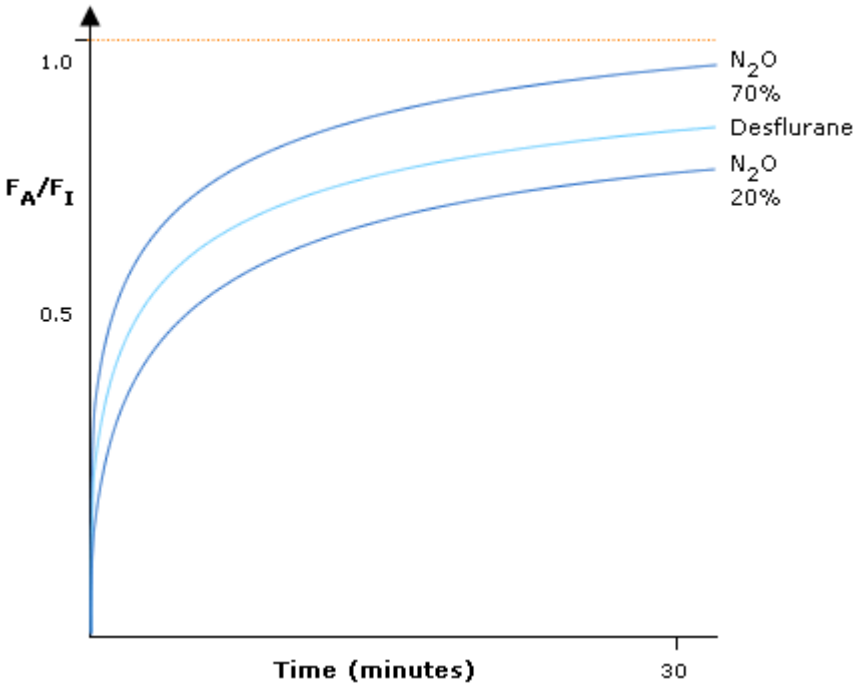
Although this has a higher B:G PC than desflurane, it has a faster onset than desflurane which can be explained by the following:



Concentration Effect

This is the tendency for alveolar concentration to rise towards equilibrium of FA/FI ratio more rapidly with higher concentrations of an inhaled agent.

This only applied to N_2O as it is the only agent to be used in sufficiently high concentrations to produce this effect.

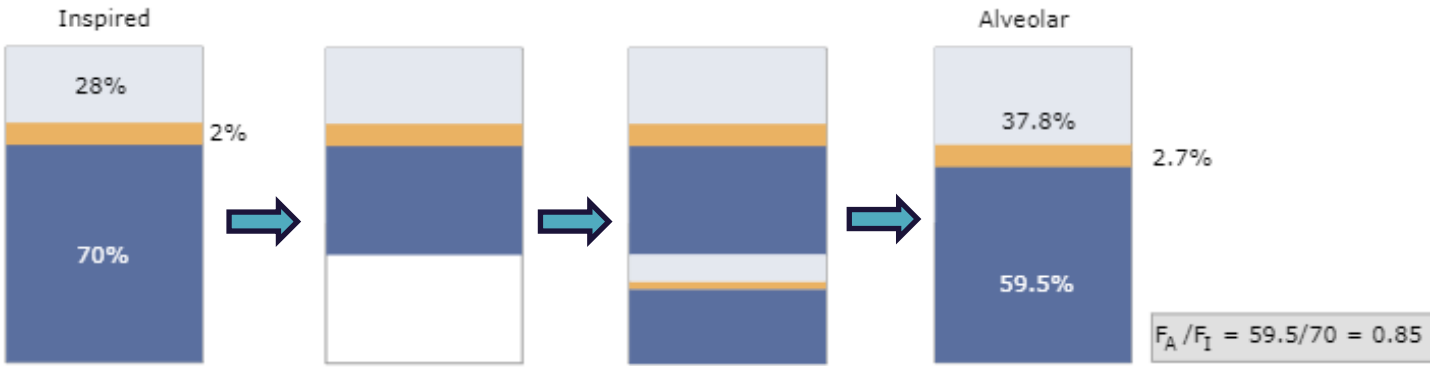


WHY?

N_2O is 20 times more soluble in the blood than nitrogen

This means that **N_2O leaves the alveoli into the blood** rapidly in comparison to N_2 entering the alveoli from the blood. This means that **fresh gas flow comes from the upper airways** in order to replace what is lost in the alveoli (otherwise they will collapse) – **Augmented Ventilation**

Consider the following diagram representing the **SECOND GAS EFFECT**:



Initially, the F_iN_2O is 70%. This diffuses 50:50 into the blood. The same fractional inspiration of the gases replaces the 35% of 'no gas in alveoli space'. This results in increasing amounts of other gases in the mixture running alongside N_2O i.e. if Sevoflurane – results in a faster FA/FI ratio and hence faster induction.

DIFFUSION HYPOXIA: This is the opposite of the second gas effect. N_2O leaves the blood and enters the alveoli more rapidly than N_2 can leave the alveoli and enter the blood. This results **in a larger dilution of gases in the alveoli** reducing the P_AO_2. This means supplemental oxygen should always be given following emergence from anaesthesia with N_2O.

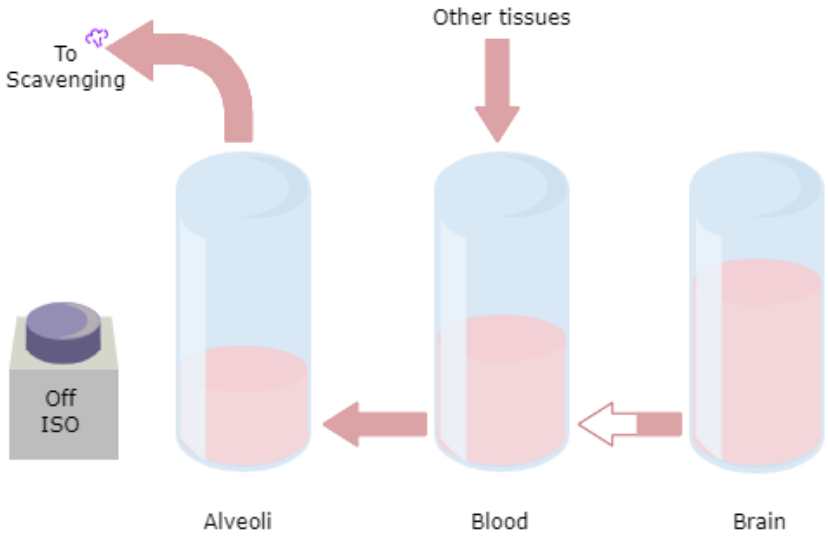
Diffusion hypoxia will mean patients at risk of airway obstruction without a fixed airway should not be given N_2O as if obstructs, reserve of O_2 will reduce.

The low B:GPC will mean that N_2O will also leave the blood and enter air filled cavities i.e. with a pneumothorax, and therefore should be avoided in these scenarios.

NB, N_2O supports combustion and should not be used in laser/diathermy airway surgery.

Offset of Anaesthesia

This is the opposite of onset. Therefore, those with a low B:GPC will also have a faster offset of anaesthetic.



Increased Mv will also increase clearance but will cause cerebral vasoconstriction (low PCO_2) which has the opposite effect.

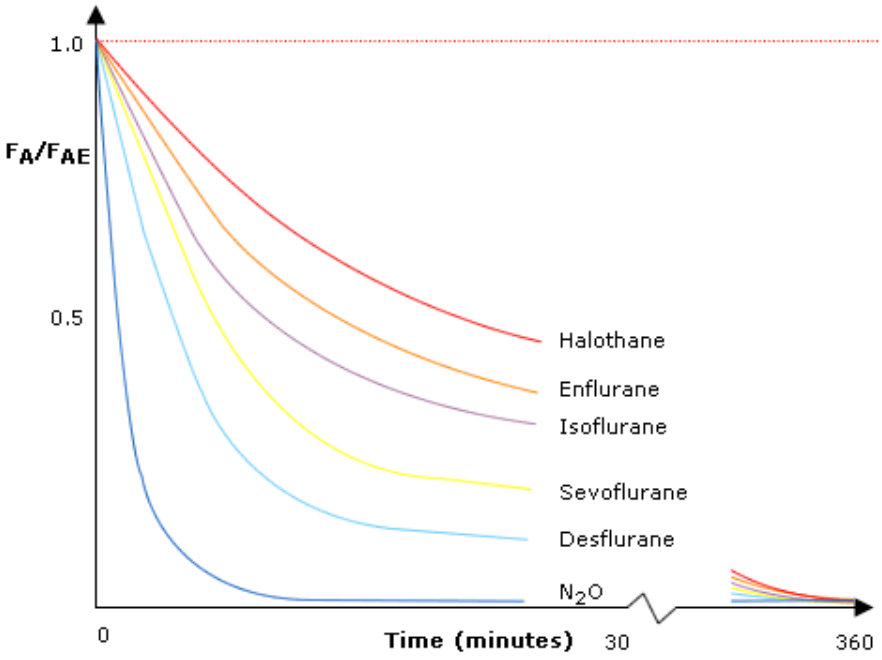
With **higher lipid solubility**, there is a **delay in emergence** because more agent transfers from the tissue into the blood (redistribution). This is **especially true with halothane**.

Wash Out Curves

The y axis cannot be F_A/F_I as this will approach infinity.

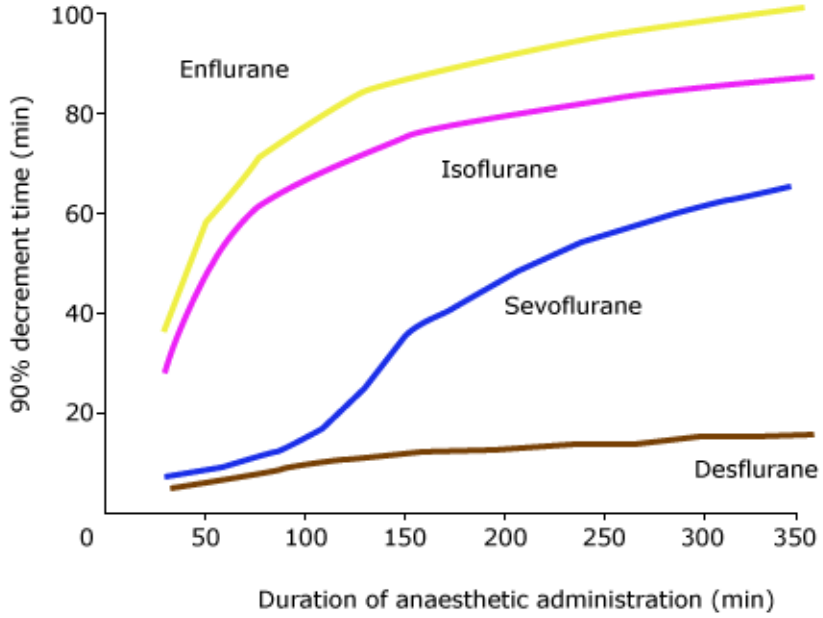
This is now **F_A/F_{AE}** where F_{AE} is the partial pressure when the vaporiser is switched off. This curve is also an example of a negative exponential process.

The fresh gas flows must be increased to wash out the anaesthetic gas existing in a breathing system – especially in a circle system.



Context Sensitive Half time (CSHT): This is the decrement time in the context of the length of time used for administration and is determined by the lipid solubility that an agent has as this governs its redistribution.

The 50% decrement in CSHT does not vary much but there is a great different in 90% decrement times following a prolonged anaesthetic (particularly after 6 hours). Desflurane has the shortest 90% decrement time after prolonged anaesthesia. Try comparing the O:GPC values with the graph shown.



Metabolism

AGENT	Metabolized (%)	Ions Produced	Other Products
Halothane	20	F, Br, Cl	Trifluoroacetic acid (CF_3COOH)
Sevoflurane	3-5	F	Hexafluoroiso-propanol ($CF_3CHOHCF_3$) CO_2 ***(unique metabolite)***
Enflurane	2	F, Cl	Trifluoroacetic acid Difluoromethoxy-difluroacetic acid (CHF_2OCF_2COOH)
Isoflurane	0.2	F, Cl	Trifluoroacetic acid
Desflurane	0.02	F	Trifluoroacetic acid

Halothane is the most highly metabolised agent.

Of the ethers, Sevoflurane (isopropyl-methyl-ether) is metabolised more than the methyl-ethyl ethers but is the only agent that is not metabolised to trifluoracetic acid.

This occurs in the liver by **CYP2E1** which attacks the C-halogen bonds and is responsible for trifluoracetic acid production which is implicated in halothane hepatitis. This is **induced by chronic alcoholism** which increases the MAC of agents.

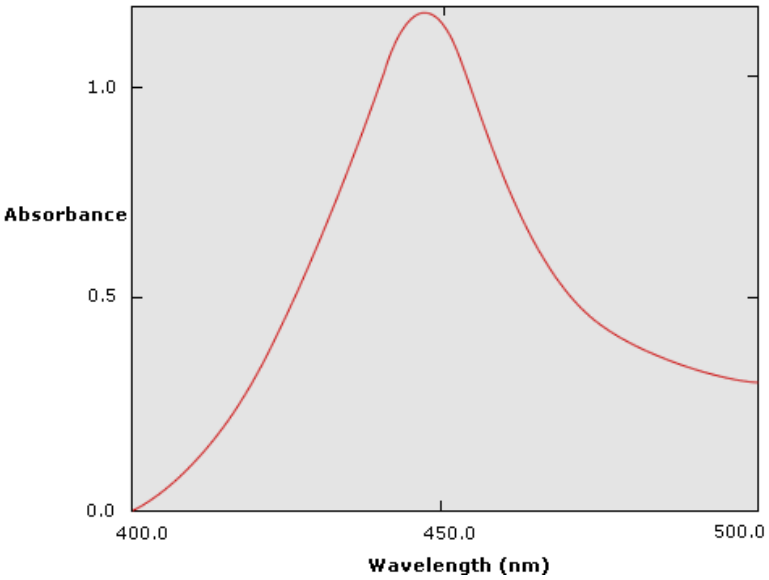
Cytochrome P450 System

(07c_07_06)

These enzymes are mainly embedded in the lipid bilayer of the smooth ER of the liver and are responsible for **phase 1 reactions**.

They are **mono-oxygenase enzymes** responsible for the **synthesis and metabolism of endogenous substances** i.e. steroid hormones, bile acids, arachidonic acid derivatives, cholesterol and retinol. Also responsible for the metabolism of **toxic products and exogenous compounds**.

Cytochrome means *cell colour* and is what gives the liver its red colour. They **contain iron** and in their reduced state, they combine with Carbon monoxide to absorb light at a wavelength of 450 nanomicrons – hence the name!



Note, they are also located in other tissues such as kidneys, brain, adrenals and gut but their concentrations are much less than that of the liver.

Nomenclature

- **CYP** = cytochrome P450 (root)
- **2** = genetic family (18 human families)
- **D** = genetic subfamily (44 subfamilies)
- **6** = specific gene
- ***1** = individual allele

CYP2D6

Subfamilies share 55% of amino acids. Families share 40% amino acids.

Role of CYP450 Enzymes

LIVER:

- **Cholesterol → Bile Acids**
  - CYP**7A**
  - CYP**27A** (also located in vascular endothelial cells)
- **Endogenous steroid production**
  - CYP**11**
  - CYP**17**
  - CYP**19** (also present in adipose tissue, gonads, brain and placenta for oestrogen production)
  - CYP**21**
- **Metabolism of toxins**

KIDNEYS: Involved in the production of the **arachidonic acid metabolites:**

- **Epoxyeicosatrienoic acid (EET):** Involved in **renal vasodilation** and glomerular permeability
    - CYP**2C**
- **Hydroxyeicosatrienoic acids (HETE):** Involved in **renal vasoconstriction**, glomerular permeability and **inhibits Na^+ reabsorption** via inhibition of Na^+/K^+ ATPase and Na^+/Cl^- cotransporter in the thick ascending limb of the nephron
    - CYP**4A**

BRAIN: Involved in the production of steroid hormone and prostaglandin metabolites for

- Regulation of peptide hormone release from hypothalamus/pituitary
- Regulation of cerebrovascular tone by arachidonic acid metabolites
- Regulation of progesterone and corticosteroids in the brain influencing mood via GABA receptors

Pharmacological Role

As mentioned above, the CYP450 enzymes are involved in phase 1 metabolism (lipophilic → hydrophilic) also important in extrahepatic sites: **gut wall** (absorption) and **kidney** (excretion).

Enzymic activity is dependent on:

1. **Genetic variability**
2. **Enzyme inducers**
3. **Enzyme inhibitors**

Isoforms in drug metabolism

Isoform: versions of proteins with small differences to each other.

The most important families involved are **1, 2 and 3**. Within each subfamily are several isoforms, each encoded by a single gene (see above).

Most drugs are metabolised by several isoforms, some drugs only by 1 isoform. Those with a large proportion of drug metabolised by a specific isoform will be most affected if interactions through induction/inhibition take place.

CYP1 Family

CYP1A1 and **CYP1A2** are the most important isoforms involved in drug metabolism in the CYP1 family

CYP1A

Metabolises polycyclic aromatic hydrocarbons i.e.:

- Theophylline
- Propranolol
- Caffeine

Induced by:

- Smoking
- Ingesting charbroiled meat
- Phenobarbital
- Phenytoin

CYP1A2:

- Strongly inhibited by ciprofloxacin and fluvoxamine (an SSRI)
- Moderately inhibited by cimetidine

These may produce toxic levels of theophylline!

CYP2 Family

CYP2C, **CYP2D** **and** **CYP2E** are responsible for the majority of drug variation with C and D subfamilies having significant genetic variation.

CYP2C9 – Absent in most afro-caribbeans and 1% caucasians

- Pro-drug losartan
- S-Warfarin
- NSAIDs
- Phenytoin

Inhibited by:

- Fluconazole (strongly)
- Amiodarone (moderately)

Warfarin effect increases 3-fold when taken with fluconazole

CYP2C19 – absent in 20-30 % of Asians and 3-5 % of Caucasians

- Diazepam
- Phenytoin
- Omeprazole

Inhibited by:

- Omeprazole and other PPIs (strongly)
- Ketoconazole
- Cimetidine

CYP2D6 – alone is responsible for the metabolism of >25% of drugs. absent in 7-10 % of Caucasians and 1-3 % of non-Caucasians. Up to 30 % of East Africans have multiple copies of the enzyme and are extensive metabolizers. Not inducible by pharmacologic agents

- Analgesics - codeine, tramadol
- Beta-blockers - atenolol, metoprolol
- Tricyclic and SSRI antidepressants
- Antiarrhythmics, such as flecainide
- Ondansetron

Inhibited by:

- Fluoxetine, paroxetine, Quinidine (strongly)
- Amiodarone (moderate)
- Cimetidine (moderate)

CYP2E1 – Responsible for the metabolism of:

- Volatile anaesthetic agents
- Ethanol
- Paracetamol

Induced by isoniazid and chronic alcohol consumption.

Inhibited by disulfiram and acute alcohol consumption.

CYP3 Family

Has 4 isoforms: CYP3A3, 3A4, 3A5 and 3A7.

CYP3A is responsible for 70% present in the GI tract and is responsible for the metabolism of:

- Calcium channel blockers, such as nifedipine
- Benzodiazepines, including diazepam and midazolam
- Antihistamines, including chlorphenamine
- Cisapride
- Lidocaine
- Fentanyl and alfentanil

Inducers	**Inhibitors**
Rifampicin	Cimetidine
Glucocorticoids	Erythromycin
St John's Wort	Amiodarone
Phenobarbital	Grapefruit juice
Carbamazepine	Ketoconazole
Phenytoin	

Genetic Polymorphism

As seen above, this is important as it changes individual response to drugs and could lead to toxicity. The most important are ***CYP2C9***, ***CYP2C19*** **and** ***CYP2D6*****.** There are 3 groups patients can be classified into:

1. **Poor Metaboliser (PM).** These can be represented by the allele (*number) of the **abnormal** CYP gene i.e. CYP2D6*10 in Asians
2. **Rapid Metaboliser (RM)**
3. **Ultra-rapid Metaboliser (UM).** From gene duplication and overexpression of the enzyme most commonly found with CYP2D6.

CYP2D6

Poor metabolisers: Caucasians: 7-10%. Codeine and tramadol maybe ineffective as these drugs are not metabolized to their active forms.

UM: Ethiopians 30%. Antidepressants and neuroleptics are ineffective and prodrugs tramadol and codeine → increased side effects.

CYP2C9 and 2C19

PM: Asians: 20-30%. Caucasians 3-5%. Asians have a reduced clearance of diazepam and phenytoin and require lower doses of omeprazole (higher cure rate for treatment of H Pylori).

Pathophysiology

Congenital abnormalities:

- **Congenital Adrenal Hyperplasia:** Deficiency of 21 hydroxylase (*CYP21A2)*
- **Lung Cancer** in smokers with increased CYP1A1

Acquired abnormalities:

- **Lung Cancer** with FM/UM of CYP2D6 with tobacco smoke (produces procarcinogens)
- **Procarcinogens** with CYP2E1 with aniline, chlorinated hydrocarbons and benzene.

Introduction to Pharmacokinetic Modelling

(07c_08_01)

There are 4 phases when describing pharmacokinetics of a drug:

1. Absorption
2. Distribution
3. Metabolism
4. Excretion

A mathematical model can be created to describe the **changes in plasma concentration with time**. This session will deal with the one-compartment model.

Absorption

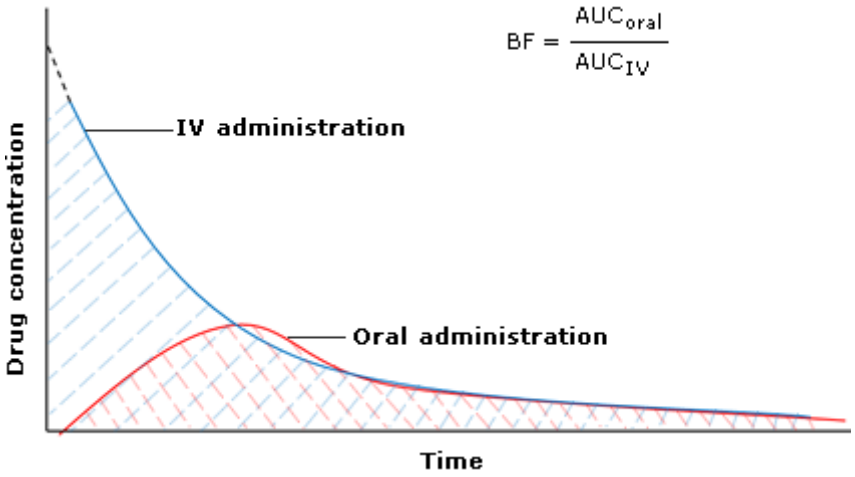
There are many routes including PO, IM, S/C, IV, S/L, transdermal, intrathecal, epidural, topical, inhalational, rectal, intraosseous, intranasal, buccal.

Some drugs are designed to act locally and not reach the systemic circulation i.e. bronchodilators, intranasal decongestants, topical steroids for eczema.

Bioavailability

The proportion of drug administered that reaches the systemic circulation. IV is always 100%.

The proportion is known as the **bioavailability fraction (BF)** (0-1). This can be measured by the **area under the curve** (AUC) when comparing IV to another route:



Factors affecting bioavailability

1. **Type of preparation** (enteric coated tablets prevent acid breakdown)
2. **Route of administration** (avoiding pre-systemic metabolism increases it)
3. **Co-administered drugs** may alter pre-systemic metabolism.

Oral tablets require absorption via gut wall and may be metabolised in the gut wall and then in the portal circulation via the liver – **1st pass hepatic metabolism**.

Elimination

Once a drug enters the systemic circulation, it may be:

1. **Metabolised then excreted**
2. **Excreted unchanged**

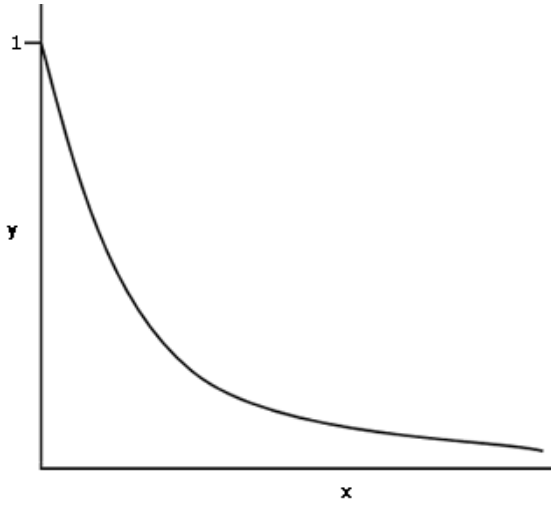
This is the only cause of a fall in plasma concentration in a one-compartmental model presuming distribution and re-distribution does not occur.

The **rate of elimination** is proportional to the **plasma concentration**. This relationship is known as a **first order relationship** between plasma concentration and rate of elimination.

Modelling

Models are tools to predict behaviour of a drug.

Understand that the following graph represents $y=e^{-x}$ which is a negative exponential function.



Simple Modelling

The rate at which a drug is eliminated is proportional to the plasma concentration. The relationship between plasma concentration and time is represented by:

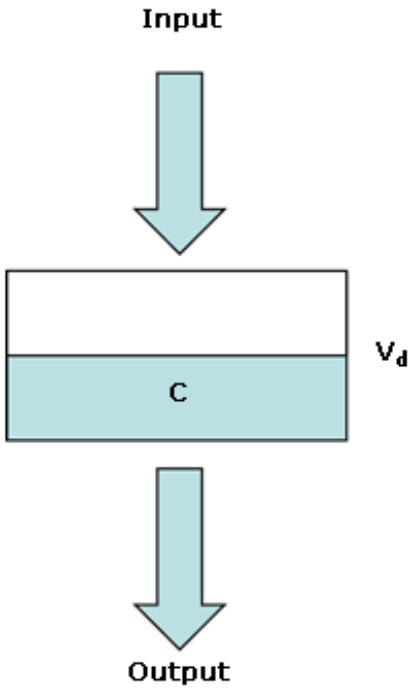
$C = C_0e^{-kt}$ (for a differential of dc/dt – see online)

This is a negative exponential relationship where:

- **C_0** = concentration at time 0 (mg/ml)
- **C** = plasma concentration
- **-kt** = - rate constant for elimination X time (no units)

The diagram on the right shows the important elements of the model which alter plasma concentration. These are:

1. **Input type** – whether boluses or infusion
2. **Volume of compartment –** V_d
3. **The output** – being the rate constant of elimination



For different drugs, the variables are the rate constant for elimination (kt) and the dose given (mg) /V_d (ml) = C_0 (mg/ml).

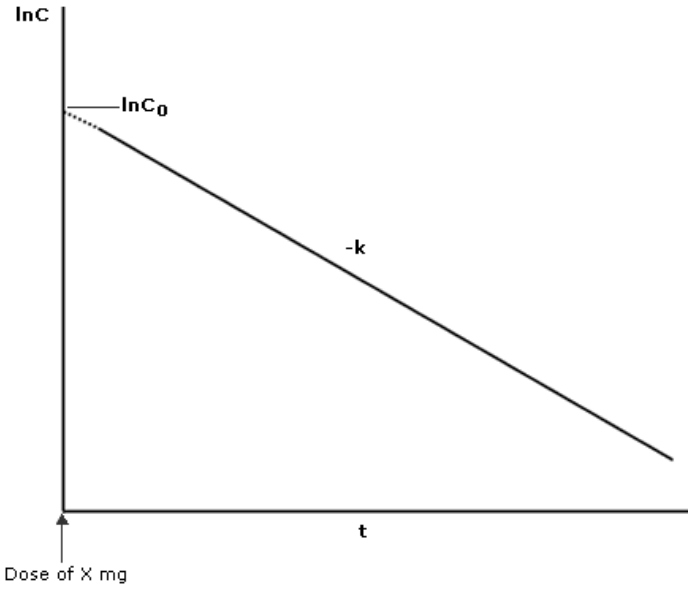
As kt is dimensionless (no units) and t is min. Then k must be min^{-1}.

Finding the constant of a given drug

This is done by taking the natural logarithms of the above equation resulting in:

$$\ln C = \ln C_0 - kt$$

This will provide a straight line and provide a **gradient of a slope which resembles -k** and intercept $\ln C_0$.



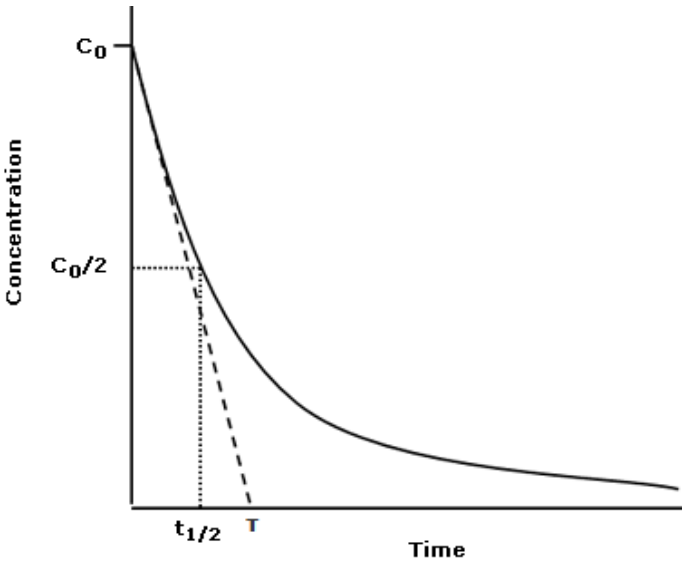
$X/V_d = C_0$ therefore:

$V_d = X/C_0$

Finding other parameters

TIME CONSTANT: (τ) = **1/k**

This represents the time it takes for plasma concentration to fall by a factor of e (or 37% of its value). Using the graph of **$C=C_0e^{-kt}$**, at time 0, the gradient of the curve will be e and therefore can be extrapolated to give this value.



HALF LIFE: ($t_{1/2}$)

This represents the time it takes for plasma concentration to fall by half.

Through deriving (see online) a relationship between time constant and half life, the equation is:

$$t_{1/2} = \tau \times \ln 2$$

ln2 is 0.693 and therefore, time constant is larger than half life.

It takes about 5 half lives or 3 time constants for elimination to be very close to completion

Clearance

CLEARANCE is defined as that volume of plasma from which drug is completely removed in unit time and has units of ml/min.

It is the ability of the body to eliminate the drug and in the model is the ratio between the volume of distribution and the time constant.

$$Cl = V_d / \tau \quad \text{OR} \quad Cl = V_d \times k$$

Therefore, clearance is the constant that relates plasma concentration of a drug to its rate of elimination at any point.

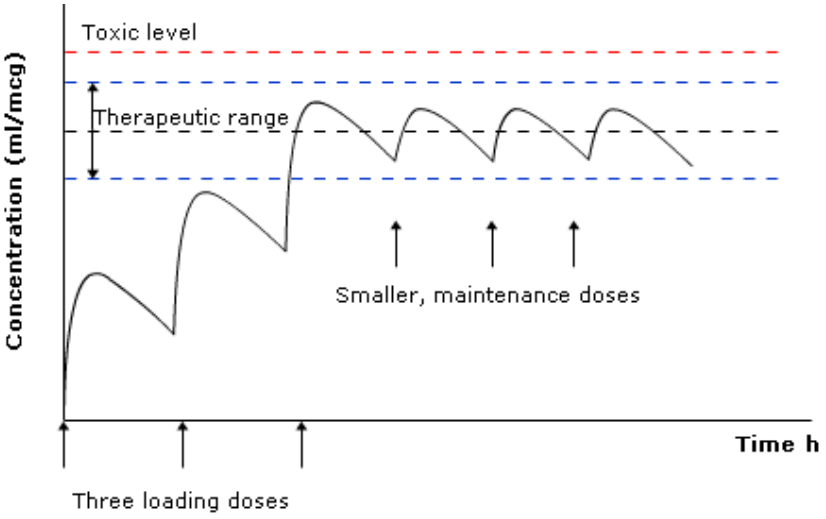
Rate of elimination = clearance x plasma concentration

Help cement this learning by doing the questions on the online module.

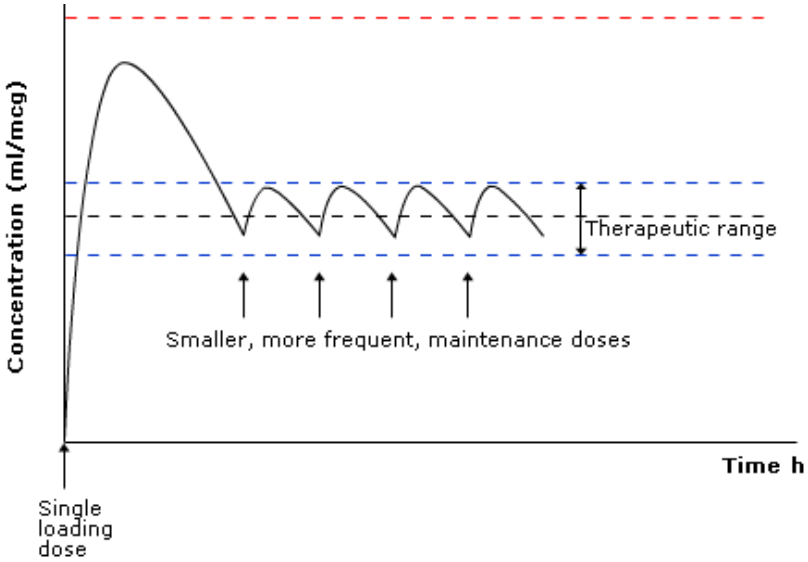
Predictions from the model

IV Bolus Doses

Initial dose of an IV drug will result in a plasma concentration of dose/V_d. This falls by a constant rate of k and after 3-time constants, the drug will be in negligible concentrations. However, if a drug is given before 3-time constants, the plasma concentration will increase that seen by the initial dose (more with smaller time-interval bolusing).



Different methods are used depending on how close the toxic level is to the therapeutic window:



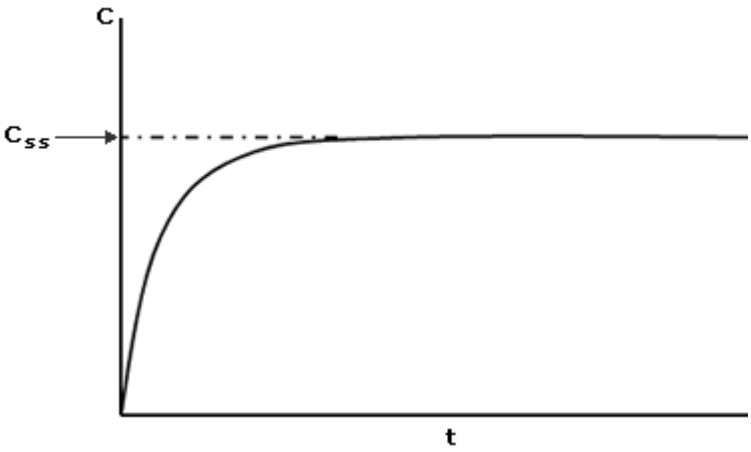
Constant Rate IV infusion

At **steady state (C_{ss}),** Input = Output.

- Input = drug infusion (mg/min)
- Output = rate of elimination.

Remember that rate of elimination = plasma concentration X clearance.

If the infusion rate of a drug was 200mg/min and the clearance is 100ml/min.



Then the C_{ss} x 100 = 200.

C_{ss} = 2mg/ml

The time it takes for plasma concentration to reach C_{ss} will be 5 half-lives or 3 time constants. The equation governing the above graph is:

$C = C_{ss}(1-e^{-kt})$

OVERALL

Volume of distribution (**Vd**): That apparent volume into which a drug disperses to explain the observed plasma concentration at time t = 0.

Time constant (**τ**): The time it takes plasma concentration to fall to 1/e of its current value (37% of its value),
OR
The time it would have taken the plasma concentration to fall to zero had the initial rate of decline continued.

Half-life (**t1/2**): The time it takes plasma concentration to fall to half of its current value: t1/2 = ln2.τ.
Rate constant for elimination (k): The inverse of the time constant: the fractional volume eliminated in unit time.

Clearance (**Cl**): That volume of plasma from which drug is completely removed in unit time.
The product of volume of distribution and rate constant for elimination (Vd.k), OR
The ratio of volume of distribution to time constant (Vd/τ).

Few drugs can be described by a simple 1 compartment model. Therefore, a more complex model is required to explain clinical observations where the drug does not follow the expected pattern i.e. plasma concentrations following a bolus may decrease much faster than expected by the rate of elimination. This is due to differences in vasculature, fat and water content etc.

Two and Three Compartment Models

(07c_08_02)

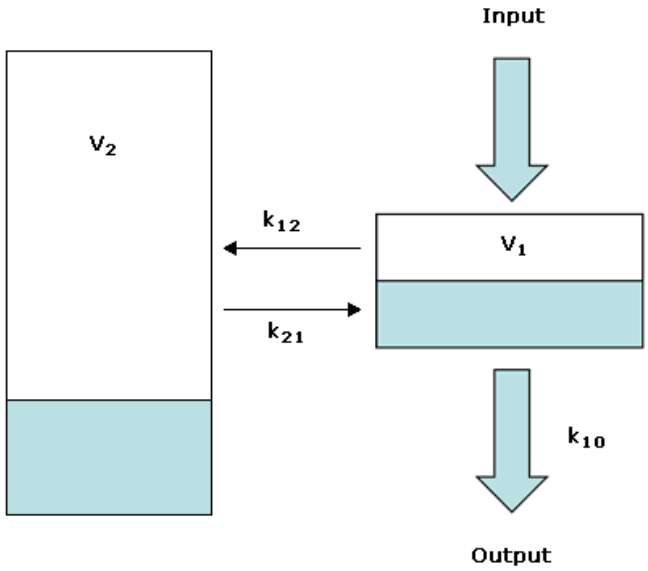
The Two-Compartment (2-C) Model

Here we add another compartment V_2. We now need **rate constants for:**

1. **Distribution (K_{12})**
2. **Re-distribution (K_{21})**
3. **Elimination** from V_1 **(K_{10})**

Think of the compartment number when remembering values of k.

K_{12} and K_{21} is dependent on the physiochemical properties of the drug (lipid and water solubilities and pKa), the vasculature and transport processes in the tissues and level of protein binding.

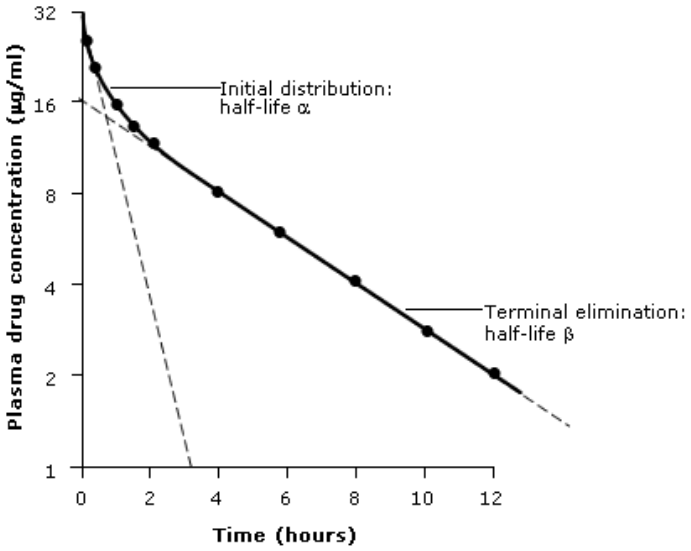


Plasma Concentration Behaviour

$$C_1 = Ae^{-at} + Be^{-\beta t}$$

This is the equation to describe the 2 dimensional model with the sum of 2 compartmental rates of elimination.

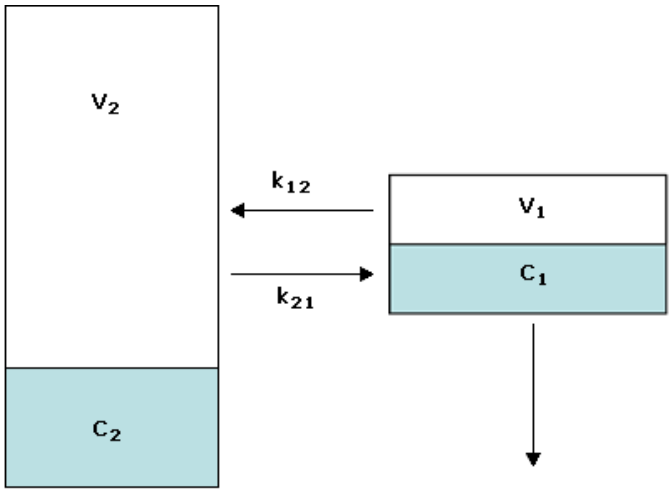
Initially, the drug will distribute by (a) at a y-axis intercept of A and once complete, the only rate of decline will be from the rate constant for terminal elimination (β). The semi-logarithmic plot becomes a curve (cf 1-C model) broken down into 2 lines.



Note that a and β are both combinations of all rate constants (k) and describe the behaviour of a drug in the body.

In a 2-C model, $\mathbf{V_d}$ is the sum of $\mathbf{V_1}$ and $\mathbf{V_2}$. Clearance out of the central compartment is now a sum of the elimination clearance out of the body $\mathbf{Cl_{10}}$ = ($V1 \times k_{10}$) and the inter-compartmental clearance $\mathbf{(Cl_{12})}$ = $V2 \times k_{21}$

NOTE: $V1 \times k_{12} = V2 \times k_{21}$



The **rate of transfer** from V_1 to V_2 is given by

C_1 (plasma concentration at volume 1) x Cl_{12}

AND V_2 to V_1 by **C_2 x Cl_{21}.**

Clinical Implications

The 2-C model predicts a faster drop in plasma concentration than a 1-C model immediately following a bolus but also a longer terminal elimination phase due to redistribution.

With **multiple boluses** there will be fall in the rate at which the plasma concentration drops immediately after further boluses due to a reduced concentration gradient between the 2 compartments as the 2nd compartment fills.

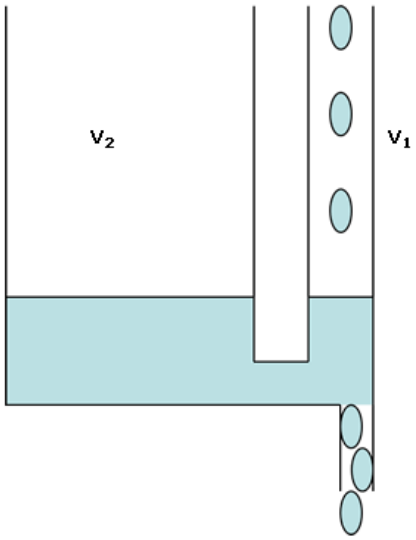
This will be a constant drop in rate until the 2nd compartment is filled. At this point, there will be an equal concentration of drug in both compartments and there is no overall redistribution/distribution. This is the **steady state.**

Infusion

Steady state is where:

INPUT = OUTPUT

Infusion rate = clearance x C_{ss}.



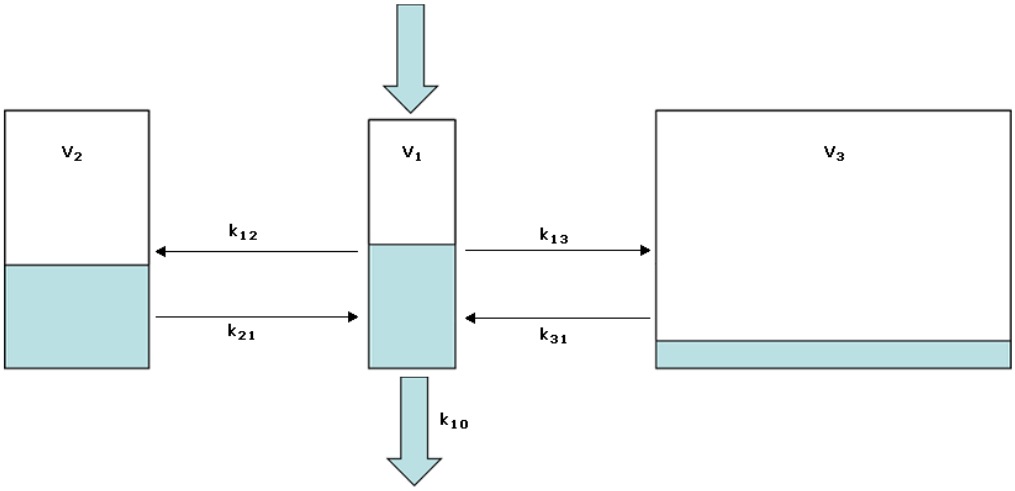
Once the infusion stops, the concentration from the central compartment drops favouring redistribution. This is represented by the **hydraulic model** on the diagram on the right.

The time at which the plasma concentration falls is dependent on the inter-compartmental and elimination clearances:

1. Fast elimination clearance but slow intercompartmental clearance – C_1 will drop rapidly
2. Slow elimination clearance but fast intercompartmental clearance – C_1 will drop slowly (rapid redistribution as the plasma concentration falls slowly).

The Three-Compartmental (3-C) Model

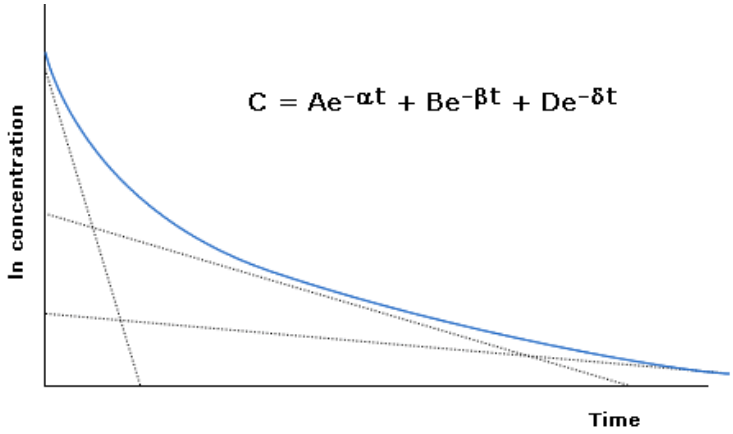
This is important for drugs given over many hours/days which the 2-C model cannot predict. **Propofol** uses this model. It is known as mammillary as both peripheral compartments are in communication with the central compartment.



$$C_1 = Ae^{-\alpha t} + Be^{-\beta t} + De^{-\delta t}$$

There are now **3 exponential processes involved** and the terminal phase rate constant is the slowest of all the models with the additional rate constant δ. This is the model used in TCI infusions of Propofol and remifentanil.

The intercompartmental clearance is slowest between V1 and V3. Like the 2-C model:

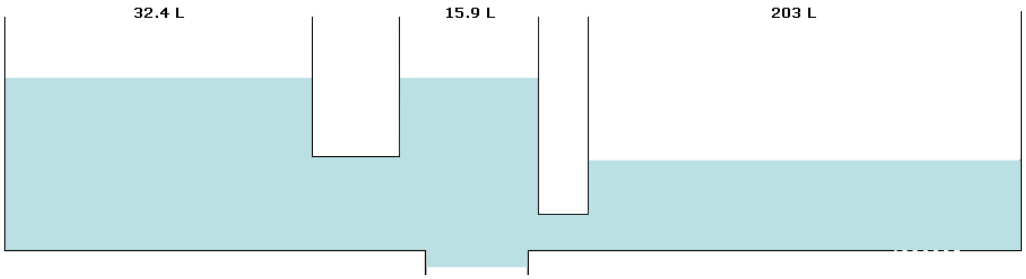


$$Cl_{13} = V_1 \times k_{13}$$

The most established model for use regarding TCI in a 3-C model is the **Marsh model** which sets a **weight-only** dependent value for the 3 compartments and the clearances specific to Propofol. The values in the table are for a 70kg man.

This can be represented by the hydraulic model below:

	Value
V_1	15.9 L
V_2	32.4 L
V_3	202 L
Cl_{10}	1.9 L/min
Cl_{12}	1.78 L/min
Cl_{13}	0.67 L/min



The **volume of distribution at steady state (V_{SS})** is about 300L for Propofol which is the sum of all 3 compartments (much larger than the volume of the whole body which shows that this is only a representation for a mathematical model).

As the rate of elimination is much faster than redistribution, the effect of Propofol will fall rapidly despite large stores in the 3rd compartment particularly.

Half-Lives

There are 3 separate half-lives representing:

1. **Rapid initial distribution:** t1/2α OR ln2 X 1/α;
2. **Intermediate elimination and distribution:** t1/2 β = ln2. 1/β
3. **Terminal elimination half-life:** t1/2δ = ln2. 1/δ

(which represents re-distribution and elimination)

Opioids and pKa

Opioids are weak bases. The lower the pKa, the greater the unionised proportion in the blood and therefore, assuming all equal lipid solubility and metabolism, the lower the pKa will result in faster inter-compartmental clearances.

	pKa
Alfentanil	6.5
Remifentanil	7.1
Morphine	8.0
Fentanyl	8.4

However, there are different lipid solubilities and clearance per unit weight values for each of the opioids resulting in multifactorial influences on rate or distribution.

	V_1 (L)	V_2 (L)	V_3 (L)	Cl_{10}(ml/min)	Cl_{12}(ml/min)	Cl_{13}(ml/min)
Alfentanil	8.9	13.7	12	357	923	152
Remifentanil	5.2	10	5.4	2628	2050	77
Morphine	14.2	258		1700	1683	
Fentanyl	7.4	34	276	608	3462	1650

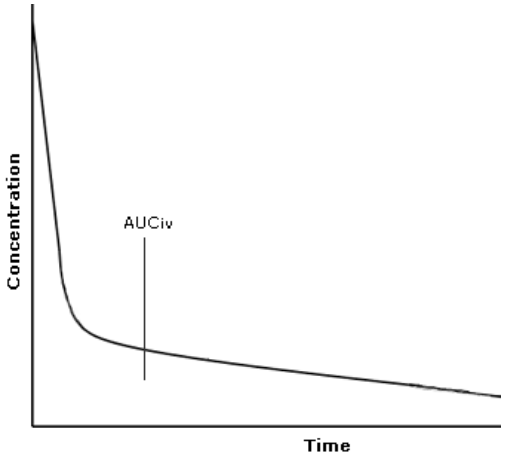
JUST REMEMBER, THESE VALUES FOR THE MATHEMATICAL MODEL ARE HARD TO PREDICT FROM PHYSIOCHEMICAL AND PHARMACOKINETIC PROPERTIES OF DRUGS AND ARE PURELY ***OBSERVATIONAL VALUES****.*

From understanding these principles, one can now appreciate a comparison between an infusion of ***propofol*** *and* ***fentanyl****. They are very similar i.e. they rapidly distribute but the* ***inter-compartmental clearances of fentanyl is much greater than propofol****. Hence when a* ***fentanyl infusion is stopped****, the* ***plasma concentrations remain high*** *and there is a slower fall in plasma concentrations than that of propofol. Similarly, compare with remifentanil and alfentanil.*

Clearance and Volume of Distribution

(07c_08_03)

Clearance can be measured by the area under the curve of a concentration vs. time plot only following an IV dose:



$Cl = dose / AUC_{IV}$

We can only work out the clearance of an oral drug through the AUC if we know the bioavailability fraction. If

$BF = AUC_O/AUC_{IV}$ then…

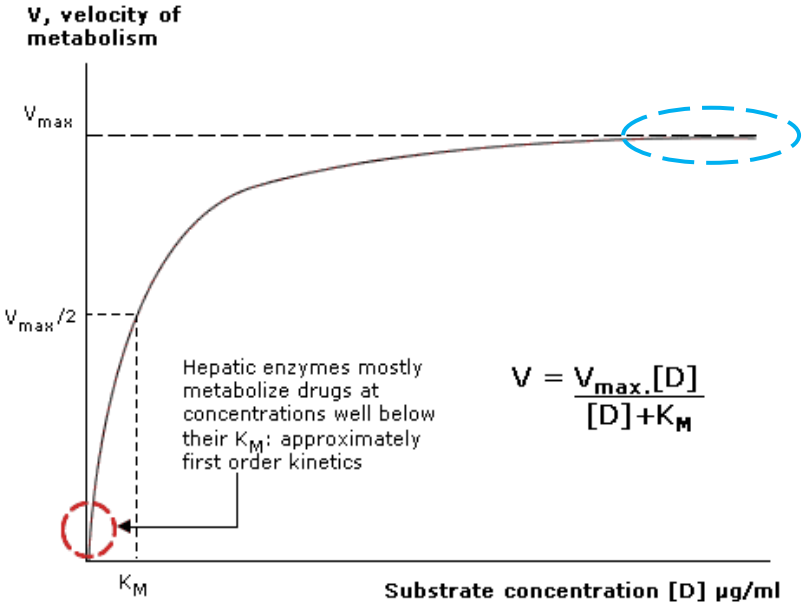
$Cl = (dose \times BF)/AUC_O$

Hepatic Clearance

This depends on **hepatic blood flow** and the enzyme activity within the hepatocyte aka **intrinsic clearance**. If you remember, this reflects the **K_M** of the enzyme.

Intrinsic Clearance

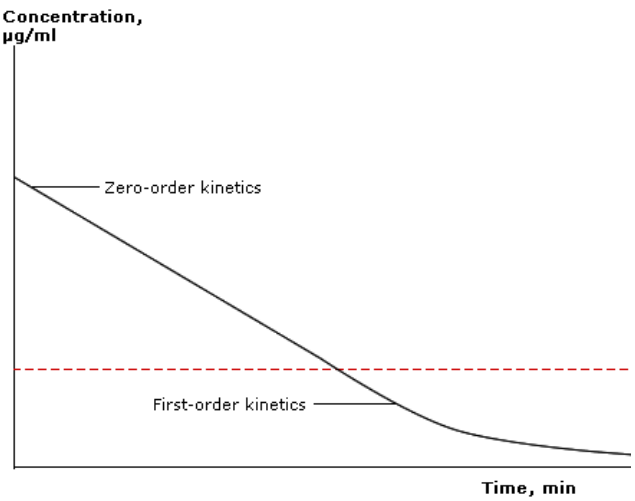
Most drugs are at a concentration well below the K_M of the enzyme **(red circle)** and therefore, all the substrate delivered will be metabolised at the maximal enzyme rate. This is known as **FIRST-ORDER KINETICS.**



Occasionally, drugs may approach the concentration of K_M and a large increase in concentration may cause enzymes to exceed their maximal metabolic activity. When the enzymatic activity is maximal, the rate of metabolism is constant **(blue circle)**. **Enzyme activity is now independent of substrate concentration** and is known as **ZERO-ORDER KINETICS.**

The concentration of the drug will drop at constant rate until the enzymes are no longer maximally saturated at which point, **first-order kinetics is re-established**.

Thiopental and phenytoin may saturate their enzyme systems.



Hepatic Blood Flow

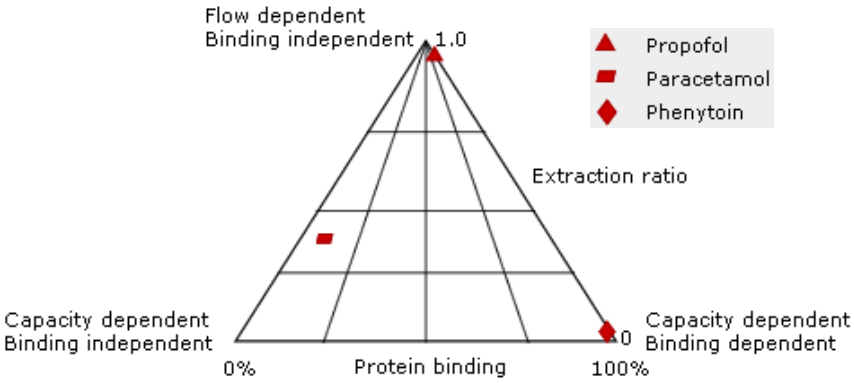
This reflects the **delivery of the substrate** to the enzyme systems and is the **limiting factor in 1st order kinetics**. Propofol and fentanyl are both dependent on hepatic blood flow and have high hepatic **extraction ratios (ER)** (concentration gradient between plasma and hepatocytes)

Drugs at concentrations above their K_M have a low ER as the intracellular concentration is close to that of plasma.

Highly protein bound drugs with low ERs (phenytoin, warfarin) may change free plasma concentrations very rapidly with any change in protein binding.

Highly protein bound drugs with high ER will not be affected by displacement from their protein binding.

These effects are best seen through **Blaschke's triangle:**

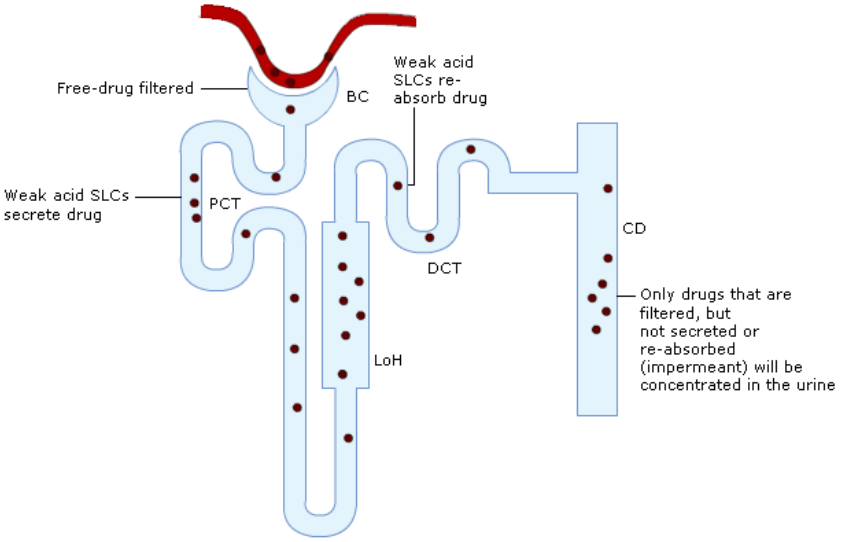


Excretion Unchanged

Not all drugs need to be metabolised to be eliminated but some may be excreted unchanged in the body. In the kidneys:

- FILTRATION: This is mainly with **highly polar, unbound drugs.**
- SECRETION: Weak acids and weak bases

Note, volatile anaesthetics may be excreted unchanged through the **inhalational route**.



Volume of Distribution (VoD)

The central compartment is the **initial volume of distribution**. This is used to calculate the initial loading dose for a target concentration in the plasma:

i.e. a target of 6microg/ml is req'd in an initial volume of distribution of 16L. The calculated loading dose would be…

96mg

A drug behaves according to a single-compartment model. Experimentally you find that it has a half-life of 70 min and a clearance of 100 ml/min. What would be its approximate volume of distribution?

10L

Physiological volumes

Intravascular Volume

If the **initial volume of distribution was in the intravascular space** (70-80ml/kg), the VoD of a drug would be less than 10L (small). It is often said that highly protein-bound drugs have a small VoD: this is not necessarily true. Only unbound drug can distribute, so highly protein bound drugs will simply distribute more slowly. Propofol is more highly bound than fentanyl (98% compared with 83%) but both distribute throughout a large volume of distribution, fentanyl more rapidly than propofol.

A drug to remain in the intravascular space would be **large and polar** and highly protein bound. An example is heparin with an initial VoD of about 40-70ml/kg.

Extracellular Space

14L – a drug that is restricted to this compartment would be **small and polar, unable to pass through cell membranes**. The typical example being muscle relaxants – their VoD is typically 14L.

Intracellular Volume

Total body water is **42L**. These drugs must be **small** and **able to pass through cell membranes**. An example is **ethanol**. Deuterium (an isotope of hydrogen) can be used to measure this volume as it distributes freely.

Too Large Volume of Distributions?

How can this be explained?

- Very lipophilic drugs can enter adipose cells.
- Some drugs may enter cells through active transport mechanisms such as iodine → thyroid
- Some bind strongly to proteins or nucleic acids within the cell i.e. chloroquine

Drug	Volume Distribution (L)
Vecuronium	12
Neostigmine	15
Phenytoin	45
Temazepam	98
Ondansetron	140
Adrenaline	250
Propofol	305
Fentanyl	320
Digoxin	490
Chloroquine	15 000

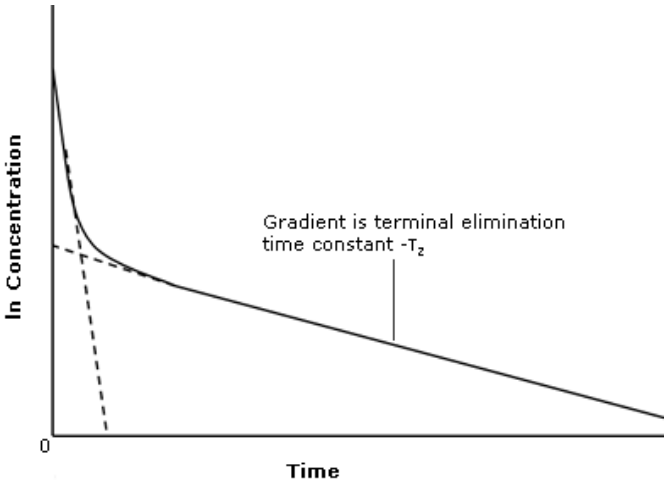
Calculating total Volume of Distribution

Remember that the total combination of volumes in a model is reflected by the **volume of distribution at steady state (V_{SS}).**

In a 1-C model, the V_d is the dose/concentration at t=0.

In a multi-compartmental model, the V_{SS} is measured from the terminal elimination phase.

This time constant is known as **T_Z** which is the same as 1/β for the 2-C and 1/δ for the 3-C model.



$V_{SS} = Cl / T_Z$

We know that Cl = dose x BF / AUC_O

Therefore,

$V_{SS} = (BF \times dose)/(AUC \times T_Z)$

Other Factors Affecting Clearance and Volume of Distribution

Inter-individual variation

- **Age:** alters the proportion of body water
- **Gender:** lean body mass affects VoD
- **Genetic disposition:** isoform of enzyme → altered metabolism and clearance
- **Co-administration of other drugs:** enzymatic alteration and protein binding

Hepatic Failure

- **Ascites will increase the initial VoD requiring a larger initial bolus dose.**
- **Reduced protein synthesis complicates the calculated loading doses**
- **Metabolic activity declines** on drugs depending on hepatic blood flow and intrinsic activity.

Renal Failure

- **Increased initial VoD requiring a larger initial bolus dose**
- **Reduction in clearance in drugs dependent on renal excretion.**

Reinforce your understanding of these principles by attempting the questions on the online module

Target Controlled Infusions

(07c_08_04 **AN** 07c_09_02)

Propofol

The first 3-C model to be described was the **Marsh model**. The plasma concentration for propofol in induction of anaesthesia is about **6µg/ml** and to maintain anaesthesia is between **3-10µg/ml.** It requires the target concentration and the weight of the patient.

	Value (70kg)
V_1	15.9 L
V_2	32.4 L
V_3	202 L
Cl_{10}	1.9 L/min
Cl_{12}	1.78 L/min
Cl_{13}	0.67 L/min

Q: What is the initial bolus dose given?

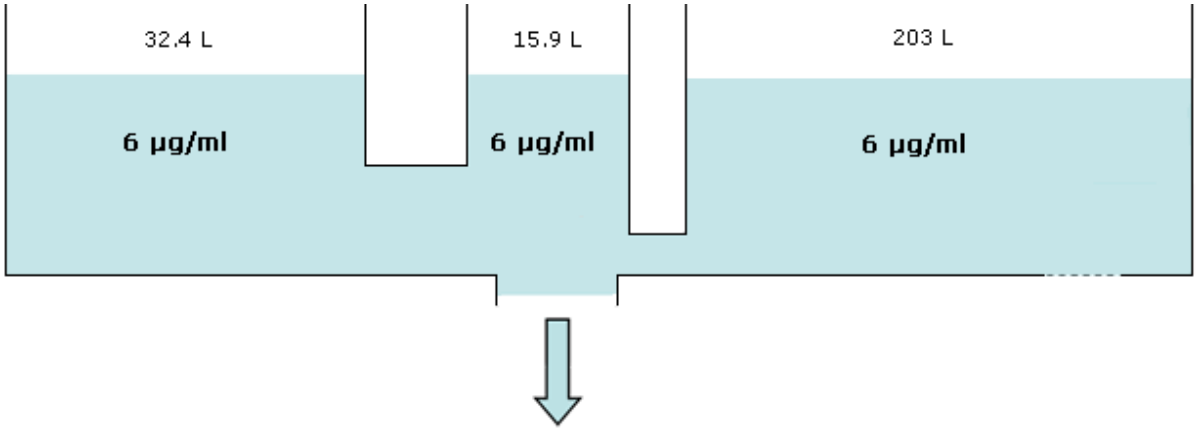
Bolus: As the initial bolus may take up to 30s, the TCI gives a little more that what is calculated from VoD and target plasma concentration to compensate for the little amount of elimination and distribution that has occurred.

Maintenance: Initially, the pump will deliver the same amount of drug as is eliminated and distributed (the sum of all 3 clearances) for **5 mins**.

***Q: How much of 1% propofol will be delivered over the next 5 mins to maintain* 6µg/ml?**

As the concentration difference reduces between compartments, the rate of distribution will drop and hence the model will drop its infusion rate.

Steady State: the only replacement that needs to occur with the TCI is elimination from the central compartment. The **rate of elimination of propofol at steady state is:**



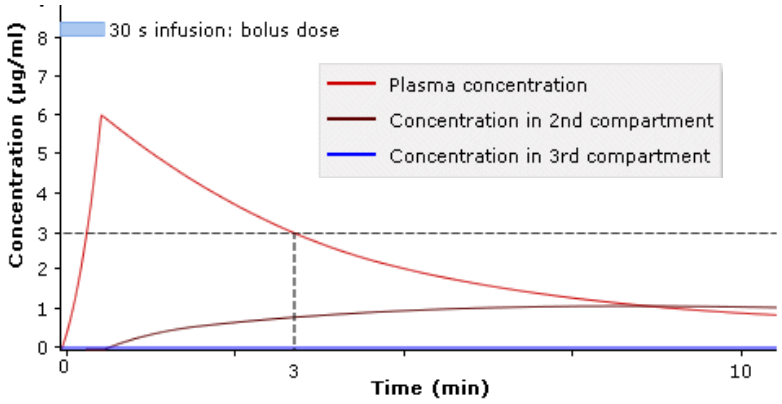
Q: If 6µg/ml is required, how much more mg/min propofol needs to be replaced?

Stopping an infusion: *How long will it take for it to drop to 3µg/ml?*

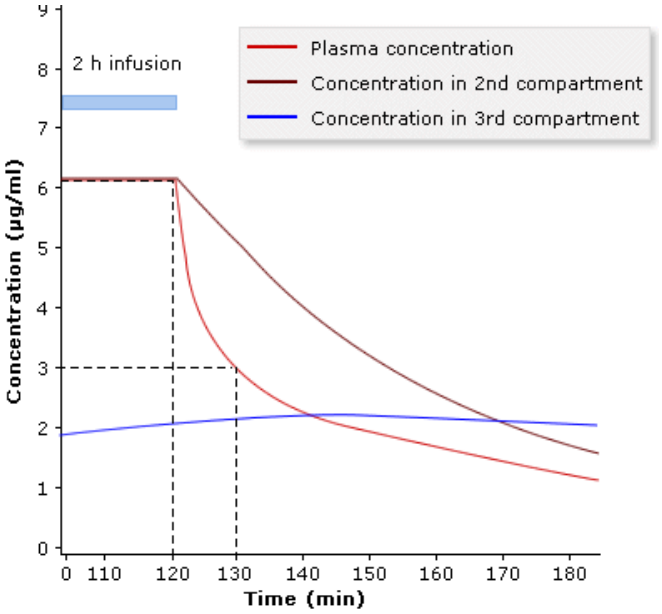
This is a difficult calculation that the lecture does not expect us to calculate but need to understand that Cl_{10} is faster than either intercompartmental clearance.

After initial bolus: the plasma concentration will drop rapidly. It takes about 3 mins.

This diagram shows that initial distribution occurs to the 2nd compartment. Very little will reach the 3rd compartment.

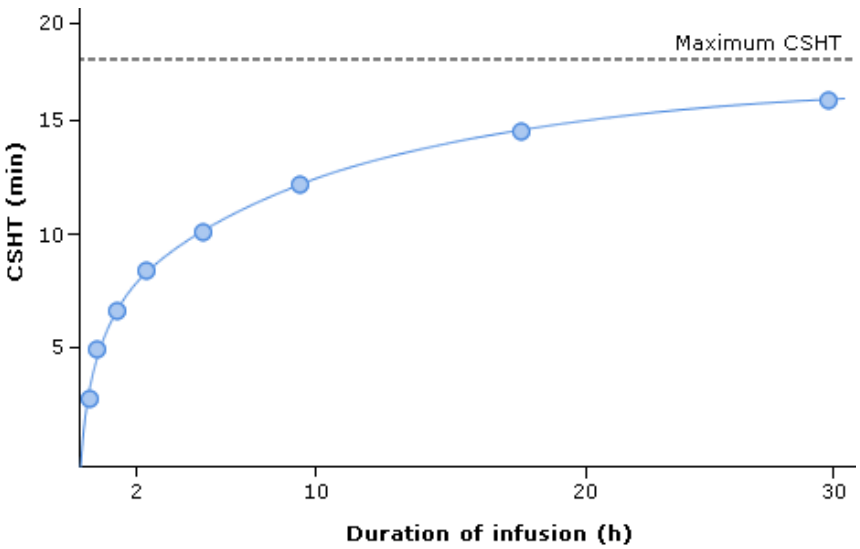


After steady state with the 2nd compartment: redistribution from the 2nd compartment occurs without distribution into the 2nd compartment. This will result in a slower drop in concentration and will take about 8mins.



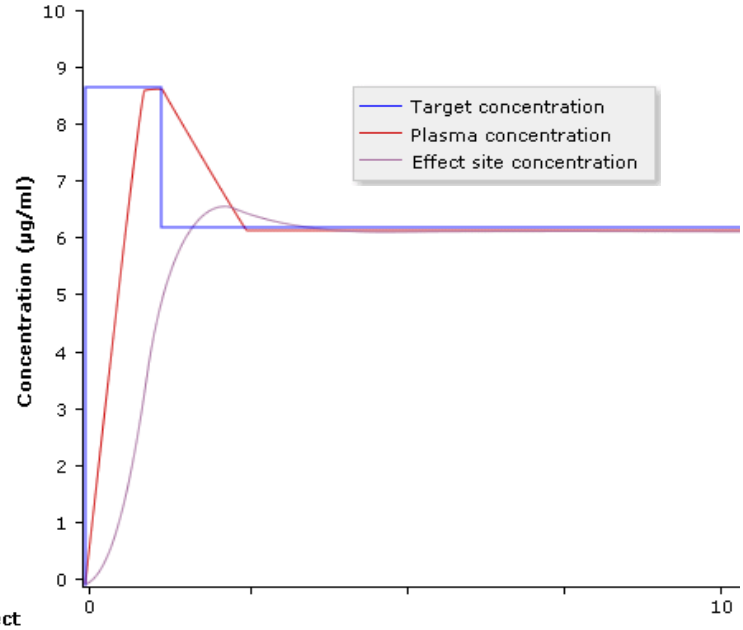
CONTEXT SENSITIVE HALF TIME: This is what the above illustrates where the half-time is dependent on the length of infusion where the longest possible would be at steady state.

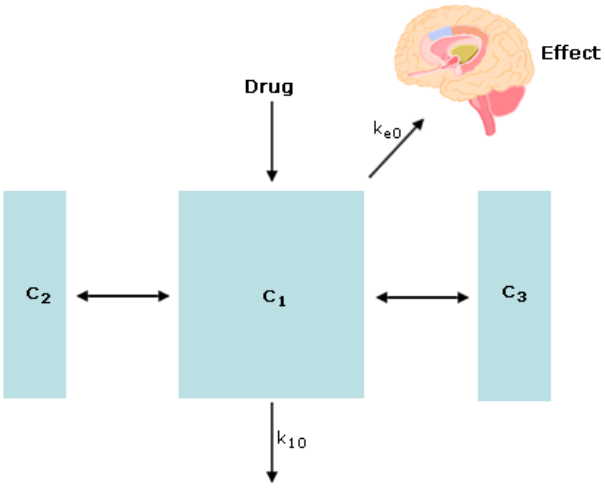
The maximum for propofol would be still short at 18mins due to the rapid elimination greater than intercompartmental clearance.



Effect site concentration i.e. the brain, with propofol will lag behind the plasma concentration. Induction may be sped up by setting a higher initial plasma target concentration for just 1 minute and then reduce concentration to the required target. This however may cause CV instability.

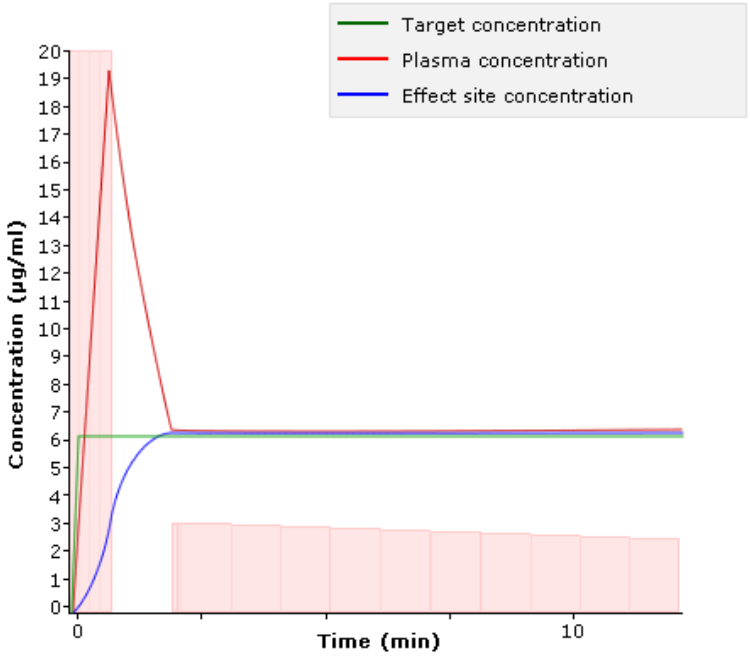
The diagram shows initial set at 8.5µg/ml and then dropped to 6µg/ml. Note the lag of the effect site concentration.





Previous pharmacokinetic-pharmacodynamic studies have enabled us to work out a rate constant for the central compartment to effector site concentration known as $\mathbf{k_{e0}}$ to which the half life is $t_{1/2ke0}$. This now enables a more rapid induction with minimal effect on CV stability. This model is known as the **Schnider model**.

It is important to note that the Marsh model delivers a much larger dose of propofol than does the Schnider model (even when Schnider is in effect mode).



The Schnider model used to target effect site concentration. Note the high overshoot in plasma concentration, due to the model having a smaller, fixed central compartment volume compared with the Marsh model. Also note that the infusion stops once the initial bolus has been given, it re-starts as plasma concentration falls

Remifentanil

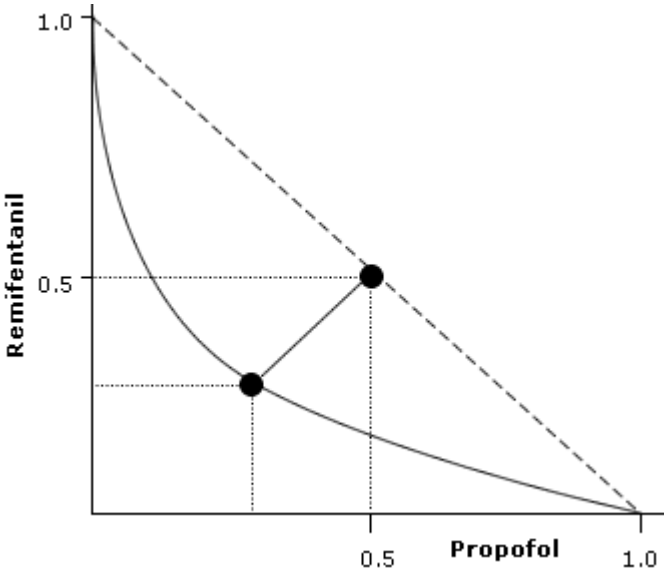
Is very potent with a relatively small VoD at steady state (V_{ss}) and has a rapid elimination. This is known as the **Minto model** which also has a k_{e0} component.

	Value
V_1	5.2 L
V_2	10 L
V_3	5.4 L
Cl_{10}	2628 L/min
Cl_{12}	2050 L/min
Cl_{13}	77 L/min

Initial targets are between 4-8ng/ml when in combination with propofol. This is reduced by almost a 3rd in synergism with propofol. This is represented by the **isobologram:**

The dashed line represents additivity and the solid line represents the synergistic (concave) effect. The arrow shows that 30% of each drug is required (rather than 50% for the additive effect) to produce a response.

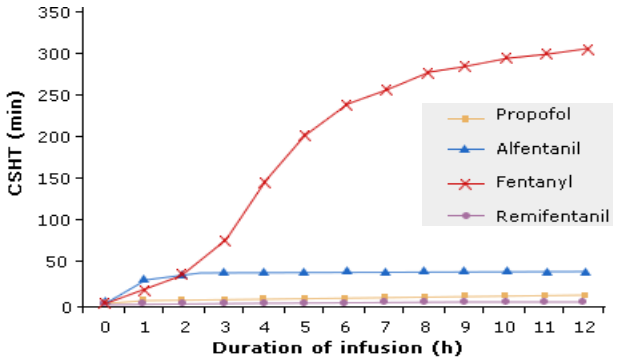
What would happen to the line if drugs were antagonistic to each other.



Due to **low volumes of distribution**, the **context sensitive half-time** does not vary as much as with propofol (from 3 to a maximum of 8mins).

Context Sensitive Half Time of Other Agents

Fentanyl has the greatest variation of CSHT as redistribution rapidly fills up the central compartment following elimination via K_{10}.



Ideal Drug for TCI

- The drug should have a short and predictable CSHT even after long infusions
- If the drug is lipid soluble, then it should have rapid elimination and slow re-distribution to allow plasma concentrations to fall below effective levels before re-distribution is significant
- There should be no active metabolites: effect should be predictable from plasma concentrations
- Ideally it should have non-organ dependent metabolism so that the model is minimally affected by organ failure
- Minimal adverse CV effects especially during effect site targeting.

More Information about TCIs

TCI systems are referred to **open-loop systems** as there is no measurements of actual concentrations during the infusion:

- Blood target: open-loop blood targeted TCI
- Effector site target: open-loop effect site targeted TCI

There are 3 components of a TCI system including a **user interface,** a **computer** or one or more microprocessors and an **infusion device**.

Calculations to alter the infusion rate occurs at discrete intervals, usually every 10s.

Branded Models for TCI Infusions

- **PROPOFOL:**
  - **Marsh** (weight and central compartment volume is a linear function of weight)
  - **Schnider** (age, and lean body mass with a fixed central compartment volume)

- **REMIFENTANIL: Minto** (also for propofol)
  - 4-6 ng/ml for adequate analgesia during laryngoscopy and tracheal intubation
  - 6-8 ng/ml are usually necessary during painful operations such as laparotomy
  - 10-12 ng/ml are required during cardiac surgery

- **ALFENTANIL: Maitre**
- **FENTANYL: Shafer** (note, this model has no covariates)
- **KETAMINE: Domino**

With combined propofol and remifentanil infusions, it is best to start the propofol infusion first as it rises slower than remifentanil.

Pharmacokinetic Principles in Different Patient Groups

(07c_09_01)

Some interindividual variability is explained by fixed effects such as age, gender and weight but there will still be some residual variability attributed to pharmacogenetic differences.

Neonates

Absorption

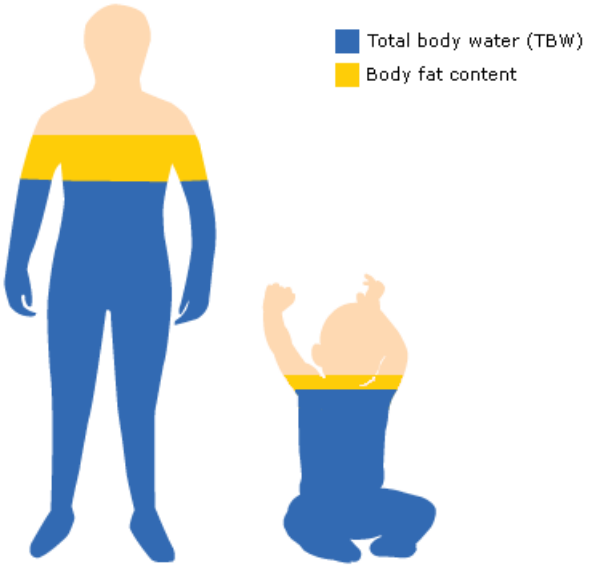
- **Enteral Route**
  - **Slower rate** of absorption due to *prolonged gastric emptying* and *intestinal transit time*
  - **Gastric pH** is *less acidic* in neonates
  - **Increased proportion absorbed** as the transit time is less and hence there is greater **contact time** with the mucosa
- **Rectal Route**
  - There is a difference in venous drainage systems in the rectal cavity. Therefore the drug position in the rectal cavity may vary and produce a range of effects
- **Transdermal**
  - **Rapid absorption** because the stratum corneum is thin.

Distribution

Total body water is **80%** of total body weight in a preterm baby. Proportionally, doses of water-soluble drugs will need to increase to prevent lower tissue concentrations.

Lower body fat and **increased BBB permeability** will lead to increased concentrations of lipid soluble drugs in the brain.

Decreased protein binding allows increased availability of unbound drug.



Metabolism

Depends highly on the size of the liver. In neonates, **enzyme activity is immature** and phase I metabolism is reduced. Phase I metabolism increases over the first 6 months and can achieve adult rates in the first few years (depending on the drug). It then slows again during adolescence until late puberty.

NOTE, this is highly variable according to the drug and some may reach adult rates (Km) by 4 weeks

Phase II metabolism varies considerably.

Elimination

GFR is 20-40% of the **adult rate** so drugs removed by this method are eliminated slowly.

Elderly

Absorption

Slower gastric emptying but this remains clinically insignificant.

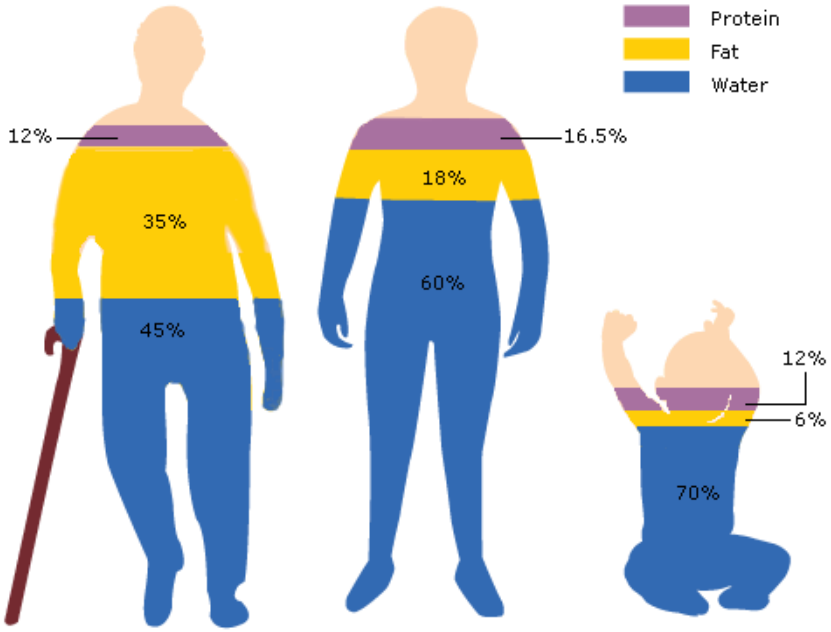
Distribution

There is a **smaller TBW** and this means that water soluble drugs has a small compartment for distribution and hence requires less equivalent doses to an adult.

Larger body fat ratio

Decreased albumin levels which may increase the unbound fraction of drugs.

Reduced muscle bulk results in a reduction in muscle blood flow and hence drugs such as remifentanil will take longer to metabolise.



Metabolism

Reduced hepatic blood flow and **enzymatic activity** which means there will be a **higher bioavailability** of drugs that undergo 1st pass metabolism. There will also be a slower reduction in plasma clearance of drugs dependent on hepatic blood flow.

Elimination

There is a **decrease in GFR** and **tubular secretion** which may lead to toxicity of drugs cleared by the renal route.

Pregnancy

Absorption

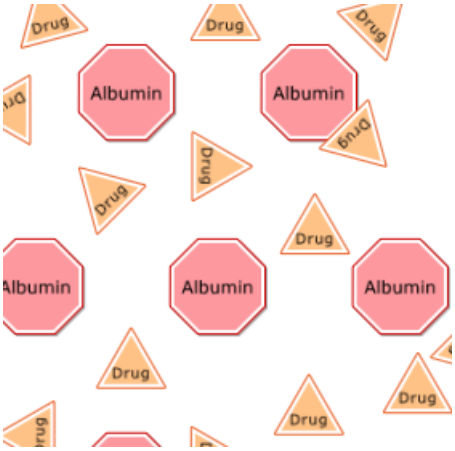
Delayed gastric emptying leading to increased uptake of drugs absorbed in the stomach and reduced uptake of drugs absorbed in the intestines. This has been related to **increased progesterone levels**. There is also changes in the relative amounts of gastric acid and mucus secretion.

Distribution

Increased TBW and fat causes an **increased VoD**.

There is an increased plasma volume and therefore, there is **plasma dilution of albumin**. The increased free fatty acids also **compete with acidic drugs** for the binding sites on protein. Therefore, there is an **increased fraction of free drug**.

NB alkaline drugs bind to alpha-glycoprotein and hence their concentrations remain consistent during pregnancy.



Metabolism

Increased cardiac output causes an enhanced clearance of drugs from **increased hepatic blood flow**.

There is also an **increased enterohepatic circulation** which may result in potentiation of certain drugs.

Placental enzymes may metabolise various neurotransmitters and endogenous compounds. **Placental lactogen → degradation of insulin**.

Elimination

No change in clearance but an **increased volume of distribution** which will result in a prolonged half-life.

Obesity

The most important issue is the **relative increase in total body fat**. It is very hard to obtain useful measurements to alter the drug doses according to the change in pharmacokinetics.

As well as BMI, there are the following ways of describing body mass which *may* be useful in determining the pharmacokinetics.

Measurements

Ideal body weight (IBW): This is a calculated *estimate of lean body mass* and is corrected for gender and height. For males, this is simply:

HEIGHT in cm – 100 In females, negate 105.

Lean body mass can be calculated with the following formulae (cm/kg):

- Male = (1.1 x weight) – (128 x (weight/height)^2)
- Female = (1.07 x weight) – (148 x (weight/height)^2)

Body Surface Area (BSA): There are 2 common formulae for this:

- **DuBois equation:** Body surface area (m^2) = 0.007184 x (height)$^{0.725}$ x (weight)$^{0.42}$
- **Mosteller equation:** Body surface area (m^2) = (height x weight)/3600)$^{0.5}$

Absorption

The following may influence absorption of a drug:

1. Increased BSA
2. Increased cardiac output
3. Improved gut perfusion

These in fact have no clinical significance in absorption

Distribution

VoD changes of lipophilic drugs due to relative increases in adipose tissue mass.

There are also larger organs, increased blood volume and an increase in lean body mass which can also affect **hydrophilic drug VoD**.

These are clinically significant. There is no change in plasma protein concentrations.

Metabolism

Increased phase II metabolism leading to reduced effectiveness of drugs metabolised by this route including lorazepam and oxazepam.

Elimination

Conventional clearance equations may be inaccurate in the obese. **Overestimations** occur with actual body weight and **underestimations** occur with ideal body weight.

Critically Ill Patients

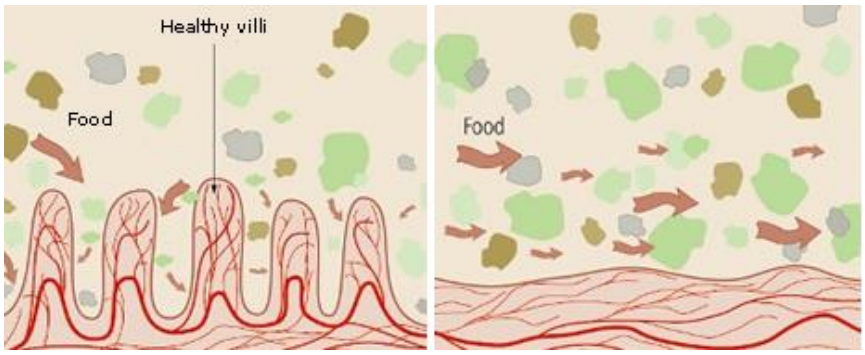
Pharmacokinetics change as a result of:

- Organ dysfunction
- Acute phase response
- Therapeutic interventions
- Drug interactions

Absorption

The **bioavailability** of drugs are usually **significantly reduced** in critical illness and hence the preferred route of administration is IV. This is because of:

1. **Perfusion abnormalities** – blood is redirected to vital organs and reduced to the GI tract
2. **Intestinal atrophy** occurs following starvation along with reduced enzyme functionality
3. **Motility dysfunction** from hypoperfusion and use of opioid analgesics.



Distribution

pH changes will affect the unionised/ionised fraction of drugs. With a greater unionised proportion, there will be greater VoD of drugs.

Fluid shifts causes **increase interstitial fluid** from leakage from capillaries (increased permeability), reduced oncotic pressure (reduced albumin). This will cause a greater VoD of hydrophilic drugs.

Reduced plasma proteins will increase the unbound fraction of a drug.

Metabolism

Hepatic extraction ratio is dependent on:

1. Protein binding
2. Enzyme activity
3. Hepatic blood flow

Drugs **dependent on hepatic blood flow** (**hepatic extraction ratio >0.7**) will be affected by the CVS. During early stages of sepsis, hepatic blood flow increases. In hypoperfusion states, hepatic blood flow decreases.

Drugs with **low hepatic extraction ratios** are **dependent on enzyme activity** which is decreased by cytokines and acute phase proteins. It is known that enteral feeding increases the enzyme activity and hence clearance of these drugs.

Elimination

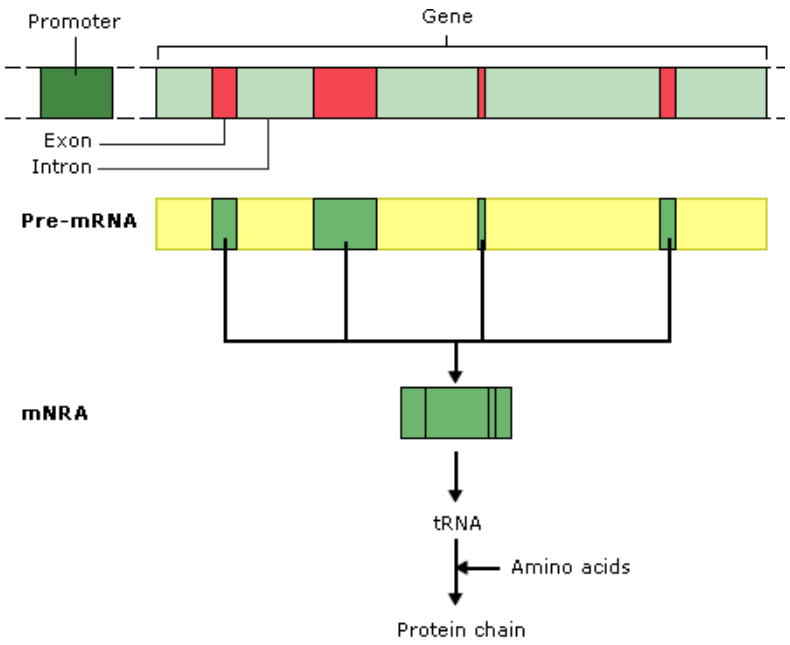
Renal dysfunction is common and there needs to be dose modifications for those with renal dysfunction and may need to be monitored if the therapeutic range is close to the toxic range.

Interindividual Variation in Drug Response

(07c_09_03)

mRNA is formed from DNA which contains both exons and introns. Only the exons are formed into mRNA from pre-mRNA which is known as **splicing**.

Some genes have different promoters/promoter conditions and hence different variations of the exons may be spliced to form mRNA. This is known as **alternative splicing**.



Pharmacogenomics is the study of how the entire genome influences drug response.

Pharmacogenetics is the study of how 1 gene influences drug response.

Single Nucleotide Polymorphisms (SNP)

A single nucleotide **substitution** in an allele will cause either:

1. Altered codon for the same amino acid (no change)
2. Different amino acid affecting up to the quaternary protein.
3. Stop codon → truncated protein.

Deletions or **additions** cause a frameshift mutation.

Pseudocholinesterase

This mutation is associated with **succinylcholine apnoea**. Also affects mivacurium metabolism.

Allele	SNP	Type	Frequency	Activity %	Apnoea duration
Eu Normal	nil	Normal	0.98	100	6 min
Ea Atypical	A209T	Substitution	0.02	30	2 h
Ef Fluoride resistant	C728T		0.003	40	1-2 h
Es Silent	G351A	Frameshift & early truncation (stop codon)	0.0003	absent	3-4 h

It is **autosomal recessive** so patients are usually symptomatic if homozygous for abnormal alleles. Heterozygotes only have mildly prolonged symptoms. EaEa is the most common homozygous abnormality. EsEs gives the most prolonged period of apnoea following succinylcholine administration.

Dibucaine Number

Dibucaine is a local anaesthetic. When benzoylcholine is mixed with plasma cholinesterase, a light emitting reaction is produced which dibucaine can inhibit by binding to the plasma cholinesterases. The presence of an atypical gene will reduce the amount of light that is inhibited i.e.

- E^UE^U – 80% of light is inhibited → Dibucaine number of 80
- E^aE^a – 20% of light is inhibited → Dibucaine number of 20

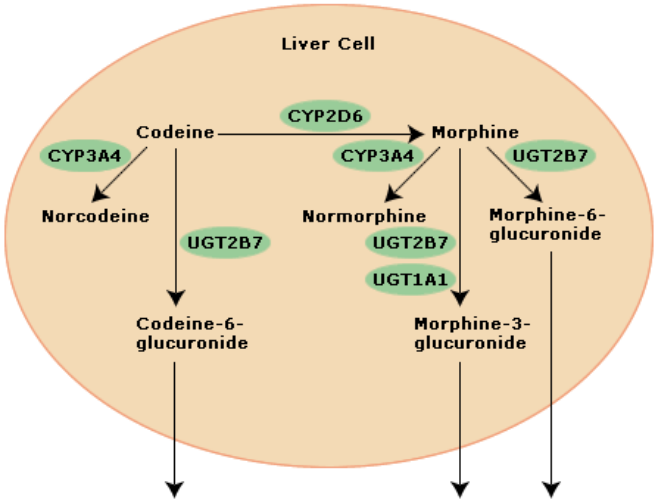
Fluoride can also inhibit this reaction and is used to detect the fluoride (E^f) gene. No inhibition of light will occur if homozygote for the silent (E^s) gene which happens to be the most potent inhibitor of suxamethonium breakdown causing prolongation of action to approximately 6-8h.

Other Enzymes

CYP2C9	CYP2C19	CYP2D6
S-warfarin	Omeprazole	Codeine
Phenytoin	Clopidogrel	Tramadol
Losartan	Diazepam	Oxycodone
Diclofenac	Propranolol	SSRI

CYP2D6

Reminder of CYP450 enzymes. The CYP2 family being the most prevalent. The CYP3A4 metabolises 35% of all drugs but its mutations have not been associated with clinically significant changes to drug response.

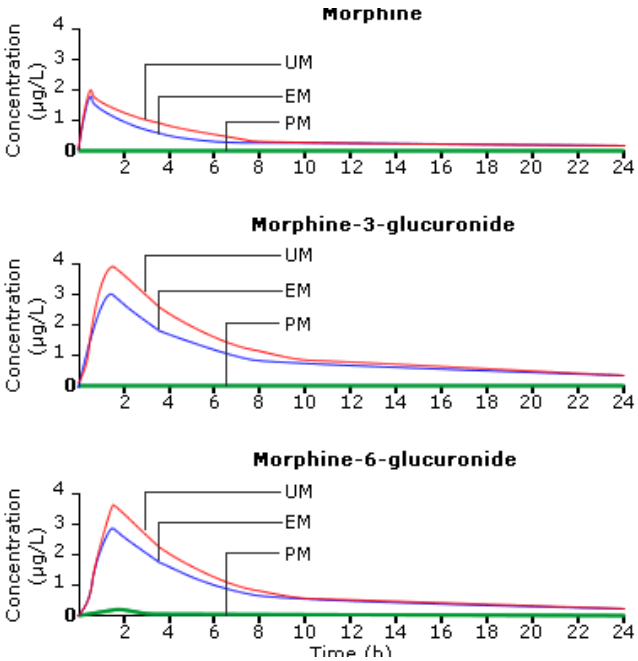


CYP2D6 mutations cause a significant effect on some opioids.

It is responsible for **codeine → morphine** and also **tramadol → O-methyl metabolite** (1000x potency to the μ-opioid receptor than tramadol).

REDUCED: CYP2D6*2, *10 and *17

ABSENT: CYP2D6*3, *4, *5 and *9 **(PM)**



In addition, some patients show **gene duplication** resulting in a larger proportion of drug conversions and increased s/e. **(UM)**

These graphs show the difference in levels of metabolites following administration of codeine in patients with different pharmacogenetics for CYP2D6 where:

- **UM –** Ultrafast Metabolisers
- **EM –** Expected Metabolisers
- **PM –** Poor Metabolisers

Morphine can also be excreted in breast milk and more common in UMs if on codeine.

CYP2C19

Clopidogrel is a prodrug and is metabolised by CYP2C19 to its active form responsible for binding to and inhibiting the ADP dependent receptor for platelet aggregation.

Type of metabolism	Genotype	Phenotype (platelet inhibition)	Therapeutic implication
Ultrafast (5-30%)	*1/*17 *17/*17	Increased	Normal dose
Extensive (35-50%)	*1/*1 (wild type)	Normal	Normal dose
Intermediate (18-45%)	*1/*2 *1/*3	Reduced	Alternative antiplatelet e.g. prasugrel or ticagrelor
Poor (2-15%)	*2/*2 *3/*3 *2/*3	Little	Alternative antiplatelet

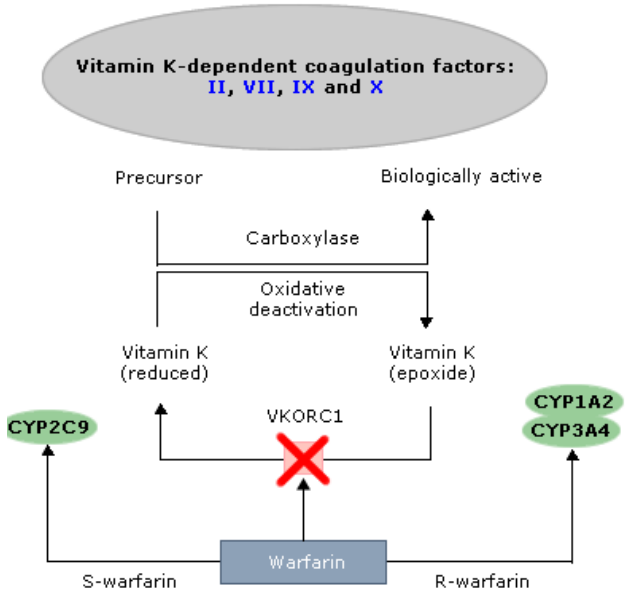
*17 has increased activity

*2 and *3 have reduced activity

NOTE: *Wild type always has a *1 as its final designation*

CYP2C9

Responsible for the metabolism of S-Warfarin. S-warfarin is responsible for the **inhibition of VKOR (Vitamin K epoxide reductase)** which is responsible for the recycling of Vitamin K which in itself is responsible for the activation of factors II, VII, IX, X, Proteins C and S.



NOTE VKOR as well as CYP2C9 show significant genetic variation:

- VKORC1 (subunit 1) mutations are located in non-coding regions.
- CYP2C9 substitutions are within the transcribed region of the gene.

There are treatment algorithms to calculate warfarin dose required based on genetic and non-genetic factors i.e. age, weight, height, VKORC1 and CYP2C9 phenotype, race and other meds.

Acetyltransferase

N-acetyltransferases (NAT1 and NAT2) enzymes are responsible for **hepatic phase 2 acetylation**. These 2 subtypes are found on chromosome 8.

NAT-1	NAT-2
Para-aminobenzoic acid (PABA)	Isoniazid
Paracetamol	Hydralazine
Sulfamethoxazole	Dapsone

Slow acetylators have the NAT-2*5 allele which are autosomal recessive. 50% of Caucasians are slow acetylators.

NAT are also involved in **processing carcinogens**:

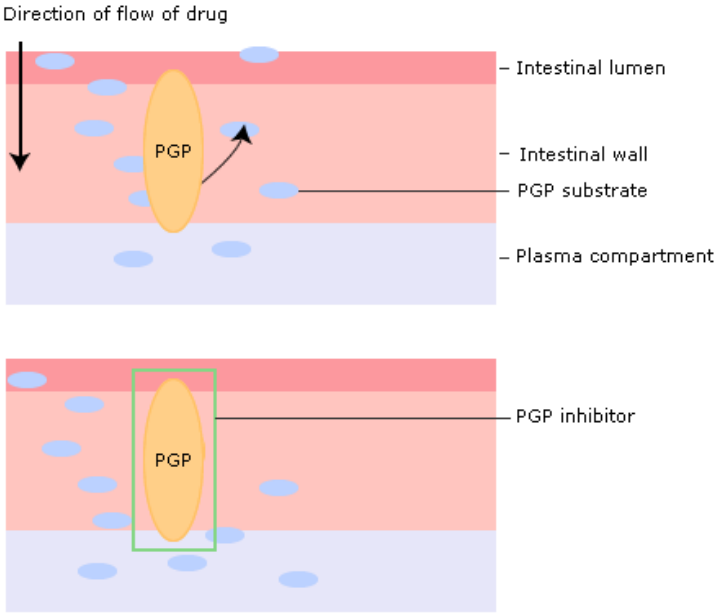
- **Fast acetylators** are at higher risk of colon cancer
- **Slow acetylators** are at higher risk of bladder cancer

Genetic Variation in Transport Proteins

P-Glycoprotein (PGP) AKA *ABC Transporter* AKA *Multi-Drug Resistance Protein 1*

Product of the *ABCB1 gene* and is present in **intestinal epithelium**, **hepatocytes**, **proximal tubular cells** of the kidney and in **vascular endothelium in the BBB.**

Think of it that this protein is involved in preventing drug movement the way you want it. A wild-type of PGP will increase its activity and hence **reduce oral bioavailability**.



PGP inhibitors include:

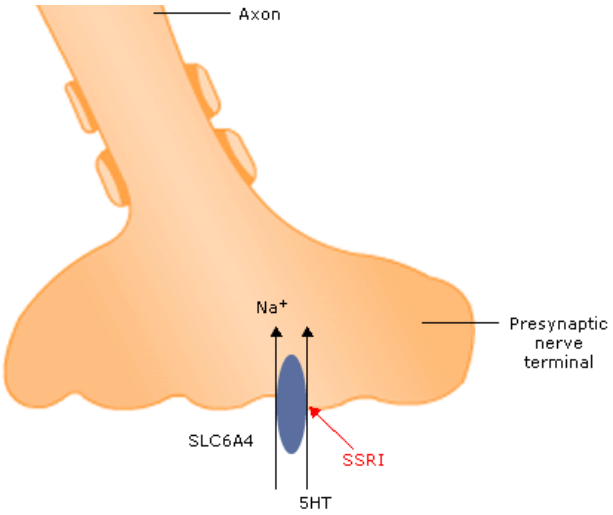
- Amiodarone
- Verapamil
- Ciclosporin

These happen to be inhibitors of CYP3A4 and will increase the bioavailability of concurrently administered drugs.

Solute Carriers

These are responsible for multiple transport mechanisms including the following neurotransmitters:

- SLC6A1 for GABA
- SLC6A2 for noradrenaline
- SLC6A3 for dopamine
- **SLC6A4** for serotonin (5HT)



These variations have been linked to personality disorders and **responsiveness to SSRIs**. SLC6A4 has a **short (S)** or a **long (L) allele**. L/L has 3-fold greater serotonin reuptake activity. Those with the S/S genotype are less likely to respond to SSRIs.

Genetic Variation in Receptors

Receptors have variability through alternative splicing between tissues.

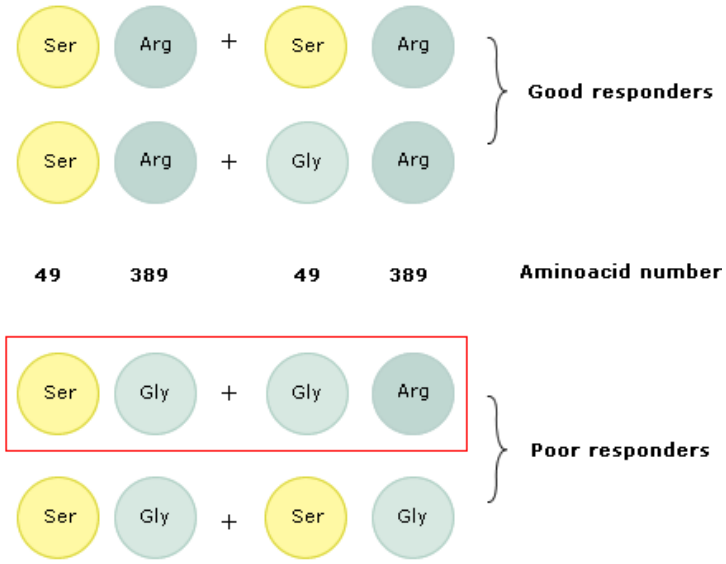
They can be seen to have genetic differences between different individuals which may alter **drug binding** or a **change in normal conformation** once bound. The 2 important **G-proteins** involved are:

- β1-adrenoceptor
- μ-opioid receptor

β1-adrenoceptor

Metoprolol is seen to improve L ventricular remodelling in hypertensive patients. **Good responses** are seen in the following ADRB1 genotypes:

- *Wild type* (normal alleles)
- *Heterozygotes* (single SNP at amino acid number 49)



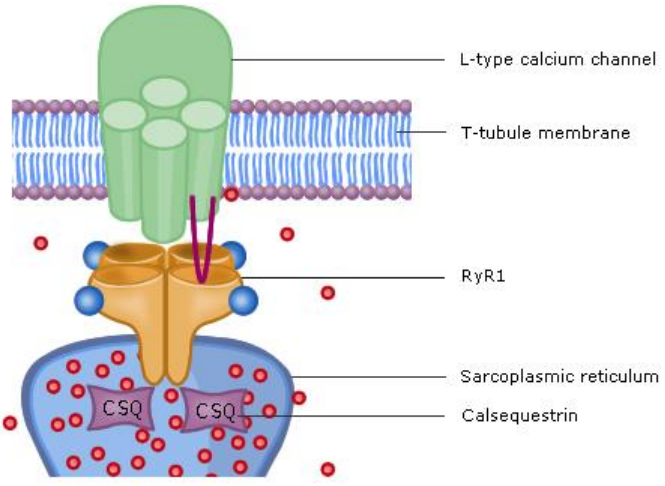
No responses occur in SNPs that have a *homozygous genotype* or in a single SNP in an important position (389). These are also associated with increased incidence of essential hypertension, cardiomyopathy and congestive cardiac failure. More common in Afro-Caribbeans.

μ-opioid receptor

MOR is the gene and has 2 promotor regions. It undergoes alternative splicing in different tissues. The most prevalent gene is ***MOR-1*** and a mutation exists which causes a single amino acid change and increases the EC50 (or the K_D) of morphine and morphine 6-glucoronide.

Ryanodine Receptor

Ligand-gated ion channel found in close association with L-type VG Ca^{2+} channels and IP3 receptors. In those with malignant hyperthermia, 25% have a ryanodine receptor gene *RYR1* mutation. This results in increased calcium release.



Clinical Pharmacogenetics Implementation Consortium

Involved in the regulation of genetic testing prior to drug administration. They have issued guidelines for codeine, warfarin, clopidogrel and simvastatin.

Cancer Therapy

Trastuzimab (HERCEPTIN) is a monoclonal antibody that is responsive to cancers overexpressing HER2 protein.

Imatinib is an inhibitor of tyrosine kinases in CML (Philadelphia chromosome producing continuously active tyrosine kinases).

Antimicrobials

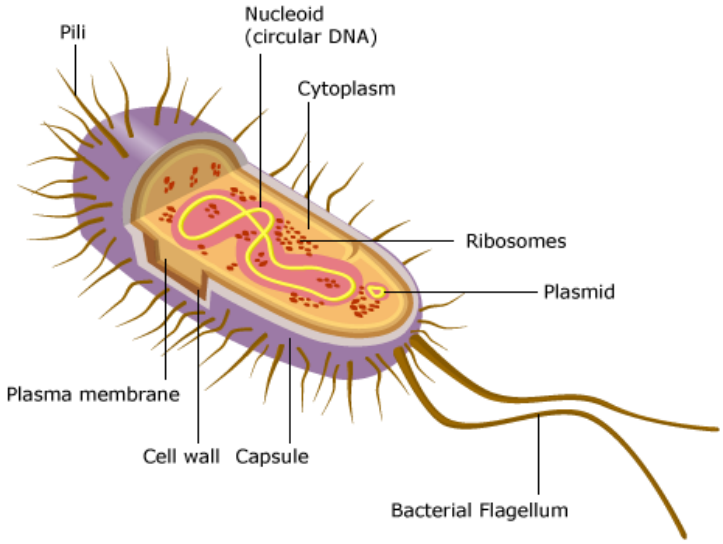
(07c_21_01 **AND** 07c_21_02)

Refers to a substance derived from a microorganism that inhibits or destroys growth of another micro-organism.

Generally classified into:

- Anti-viral
- Anti-bacterial
- Anti-fungal

Antibiotic: Includes all anti-bacterial, anti-fungal and anti-parasitic agents synthesised artificially or naturally.

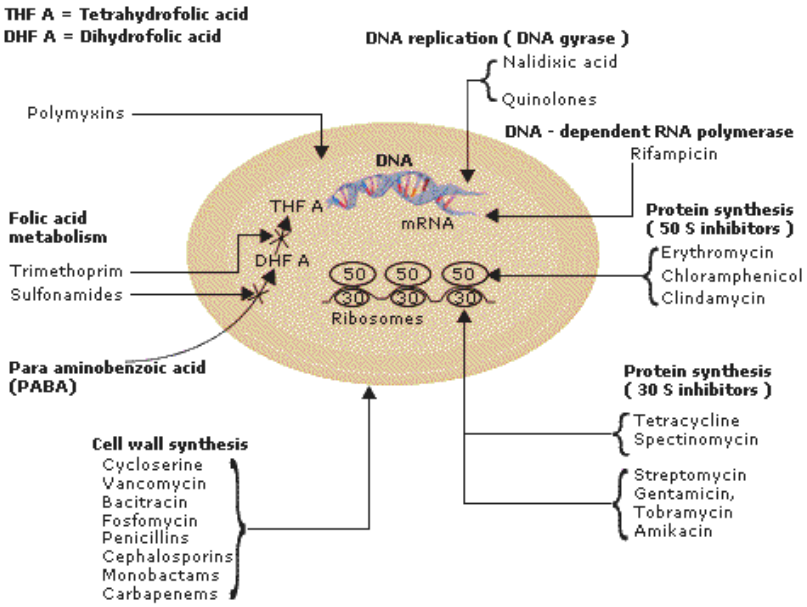


Cell Structure

Bacteria are **prokaryotes** i.e. they are unicellular organisms without nuclei. Much smaller. The difference in cell structure forms the basis of antibiotic therapy to provide **selective toxicity**. This can be split into 2 main methods:

1. **Attack targets present in bacteria and not human cells** (LEFT of diagram)
    a. Bacterial cell wall
    b. Folate metabolism

2. **Attack bacterial physiological/metabolic systems that differ from humans** (RIGHT of diagram)
    a. Inhibition of ribosome function
    b. Inhibition of nucleic acid synthesis

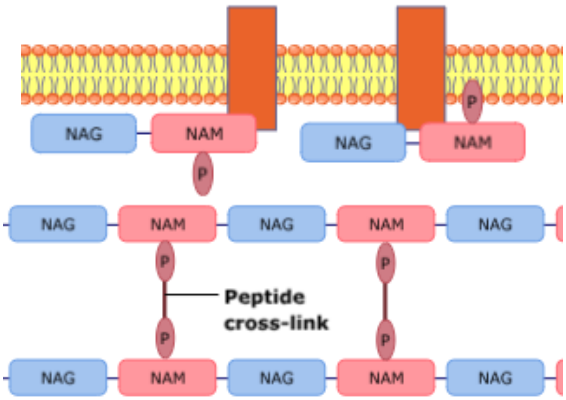


Bacterial Cell Wall Synthesis

Made up of a linear **peptidoglycan polymer** held together by cross linkage and functions to give the cell wall integrity to withstand an osmotic gradient.

Peptidoglycan Synthesis

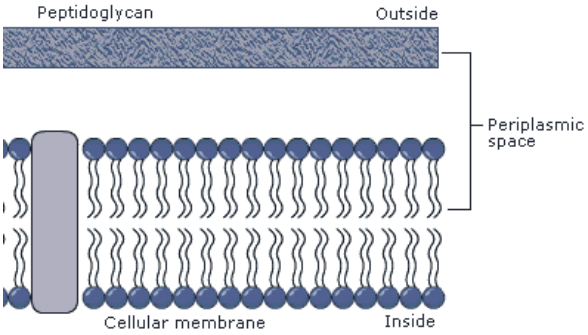
Made up of alternating peptidoglycans (amino sugars) N-acetylglucosamine (**NAG**) and N-acetylmuramic acid (**NAM**) held together by **glycosidic bonds** and 4 or 5 amino acid side chains attached to NAM crosslinking to a similar side chain on another NAM group by **transpeptidase**.



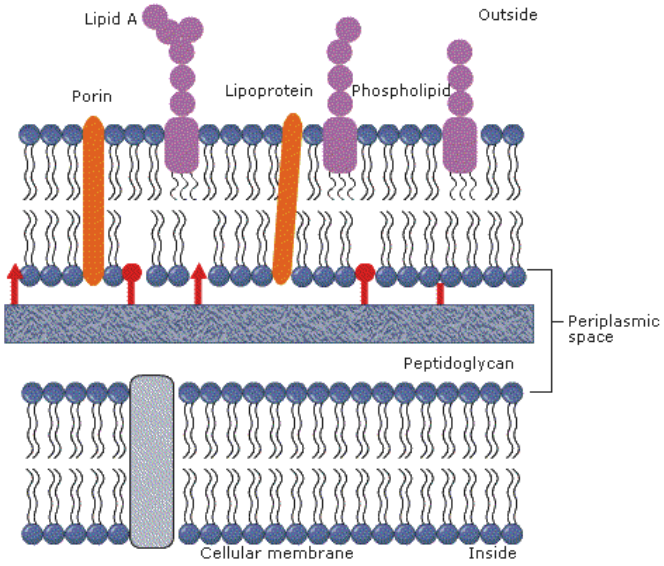
NAM and NAG with the peptide side chain are prepared on the cytoplasmic side of the cell membrane and attaches to a protein (bactoprenol aka Lipid II) which then translocate it out of the cell to integrate with the growing peptidoglycan layer using **autolysins** to break the bonds and then the **transglycosylase** (forms a glycosidic bond) enzymes.

Gram Positive vs Gram Negative

Gram Positive: Made mostly of peptidoglycan interspersed with teichoic acid. It is much **thicker** (50-90% of thickness) with more cross linkage.

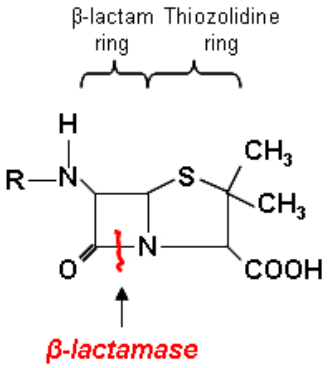


Gram Negative: More complicated: Outside the cell membrane is a **thin** layer of peptidoglycan (5-10% of thickness) and outside of this is a membrane containing porins and liposaccharides:



B-Lactams **BACTERICIDAL**

The b-lactam ring of penicillins resemble **D-alanyl D-alanine** which is one of the amino acids attached to NAM and is required in bacterial cell wall synthesis. It acts a **suicide substrate** for **transpeptidase enzymes** and results in no peptide links, a weak cell wall which results in osmotic lysis.



Therefore, the transpeptidase enzymes and transpeptidase/transglycosylase enzymes are known as **Penicillin Binding Proteins (PBP)**.

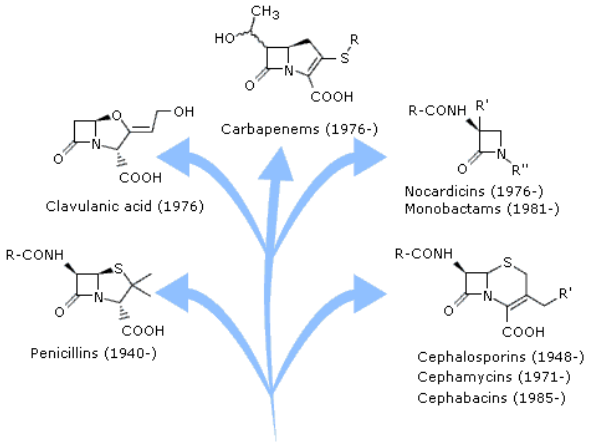
RESISTANCE: Bacteria may produce **b-lactamase** which degrades the b-lactam ring. Altered permeability in porins. Altered PBPs.

PENICILLINS:

Category	Example	Spectrum of activity
Narrow spectrum B-lactamase - sensitive	Benzylpenicillin Phenoxymethylpenicillin (Pen V)	*Streptococci, Neisseriae, Treponema pallidum*
Narrow spectrum B-lactamase - resistant	Flucloxacillin Methicillin	*Staphylococcus*
Extended spectrum	Ampicillin, Amoxicillin, Co-amoxiclav	Non-B-lactamase producing Gram +ve e.g. *E.coli*, *haemophilus*, *Salmonella*

Limitations

- Breakdown by gastric acidity when given orally
- Rapid excretion by kidneys
- Restricted spectrum. Inflammation necessary to pass through bone and CNS.
- B-lactamase



This had led to further modifications of the penicillins. Clavulanic acid and tazobactam are b-lactamase inhibitors.

Excreted unchanged in urine by tubular secretion. This can be blocked by **probenecid** to allow increased concentrations

Other B-Lactams (10% cross-reactivity)

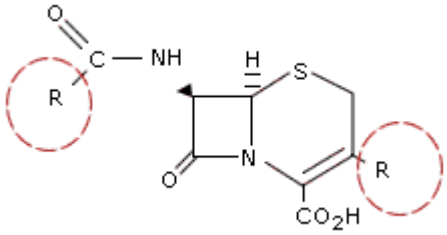
***CARBAPENEMS*:** i.e. Meropenem, Imipenem

These have **high affinity to PBPs** and are able to traverse the outer membrane of Gram -ve cell walls via different proteins to penicillins and cephalosporins. Used for resistant organisms and has a broad spectrum of activity and is also resistant to B-lactamases.

***MONOBACTAMS*:** Aztreonam (the only available compound)

Only gram -ve. It passes through the outer membrane to bind to PBPs and is resistant to hydrolysis by most b-lactamases. It has no activity against gram +ve and hence should never be used alone.

***CEPHALOSPORINS*:**

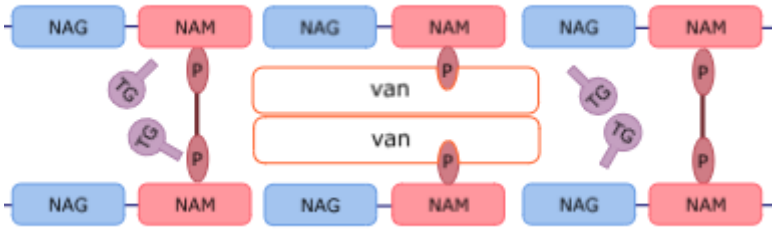


Structurally related to penicillins where the b-lactam ring is fused to a 6 membered **dihydrothiazine** ring (rather than a 5-membered thiazolidine ring). Altered by changing the -R groups

They differ as they are stable to staphylococcal penicillinase but lack activity against enterococci. They work in the same way by **binding to PBPs** and preventing transpeptidase activity.

Generation	Example	Description	Activity
1st	Cefalexin, Cefaclor	Narrow spectrum	Best activity v Gram+ve Some Gram -ve cover (*E.Coli, Klebsiella, Proteus*)
2nd	Cefuroxime	Extended spectrum	Slightly less effective against Grame+ve Gram -ve cover better (+*B.fragillis, H.influenzae*)
3rd	Ceftriaxone, Cefotaxime, Ceftazidime	Broad spectrum – enhanced resistance to b-lactamase.	Less effective against Gram +ve but Grame -ve cover better (e.g. *ceftazidime against P. aeruginosa*) Some have better CNS penetration (cefotaxime, ceftriaxone)
4th		Broad spectrum	Not available in the UK

***Glycopeptides*BACTERIOSTATIC**



Complex heterocyclic structures that are too bulky to penetrate the outside gram-negative bacteria. Therefore, they are **only effective against gram positive bacteria**.

They bind to the peptidoglycan monomer peptides to block function of the PBPs.

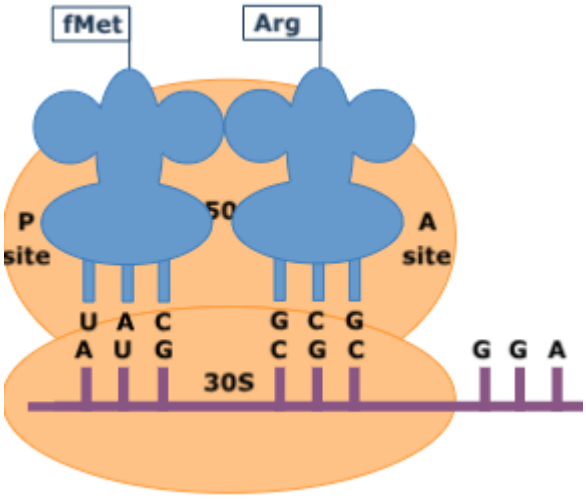
Vancomycin and **Teicoplanin** are effective against **MRSA**.

Vancomycin cannot be absorbed orally so is only oral for C. diff infections. 90% excreted unchanged in urine and is therefore monitored due to toxicity:

- OTOTOXICITY – discontinue if tinnitus occurs
- HISTAMINE RELEASE – hypotension, tachy and widespread rash (**red-man syndrome**)
- PHLEBITIS – Dilution of IV preparation required.

Teicoplanin has 2-4 times the potency of vancomycin and a longer duration of action (half-life 33-190h) for once daily administration. More active against streptococci and enterococci.

Bacterial Protein Synthesis Inhibitors



Bacterial Ribosomes have **50s** and **30s subunits** whilst human ribosomes are 60S and 40S. Like humans, mRNA is transcribed from bacterial DNA. Then for translation:

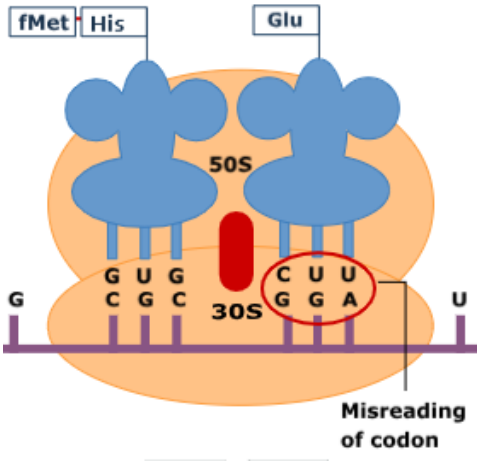
30S binds to the mRNA prior to the start codon. tRNA attaches to the start codon via a complementary anticodon carrying the amino acid **formyl-methionine** (**fMet**) to form the **initiation complex**.

The 50s subunit has an **A-site** and a **P-site** where the tRNA is transferred from the former to the latter to allow **elongation** and build peptide bonds between the amino acids where the tRNA at the P-site leaves the ribosome. The ribosome then advances by one codon known as **translocation**.

Termination occurs when the stop codon is reached in which there is no tRNA to bind with an appropriate anticodon. The protein is then released from the ribosome.

Aminoglycosides

Amikacin, Gentamicin, Tobramycin, Streptomycin



These bind **irreversibly** to the **30S subunit** to interfere with tRNA binding to the A-site or transfer of tRNA from A to P-site – mRNA is now not read or misread so that the proteins produced are non-functional.

They are **large polar molecules** which need active transport to gain access into bacterial cells. May be inhibited by divalent cations Mg and Ca, acidosis and low O_2 tension. Therefore, they are often used in conjunction with b-lactams as they have a synergistic effect. B-lactams disrupt the cell wall allowing aminoglycosides to enter more easily.

KINETICS:

- Low protein binding
- Low volume of distribution – in extracellular fluid (large, polar molecules)
- Not metabolised and excreted unchanged

TOXICITY:

- **Ototoxicity** (mainly vestibular) from accumulation in the inner ear perilymph
- **Nephrotoxicity** – reversible on discontinuation, highest risk being age.
- Muscle weakness – reduce post-junctional sensitivity to ACh and pre-junctional release.

Tetracyclines

Tetracycline, doxycycline, minocycline, oxytetracycline

Broad spectrum activity also binds to **30S subunit** in the same mechanism as the aminoglycosides. Restricted use to limit overgrowth of resistant strains.

Kinetics: Chelation by milk and with Ca, Mg and antacids. Avoid in renal and hepatic failure. Deposited in growing children bones and teeth → dental hypoplasia/staining. CI'd in pregnancy.

Macrolides **BACTERIOSTATIC/BACTERICIDAL**

Erythromycin, Clarithromycin, Azithromycin

Binds **irreversibly** to the **50S ribosomal subunit** between the A and P sites interfering with the **translocation** step.

They cover most gram +ves and gram -ve anaerobes. CSF penetration is poor but has good sputum and lung penetration. Metabolised and excreted by the liver. **CYP3A4 inhibitors** and **PGP inhibitors**.

EFFECTS:

- CV: Prolonged QT interval
- GI: Nausea, vomiting and diarrhoea → **prokinetic effect**. Avoid in porphyria

Lincosamides **BACTERIOSTATIC/BACTERICIDAL**

Clindamycin

Binds to the **50S ribosomal subunit.** Serious anaerobic and gram +ve cocci infections. Good bone penetration – good for staph bone infections. Not good against gram -ve aerobic organisms.

Fusidanes **BACTERICIDAL**

Fusidic Acid:

Gram positive cover. Forms a complex with elongation factor and GTP to prevent elongation and prevents protein synthesis.

Penetrates cerebral abscesses but not CSF. Good for bone penetration. Excreted unchanged in bile.

Inhibitors of Folate Synthesis and Metabolism

Para-aminobenzoic acid (PABA) is an essential metabolite involved in the synthesis of folic acid which is required as a precursor for the synthesis of nucleic acids.

Humans cannot synthesise folic acid and must obtain it via diet (vitamin B9).

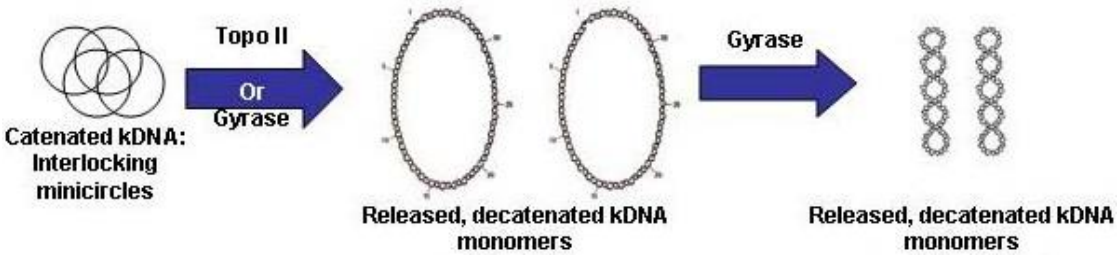
This difference is exploited and selectively inhibits nucleic acid synthesis in bacteria.

Sulfonamides: i.e. sulfamethoxazole. Analogues of PABA to interfere with normal PABA uptake into bacteria. They also inhibit **dihydropteroate synthetase** which is involved in the synthesis pathway.

Trimethoprim: Inhibits **dihydrofolate reductase** involved in synthesis of tetrahydrofolate. This enzyme is also present in human cells but trimethoprim has a 50,000x greater affinity to the bacterial form than the human. If combined with sulphamethoxazole to make co-trimoxazole – produced synergistic effects.

Inhibitors of DNA Synthesis

DNA gyrase (Topoisomerase II) is only present in prokaryotes involved in breaking both strands of DNA and relinking them. **Topoisomerase IV** is involved in DNA decatenation which is where 2 daughter chromosomes are separated after division of a bacterial chromosome.



Quinolones **BACTERICIDAL**

Ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin

All act on topoisomerase II and IV. Mostly **Gram -ve** – good for atypical pneumonias i.e. pseudomonas. They can also be used as inhibitors in human cells as chemotherapy (etoposide).

EFFECTS:

- CNS: Provoke seizures,
- TENDON DAMAGE (Achilles tendon rupture)
- CV: Prolonged QT interval
- HAEM: G6PD deficiency → Haemolytic reactions.

Nitroimidazoles

Metronidazole

Passive diffusion into bacterial cells and is reduced to its active form by ferrodoxin. It disrupts the DNA Helical structure via free radical damage.

Good for **anaerobes** and protozoa. 100% bioavailability and distributes widely in CSF, abscesses, prostate, pleural fluid. Metabolites excreted through the kidney.

SIDE EFFECTS:

- Nausea, metallic taste.
- Alcohol → disulfiram like reaction → nausea, vomiting, headache, flushing, hypotension

Rifamycin

Rifampicin

Binds to b-subunit of DNA-dependent RNA polymerase preventing transcription. Not used as a single agent as becomes easily resistant. Potent **CYP450 inducer**. Red colour secretions.

ANTIVIRALS

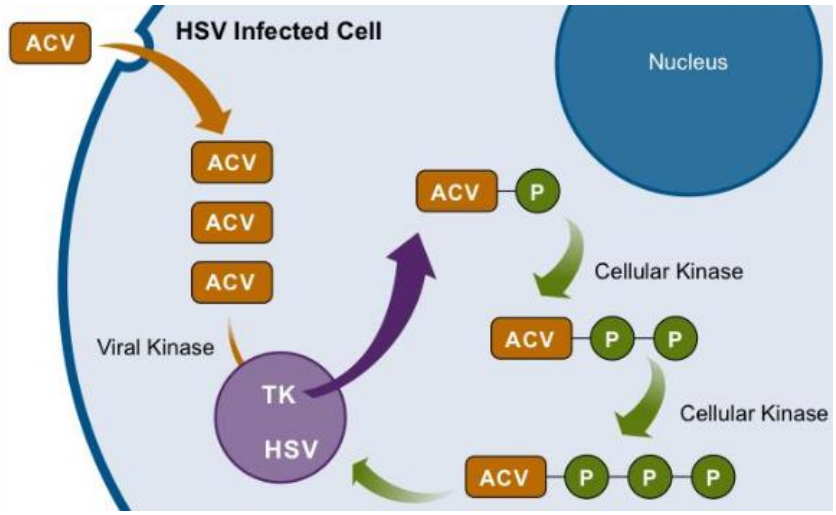
Viruses are classified into **DNA** or **RNA Viruses** and whether the nuclei is single or double stranded.

Acyclovir

Used to treat **DNA viruses: Herpes simplex and Varicella Zoster**.

Inhibits nucleic acid synthesis:

1. Cells infected with these viruses contain an enzyme known as **thymidine kinase**.
2. Acyclovir is a substrate for this enzyme
3. Converted into **acyclovir monophosphate**.
4. This is then converted into an **active triphosphate** which inhibits **DNA polymerase** and acts as a **chain terminator**



It does not eradicate them but is effective at the beginning of infection.

KINETICS:

- OB 25%
- Partially metabolised and excreted unchanged blocked by probenecid.

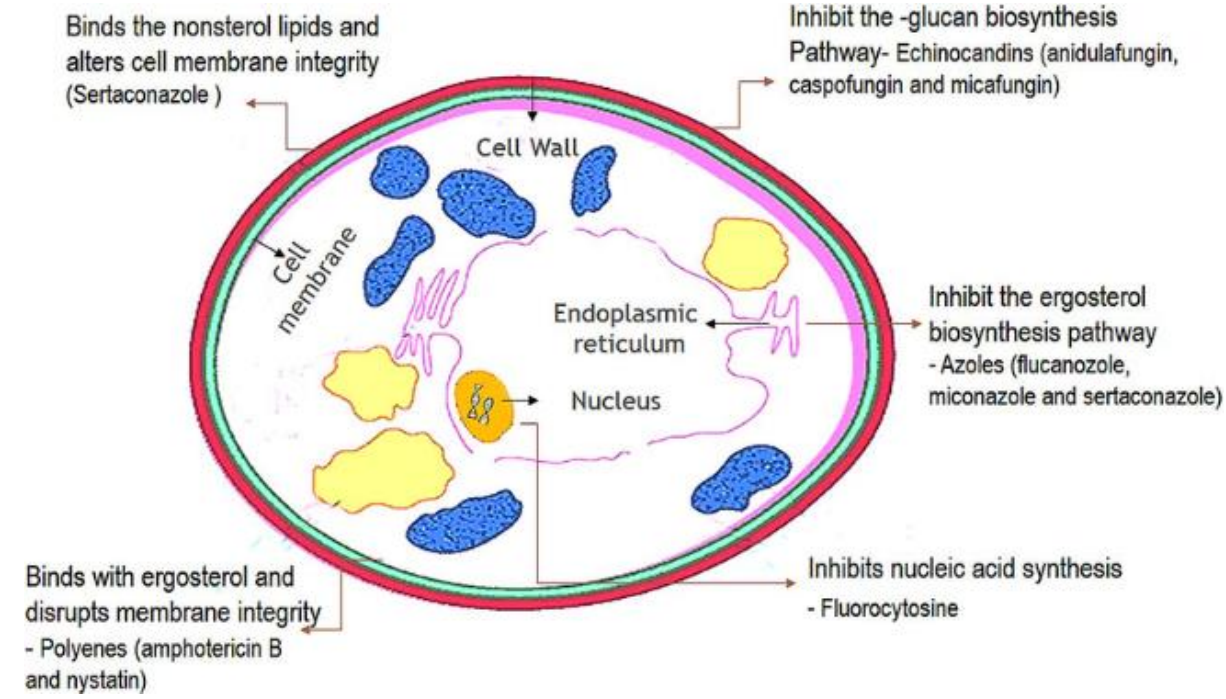
SIDE EFFECTS:

- Renal impairment
- Thrombophlebitis
- CNS tremors, confusion, seizures and coma with rapid IV.

Zidovudine

Treatment of **HIV** in combination with other antiviral agents. **Nucleoside reverse transcriptase inhibitor** (nucleoside analogue). Converted into zidovudine triphosphate binds to HIV reverse transcriptase, incorporates into proviral DNA and terminates the DNA chain. 100x more affinity to HIV reverse transciptase vs host DNA polymerase.

ANTIFUNGALS



Polyenes: Bind to ergosterol in fungal membranes → creates a transmembrane channel.

Amphotericin B: Aspergillus, candida, cryptococcus. Only available IV and can cause nephrotoxicity (levels itself do not rise in renal failure).

Azoles

- Triazoles: **Fluconazole** and **Itraconazole**
- Imidazole: **Ketoconazole** and **Miconazole**

Used for candida, cryptococcus and histoplasma. Prevent conversion of lanosterol → ergosterol which is an essential component of the cell membrane. Potent **inhibitors of CYP450.**

REFERENCE TABLES

Muscle Relaxants

Muscle Relaxant	**ED^{95}** *(mg/kg)*	**Intubating dose** *(mg/kg)*	**Onset Time** *(s)*	**Clinical Duration** *(min)*
Succinylcholine	0.3	1	60	10
Benzylisoquinoliniums				
Tubocurarine	0.5	0.5-0.6	220	80+
Mivacurium	0.08	0.15-0.2	170	16
Atracurium	0.23	0.5	110	43
Cisatracurium	0.05	0.1	150	45
Aminosteroids				
Pancuronium	0.07	0.1	220	75
Vecuronium	0.05	0.1	180	33
Rocuronium	0.3	0.6	75	33
Rapacuronium	1.2	1.5	75	15

ED^{95} *is the dose that depresses the twitch height by 95%*

Onset time *is the time to 95% depression of the 1st twitch of train-of-four*

Clinical Duration *is the time to 25% recovery of the 1st twitch of train-of-four*

Acetylcholinesterase Inhibiters

Reversal Agent →	***Neostigmine***	***Edrophonium***	***Pyridostigmine***
Dose *(mg/kg)*	0.05	1	0.1
Onset of Action *(min)*	1	1-2	>16
Duration of Action *(min)*	20-30	10	360
Distribution Half-Life *(min)*	3.4	7.2	6.7
Elimination Half-Life *(min)*	77	110	113
Total Plasma Clearance *(ml/min/kg)*	9.1	9.5	8.6
Recommended Anticholinergic	Glycopyrronium	Atropine	Glycopyrronium

Induction Agents

Agent →	***Propofol***	***Thiopental***	***Ketamine***	***Etomidate***
PHARMACOKINETIC PROPERTIES				
Water soluble?	No	Yes	Yes	No
Initial Half Life *(min)*	2	8.5	16	1
Terminal Half Life *(hours)*	4-7	12	3	5.4
Volume of Distribution *(L/kg)*	4.6	2.4	3	5.4
Clearance *(ml/min/kg)*	25	11	19	18
Protein Binding *(%)*	98	80	12	75
PHAMACODYNAMIC PROPERTIES				
Heart Rate	→	↑	↑	→
Contractility	↓	↓	↑	→
SVR	↓	↓	↑	→
MAP	↓	↓	↑	→
Respiratory	Depressed	Depressed	Bronchodilation	→
CBF	↓	↓	↑	↓

Opioids

Phamacokinetic Property	***Morphine***	***Pethidine***	***Fentanyl***	***Alfentanil***	***Remifentanil***
pKa	8.0	8.5	8.4	6.5	7.1
Unionised @ pH 7.4 *(%)*	23	5	9	90	68
Plasma Protein Bound *(%)*	30	40	84	90	70
Terminal Half Life *(hours)*	3	4	3.5	1.6	0.06 (3.6mins)
Clearance *(ml/min/kg)*	15-30	8-18	0.8-1.0	4-9	30-40
Volume of Distribution *(L/kg)*	3-5	3-5	3-5	0.4-1.0	0.2-0.3
Relative Lipid Solubility *(to morphine)*	1	28	580	90	50

Volatile Agents Pharmacokinetic Properties

Characteristics	Desflurane	Sevoflurane	Isoflurane	Enflurane	Halothane	N_2O	Xenon
Boiling Point *(^OC @ ATM)*	23	59	48	56.5	50.2	-89	-108
Blood:Gas *(@37^OC)*	0.4	0.68	1.4	1.8	2.4	0.47	0.12
Oil:Gas *(@37^OC)*	26	47	91	98	224	1.4	1.9
MAC	6.0	2.0	1.15	1.68	0.75	104	71
Metabolism *(%)*	0.02	5	0.2	2	20	0	0

Local Anaesthetics

Local Anaesthetic	pKa	Onset of Action	PB *(%)*	Duration of action	Relative Lipid Solubility	Elimination Half-life *(min)*	Relative potency
Tetracaine	8.5	Slow	75	Long	200	80	8
Cocaine	8.6	Mod	95	Short		100	
Lidocaine	7.9	Fast	70	Mod	150	100	2
Prilocaine	7.7	Fast	55	Mod	50	100	2
Bupivacaine	8.1	Slow	95	Long	1000	160	8
Ropivacaine	8.1	Slow	94	Long	300	120	8

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Listed below are the original authors of the online modules:

APPLIED CHEMISTRY

Drugs as Organic Molecules	Craig Holdstock, Mary Stocker
Interactions Between Molecules	Mary Stocker
Ionisation	Sue Hill
Isomers	Mary Stocker

PHARMACODYNAMICS

Agonists and Receptors	Tim Smith
Enzyme Induction and Inhibition	Visweswar Natarajan
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Drug Interactions	Shelley Barnes

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Absorption and Bioavailability	Damien Wood, Hannah Gardner
Inhalational Drug Administration	James Gray, Sue Hill
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Introduction to Pharmacokinetic Modelling	Sue Hill
Two and Three Compartment Models	Sue Hill
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Target Controlled Infusions	Sue Hill
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Interindividual Variation in Drug Response	Sue Hill
Antimicrobials	Geoff Lockwood

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