Pokémon or Prescription Drug?

Sentret	Enspryng	Vibrava	Geodon	Vaporeon
Phesgo	Cliscor	Flareon	Nincada	Tabrecta
Azurill	Umbreon	Zepzelca	Rayquaza	Rescriptor
Ticlid	Marowak	Inqovi	Voltaren	Blenrep
Retevmo	Vulpix	Monjuvi	Glaceon	Tukysa

Permeation

Is the ability of a drug to move throughout the body.It depends on lipid solubility* + concentration gradient**.

*Water solubility would influence permeation though aqueous phases
**Only free unionised forms of drugs contribute to concentration gradients,

Other factors include
surface area* + vascularity**

* Greater surface area leads to greater absorption of drugs.
e.g: Stomach vs Small intestine, latter has larger surface area thus greater absorption.

** High levels of vascularity allows drugs to move faster through circulation and to different tissues and compartments.

Example, giving a drug intramuscularly or intra-fat
Or thinking about how a drug is given to a patient in shock (Intravenously.)

Ionisation

About 80% of drugs can potentially become ionised.

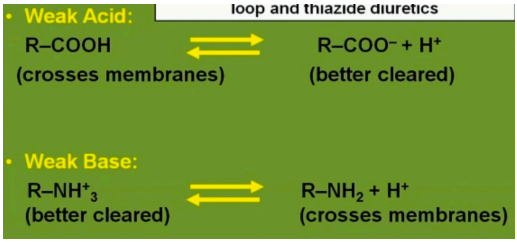
These drugs exist either as weak acids/weak bases. They can swap between an ionised (charged) or non-ionised form (uncharged)

In order to predict the form the drugs will be in a particular environment Two pieces of information are required.
1)The pH of the environment
2) The Pka* of the drug in question.

*The pH at which the drug is 50% ionised and 50% non-ionised.

Only non-ionised (uncharged) forms cross the biological membranes.
thus
Ionised forms being water soluble, are better excreted by the kidneys.

Important weak acids
Aspirin
Penicillins
Cephalosporins
Loop & Thiazide diuretics



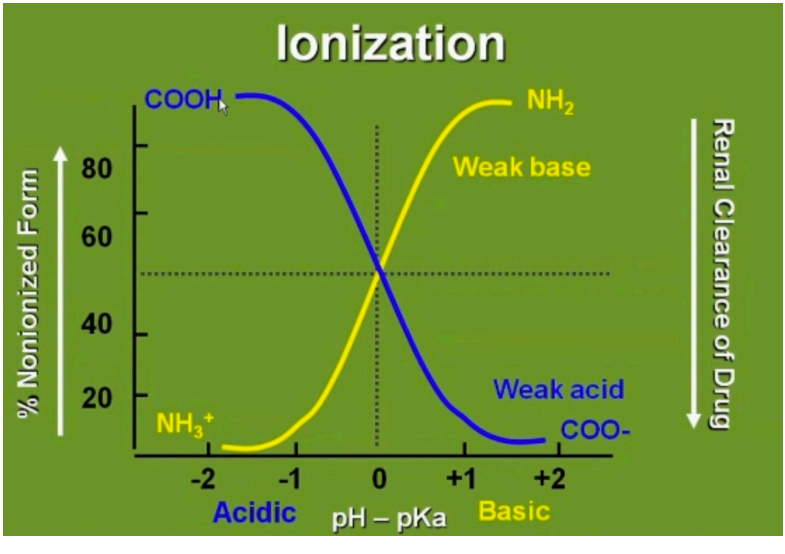
Important weak Bases
Morphine
Local Anesthetics
Amphetamines
PCP

If a weak acid drug is put into an environment with a pH lower then it's it's pKa. The weak acid drug will it exist in the non-ionised form, which is lipid soluble and can pass biological membranes

If a weak acid drug is put into an environment with a pH higher then it's pKa. The weak acid drug will exist in the ionised form, be water soluble thus cannot cross membranes and is trapped wherever it is.

If a weak base drug is put into an environment with a pH higher then it's pKa. The weak base drug will exist in the non-ionised form, be lipid soluble thus can cross membranes

If a weak base drug is put into an environment with a pH lower then it's pKa. The weak base drug will exist in the ionised form, be water soluble thus cannot cross membranes.



ph of different body compartments to memorise
Stomach = 1-2
Small intestine = 6
Blood = 7.4
Urine = 5-8

Renal clearance of the drug

Only the free drugs are filtered through the kidney, i.e not bound to plasma protein.
Of the free drugs, both ionised and nonionised will be filtered through kidney
Nonionised form can be either passively or actively reabsorbed
But
The ionised form will be trapped.

Acidification of urine will eliminate weak bases
Alkalation of urine will eliminate weal acids

Manipulating pH of Urine

To make it acidic
NH_4Cl*, Vitamin C, Cranberry juice

To make it alkaline
$NaHCO_3$, Acetazolamide.

*Amonium chloride is considered a general antidote to weak bases overdose.

Absorption

Is the entry of a drug into systemic circulation from it's site of administration.

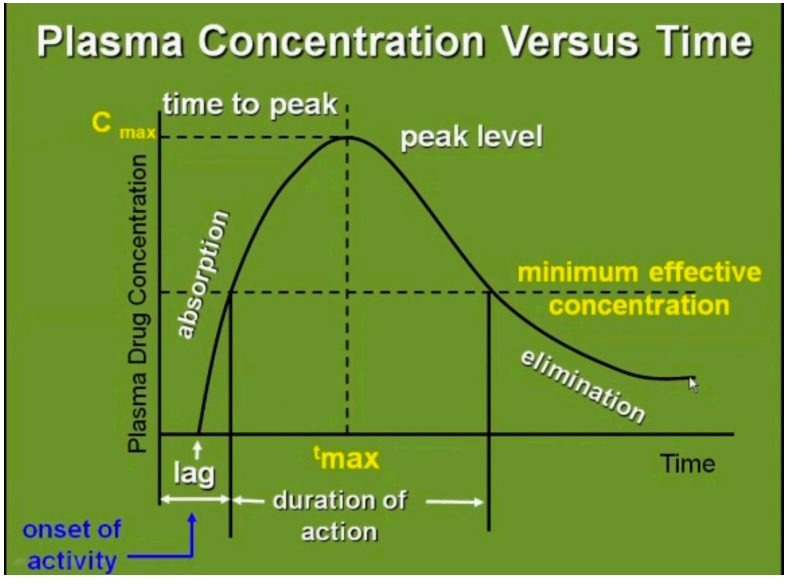
factors affecting absorption are the same factors for permeation.

IV administered drugs have a bioavailability* of 100%
* Describes the rate and concentration at which a drug reaches systemic circulation

Less than 100% of the original dose administered extravascularly will reach the systemic circulation due to variations in bioavailability.

The fastest route of absorption is inhalation and not IV because IV skips absorption

A way to think about bioavailability is, how much of the dose will get into the blood.



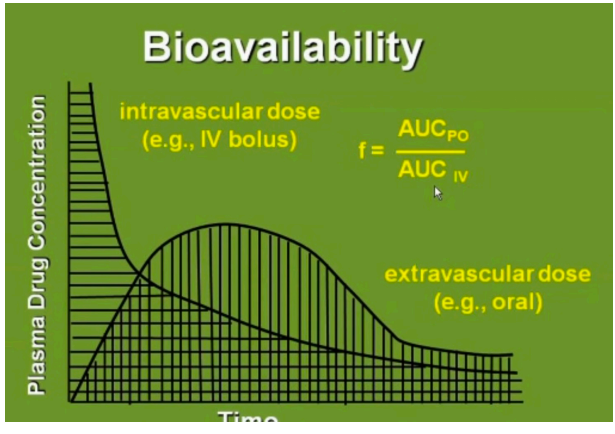
Lag time

The time a drug requires first enter the blood from extravascular route.
The **minimum effective conc**. is the first sight of pharmacological effect.
Duration of action is the time spent above the minimum effective conc.
It's possible to manipulate the absorption curve by manipulating the pH of the environment.
The extent of action of the drug also can be altered by changing the extent of elimination, also by changing pH.

Bioavailability

Can be demonstrated as the ratio of the area under the curve for an extravascular dose and an intravascular Dose

Drugs with a bioavailibity less then 100% will need their loading doses modified to take into account that less then 100% of the administered dose will enter the patients blood.

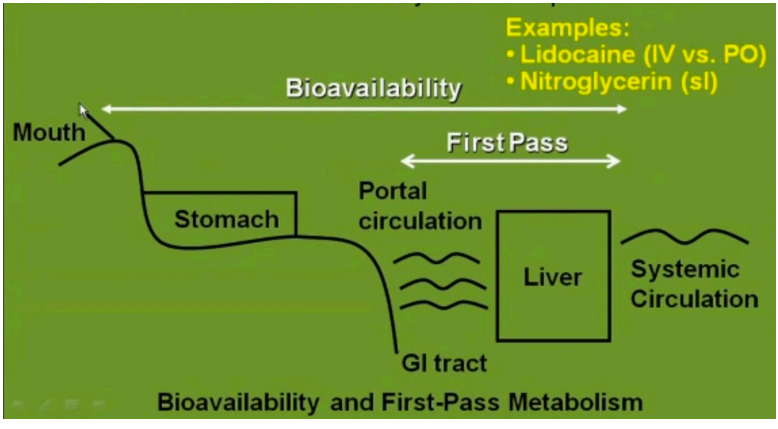


IV bioavailability is 100%
it's as standard to determine the bioavailability of other extravascular drugs.

First pass effect

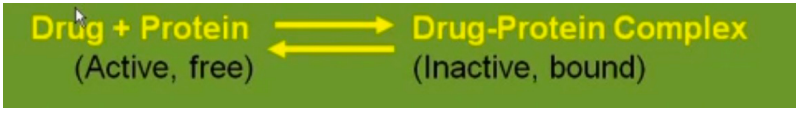
A drug administered orally first will be absorbed by portal circulation, distributed to liver where, the drug will be acted on by hepatocytes.

This will decrease bioavailability.



Distribution

Distribution of the drugs from systemic circulation to various organs and tissues
Many drugs are lipid soluble and thus are insoluble in blood.
These drugs are typically bound to a carrier protein in the plasma, in this form they are inactive.
Not all of the drug will bound to plasma protein, some exist in an active free form in the plasma.
There is an equilibrium to explain the relationship between active free drug in plasma vs the inactive bound form.



Emphasis is placed on the concept that the drug is active in the free state.
Different drugs will compete against each other to become bound to plasma proteins e.g **Warfarin** and **sulphonamide** interaction.

Distribution Barriers

Placental
Low molecular weight drugs can cross the barrier

Blood-Brain barrier
Low molecular weight drugs, lipid soluble can cross the barrier.
e.g, **Li** and **Ethanol**, despite being charged and polar. These two therapeutic drugs are small enough to pass CNS

a handy rule to remember
If it can pass the Blood-Brain barrier, then It can pass the Placental barrier too!

What properties should a drug have in order for the drug to be "Safe" for pregnant women
Ideally it shouldn't be able to cross the Placental barrier, so the drug should have the following properties:
1) Water-soluble
2) Large
3) Protein-bound (High concentration will be bound to proteins)
Property 3 most sought after

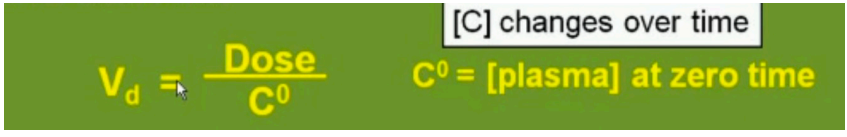
Propylthiouracil and **Methimazole** are both are used to treat hyperthyroidism.
But should be given to a pregnant woman?
Propylthiouracil as it's molecular property and characteristics does not allow it to cross the placental barrier compared to
Methimazole which may cross the Placental barrier and cause Cretinism to the fetus. According to Amboss, Propylthiouracil can be given in 1st trimester while Can be given in 2nd or 3rd trimester. **Iodides** are definitely contraindicated as they cross the Placental barrier

Phenobarbital is an anti-convulsant. It can be given to pregnant women without risk of passing placental barrier.

Apparent Volume of distribution.

It is a Proportionality factor and a primary pharmacokinetic parameter. Nothing more nothing less.

Its a parameter that predicts what percentage of a given drug will be bound to either plasma-proteins or be distributed to tissues.
Another way to think about it is that it is the theoretical volume a drug would occupy if it was distributed evenly in fluids at plasma concentration.



Vd = volume of distribution (usually expressed in liters/kg body weight)
Dose = amount of drug in the body at a specific time
Co = plasma concentration of the drug at a specific time

How the formula works.

If a dose is given to a patient and the plasma concentration of the dose at any given time measured i.e Co measured.

If the value of the Co is low this gives a Vd more then 1, and indicates to us that the drug is distributed outside of the plasma, the location of the distribution depends on the value of Vd which in turn depends on Co.

If Co is high (numerically closer to the value of dose administered) this will give a low Vd suggesting that a large amount of the drug is bound to plasma proteins.

Typically the Vd of a drug is already known.
A question may be posed with Vd and the Co of a drug being the information given.
You will be asked to calculate the current amount of drug in the patients body.

If a patient has renal or liver failure/disease/damage for a drug with a normally low Vd the Vd will increase as there will be a decrease in plasma proteins to bind to the drugs

Again as a reminder, only a free drug unbound to plasma will be pharmacologicaly active.

Redistribution

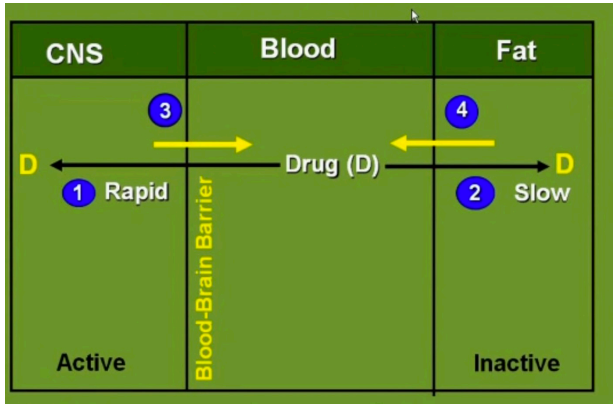
Some drugs transfer to different compartments such as fat tissue.

These are typically lipophilic lipids drugs.

Redistribution increases the duration of action of the initial dose of the drug.

e.g

Thiopental is an IV anaesthetic. It that reaches the brain from the plasma in less then a minute. This drug has a half-life in the distribution phase of 4 hours but has a half-life of 9 hours during the elimination phase. This is a consequence of the drug getting redistributed to fat via the plasma. It stays in the fat for 9 hours. Thiopental does not have an effect in the fat.

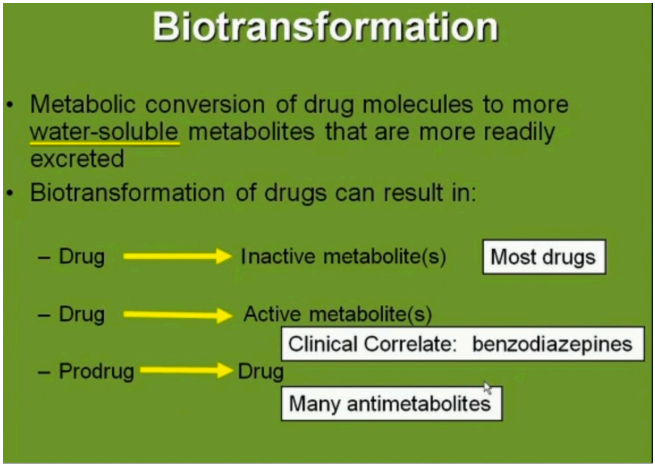


Another point drawn from the above image is that if a lipophilic drug which act upon the ins is given to a patient, that it is possible for the fat to become saturable with the lipophilic drug and thus it will transfer back to the blood. From the blood it may again cross into the CNS and have an active effect,.

In short, the elimination of the drug is delayed and the action of the drug is prolonged.

Biotransformation

Chemical modification of drugs to facilitate the elimination of the drug from the body to active a drug or to form active metabolites.



The concept drawn by the above image is that biotransformation may have different outcomes depending on the drug being metabolised.

1) An active drug is converted to an inactive metabolite in the case of most drugs.
2) An active drug is converted to active metabolites in case of **benzodiazepines**.
3) An inactive drug is converted to an active drug in case of **antimetabolites**

Biotransformation is divided into two phases, I & II

Phase I reactions involve chemical modification of the drug.
The purpose of phase I reactions is to make a lipophilic drug more polar by adding polar functional groups to the drug.
The drug may undergo **oxidation, reduction or hydrolysis** reactions.
The enzyme responsible for these reactions are the **Cytochrome P450 Isozymes**
There are at least 13 Cyp450 families and 100 enzymes.
These Isozymes are found in the smooth endoplasmic reticulum of hepatocytes.
For these Isozymes to function, Oxygen and NADPH are an absolute requirement.
Oxidation reactions can be further divided to include **Hydroxylations** and **Dealkylations** reactions.

Regarding the table below, it is not to be memorised in its entirety. Only the names of the listed CYP450 family should be memorised. Memorising the listed substrate examples is elective but not necessary. The theoretical concepts behind the inducers and inhibitors are important to understand and be able to re-explain

CYP 450	Substrate Example	Inducers	Inhibitors	Genetic Poly-morphisms
1A2	Theophylline Acetaminophen	Aromatic hydrocarbons (smoke) Cruciferous vegetables	Quinolones Macrolides	No
2C9	Phenytoin Warfarin	General inducers	—	Yes
2D6	Many cardiovascular & CNS drugs	None known	Haloperidol Quinidine	Yes
3A4	60% of drugs in PDR	General inducers	General inhibitors Grapefruit juice	No

Looking at inducers, e.g aromatic hydrocarbons which is contained in smoke. If the patient smokes.

The liver will be induced to make more CYP450 1A2 enzyme.

If the same patient is prescribed **Theophylline**, the patient will metabolise the drug faster due to increased CYP450 1A2 enzyme level due to its induction by aromatic hydrocarbons.

As a consequence the patient will have a lower plasma concentration of the drug.

Therefore if the doctor is aware of the smoking habits of the patient, a dosage adjustment of the drug will need to be made.

If the patient is convinced to stop smoking, another dosage adjustment will need to be made adjust for the lower 1A2 levels.

Inhibitors have the opposite effect, they will decrease the enzyme activity and increase the plasma concentration of the drug,.

Another e.g
A patient is suffering from chronic bronchitis.

These patients should receive bronchodilators and antibiotics, since patients with chronic bronchitis suffer from recurrent respiratory infections.

Theophylline is a bronchodilator

Macrolides are the typical antibiotic given to these patients.

However

Macrolides are CYP450 1A2 inhibitors. They will slow metabolism of Theophylline leading to increased Theophylline blood levels Ultimately Theophylline toxicity will occur.

Classic P450 inducers →

Inducers	Inhibitors
Phenobarbital	Cimetidine
Phenytoin	Macrolides (esp. erythro-)
Carbamazepine	Ketoconazole
Rifampin	"avirs"
Chronic alcohol	Acute alcohol
	Grapefruit juice

Phenytoin and Carbamazepine go hand in hand in many ways including the fact they both Induce Cyp450

Cimetidine is a high yield inhibitor of Cyp450

Grapefruit juice has active components in it that inhibit many drugs including statins

Azithromycin seems to have no inhibitory effect unlike other macrolides

Phase 1 Non-microsomal Metabolism

Are other forms of phase 1 mediated chemical modification of drugs. They do not involve the Cyp450 family isozymes.

Hydrolysis
is the addition of water molecules to break chemical bonds
accomplished by **Esterase** and **Amidases**

Pseudocholinesterase deficiency can be caused by genetic polymorphism.
If a patient suffers from this and they are given the anaesthetic S**uccinylcholine.** The patient will experience a longer lasting effect of the drug due to the slower breakdown of it.

Monoamine oxidases
Are a group of enzymes functioning to metabolise **Amine neurotransmitters**

The origins of amine neurotransmitters can be endogenous or exogenous based on whether or not it is physiologically originated in the body.
Endogenous amines neurotransmitters include **Dopamine, NE and Serotonin**

Exogenous amines neurotransmitters include **Tyramine** which is found in beer, red wine, cheese and fish.

Alcohol metabolism
Alcohols are metabolised to Aldehydes by alcohol dehydrogenases. The aldehydes are converted to acids by aldehyde dehydrogenases.
genetic polymorphisms may lead to deficiency in alcohol dehydrogenase.

Phase 2 reactions

Involve the conjugation of an endogenous compound onto a drug.
These reactions are facilitated by **Transferases enzymes.**
Different endogenous compounds can be conjugated by different transferase enzymes.

Glucuronidation

The drug is conjugated to **Glucuronic acid** by **Glucuronosyl transferase**.
The enzyme is inducible.
This process can undergo enterohepatic cycling*

Neonates have reduced Glucuronosyl transferase activity.
Morphine and **Chloramphenicol** are conjugated to Glucuronic acid.
If a neonate is given chloramphenicol they will experience chloramphenicol toxicity.
Individuals with **Gilbert syndrome** have mild reduction is Glucoronoysl transferase.
Crigler-Najjar syndrome is divided into type I and type II
In type I there is a total absence of Glucuronosyl transferase activity and is incompatible with life.
In type II there is a mild reduction in Glucuronosyl transferase activity.
* after the drug is conjugated in the liver its put into the small intestine then absorbed back to blood and brought back to liver.

Acetylation

It's important to know of genotypic variation. In a population there will be individuals who have fast and slow acetylation activity.
If you fast activity then there's no real problem.
The problem are for people who have slow acetylation activity.
These people metabolise the drugs slowly.
The drugs tend to build up leading to toxicity
one form of which is drug-induced SLE which is induced by the slow metabolisation of **Hydralazine,** a vasodilatve drug.
procainamide and **isoniazid** also have been known to cause drug induced SLE in people with slow acetylation activity.
To distinguish between non-drug induce SLE the presence of Antihistones must be identified.

Glutathione Conjugation

Glutathione is able to be depleted incase of drug overdose. e.g **Acetaminophen**.
If more then 7.5g a day is taken then the Glutathione pool in the body will become exhausted. Instead a toxic metabolite of Acetaminophen is produced which will injure hepatocytes.
Essentially Acetaminophen overdose will cause Drug induced hepatitis.

Acetaminophen is the American & Japanese word for Paracetamol.

Elimination

When we think of elimination should think of the fact we are terminating the action of the drug.

There are different methods of elimination. The two most common methods of elimination are **Biotransformation** in Liver to Inactive metabolites, which is an inactivation method by metabolism.
and
Excretion by kidneys* which is an inactivation method via removal from the body

*Don't get excretion and elimination mixed up, while excretion is a form of elimination, some drugs are long inactivated by biotransformation in the liver before they reach the kidneys.

Other forms of elimination by excretion, bile duct, lungs and sweating.

elimination half-life
is an importrant concept. It is the **TIME** taken to eliminate 50% of a **GIVEN AMOUNT** of a drug.

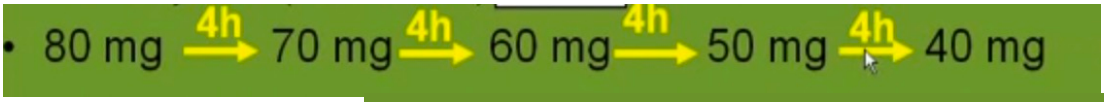
Zero order elimination rate

A constant **AMOUNT** of a drug is eliminated **per unit time**.
The current concentration/amount of the drug is in the body is irrelevant, and **per unit time** the drug concentration will always decrease in with a constant AMOUNT being eliminated.
There is no fixed half-life

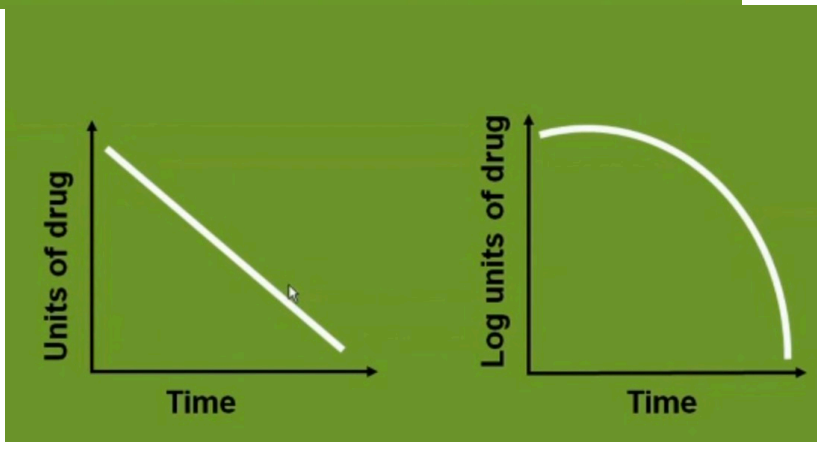
Zero order kinetics drugs: **Ethanol**, **Phenytoin** and **Salicylates**

The underlying mechanism is that the **elimination kinetics** are **saturated.**
The enzymes eliminating the drugs are at Vmax
This makes sense since we are thinking of drugs which are administered at high therapeutic doses.

At very low blood levels , Ethanol **WONT** display Zero order kinetics.



Imaging displaying **per unit time** there is a **constant amount** of drug Being eliminated



First order kinetics

There is a constant **FRACTION** of the drug being eliminated **per unit time**.

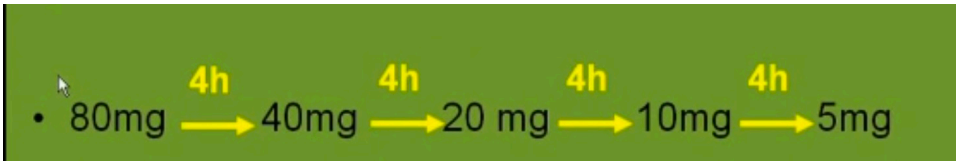
The **TYPE** of kinetics that are involved in eliminating these drugs is a typical enzyme kinetics, meaning that the enzymes are not working at their Vmax.

Half-life is constant.
The fraction being eliminated is constant
The relationship between half-life and elimination constant is inverse.
Longer half-life means lower elimination fraction. Demonstrated by the below formula.

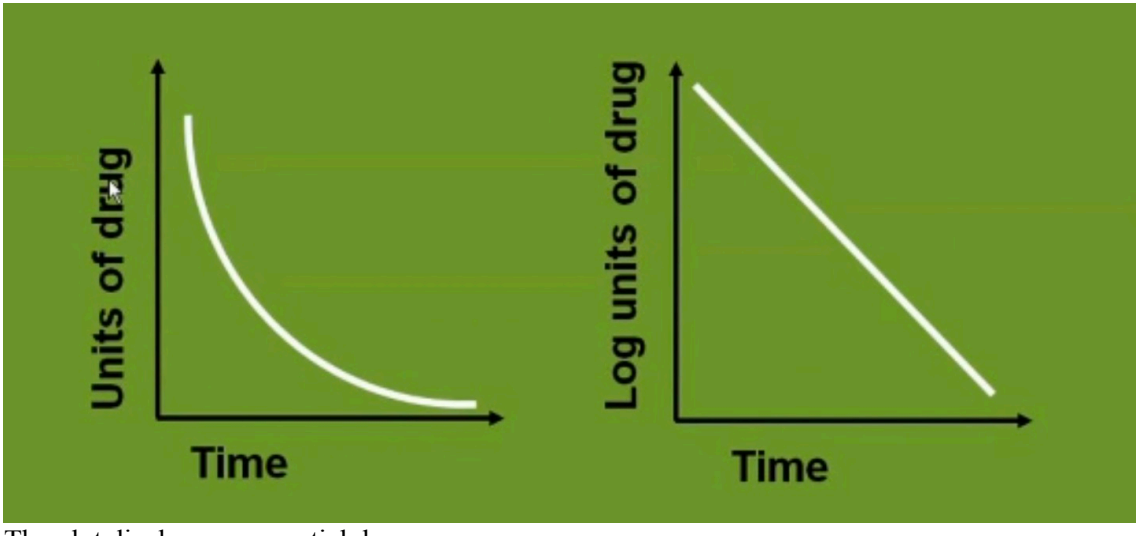
$(k): t_{1/2} = 0.7/k$

k = elimination constant.

Most drugs follow 1st Order Kinetics.



Elimination fraction is constant, is inverse to half-life.
Amount being eliminated per unit is not constant.



The plot displays exponential decrease.

Graph becomes linear
be careful not to confuse with
Zero order kinetics

Renal Elimination

Rate of elimination = glomerular filtration rate (GFR) + active secretion – reabsorption

Three factors which influences the renal elimination of drugs.

1) GFR

♂ 95–145 mL/min/1.73 m2

♀ 75–125 mL/min/1.73 m2

2) Active secretion of the drug

3) Reabsorption of the drug

Filtration through the glomerulus is a linear function and not saturable.
Ionised and nonionised forms of the drug get filtered.
Protein bound drugs WILL NOT be filtered.

Clearance

Is the **volume** of blood that is 'Cleared' of a drug **per unit time.**

First order kinetic drugs typically display constant clearance.

$$Cl = \text{free fraction} \times GFR$$

Clearance formula taking into account that only free drugs in plasma pass through kidney.

If clearance is **less** then GFR then you can assume the possibility of **reabsorption**

If clearance is **more** then GFR then you can assume the possibility of **active/passive secretion.**

Steady State

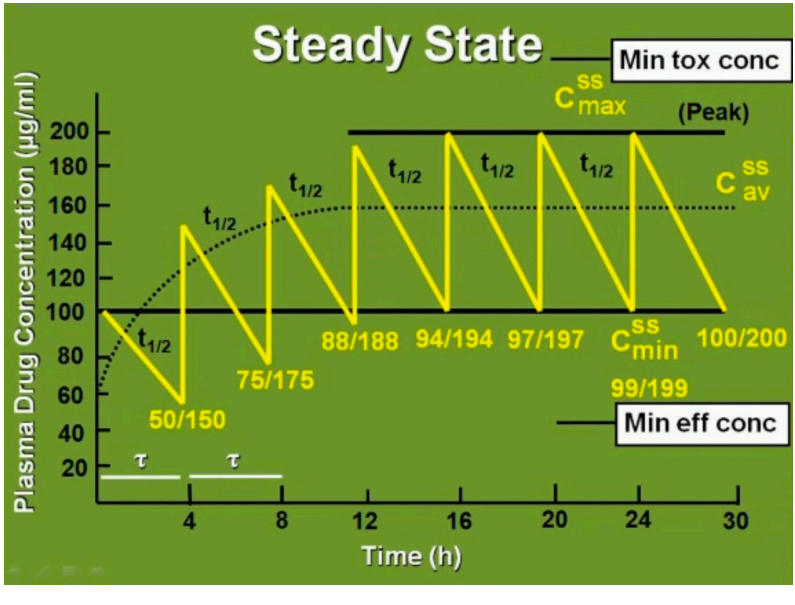
A **state** during drug administration and maintenance where A **dynamic equilibrium** is achieved in the plasma concentration of a drug, where the **rate of elimination is equal to the rate of administration.**

The plasma drug level is maintained above the **minimum effect concentration** but below the **minimum toxic concentration**, this is referred to as the therapeutic window.
This dynamic range of plasma drug concentration is most popularly achieved by dosing the patient at regular half-life intervals.

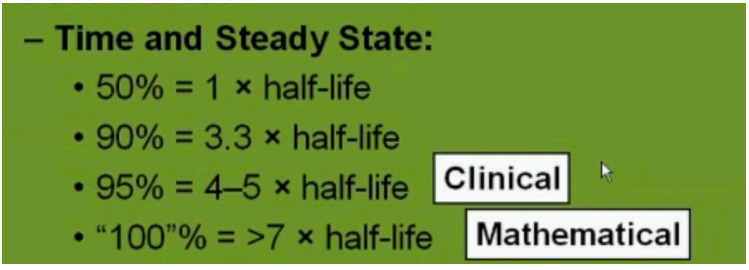
The dose that the patient is given is typically constant*

*There are exceptions where the doses given at regular intervals are not constant such as giving a loading dose followed by maintenance doses.

The **TIME** to reach the steady state depends on the **Half-life of the drug**
NOT on the **Dose size** and the frequency of dose administration!



The average plasma drug concentration is the yellow line.
It plateaus during the steady state.
Because of this, the steady state is sometimes referred to as the **plateau phase.**



After 1st dosage and half-life , 50% of the steady state is achieved.
After 4-5 doses , 95% of the steady state is achieved.
This is referred to as the clinical steady state*

*After 7 or more doses we will reach around 100% of the steady state, the Mathematical steady state, it is not sought after in clinical practice as it takes too long to achieve.

So with this knowledge if we know for example the half-life of a drug is 5 hours then we know that after 20-25 hours it will be possible to achieve a clinical steady state.

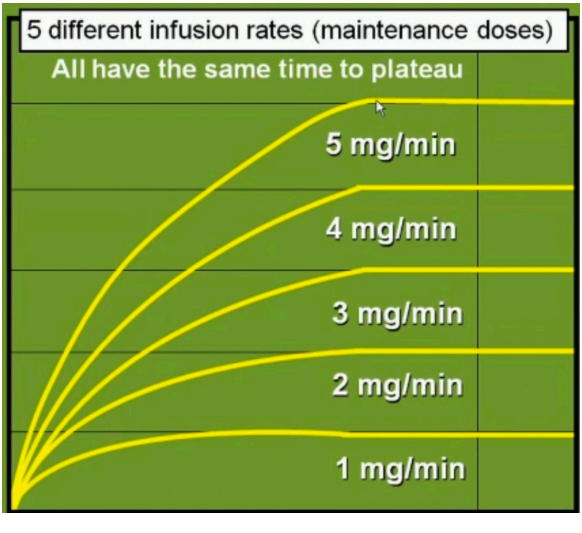
Rate of Infusion K0

Giving an infusion dose faster will not give a steady state faster, and giving a higher dose will not achieve the steady state faster.

this graph displays the independence of the rate of infusion and the time to reach steady state.

different infusion rates are displayed yet they all reach the plateau phase at the same time.

what is different however is that the higher infusion rate will have a plateau phase with higher plasma drug concentration interval



Loading Dose

If the time to reach steady state for a drug is simply too long or we cannot afford to wait to reach a steady state because of an emergency, then it's possible to reach the steady state faster by administrating a loading dose.

The loading dose is typically twice the minimum effect concentration.

after the first half-life is achieved the plasma drug concentration will be the minimum effect concentration.

Maintenance doses will then be given to maintain the steady state.

One might ask why don't we always use this method?

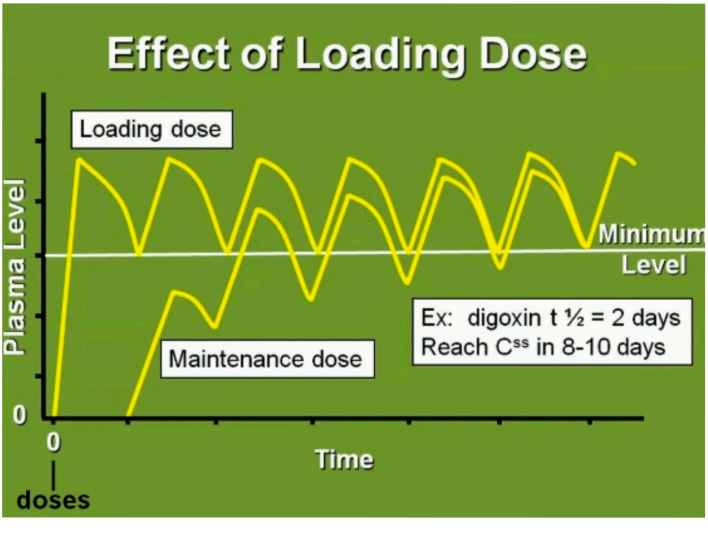
Well because it's dangerous to suddenly give a large amount of a drug.

Loading dose formula

Cp is the target drug plasma concentration

Vd is the volume of distribution

$$LD = C_p \times V_d$$



Pharmacokinetic calculations

$$V_d = D/C^0$$

Volume of Distribution
= Amount of drug in the body at a specific time / Plasma concentration of a drug at the same specific time.

Half life equation

$$t_{1/2} = 0.7 \times V_d/Cl$$

Note that half-life and Vd are directly proportional while Vd and Clearance are inversely proportional.

Infusion rate (k_0):

$$k_0 = Cl \times C^{ss}$$

Where The infusion rate is proportional to both Clearance and Css which is the target plasma concentration

Maintenance dose (MD):

$$MD = \frac{Cl \times C^{ss} \times \tau}{f}$$

Tau = Dosing interval

f = Bioavailability

Loading dose (LD):

$$LD = \frac{V_d \times C_p}{f}$$

Vd = volume of distribution
Cp =

Remember for drugs administered through IV the bioavailability will be 1!

Pharmacodynamic

Is essentially what the drug does to the body

Definitions critical to pharmacodynamics

Agonist

A drug is an agonist when binding to the receptor causes a response

Antagonist

A drug is called an antagonist when binding to the receptor does not cause a response.
The drug's only "effect" is to prevent an agonist to binding to the receptor.

Affinity

The ability of a drug to bind to a receptor.
Represented by the proximity of the curve to the Y axis, The nearer the curve to the Y axis the greater the affinity.
The affinity of drugs can be compared only if the curves are parallel with each other and for that they must have the same slope.
Curves with the same slope have the same receptor.

Potency

Compares the relative doses off two or more agonists in their ability to produce a greater magnitude of effect.
Essentially how little of a drug can I give to make the biggest effect. Represented again by the closeness of the curve to the Y axis. **This time we can only compare potency of drugs if their curves do not cross.**

Efficacy

should be thought of as the effectiveness of a drug. It's the measure of how well a drug produces a response. Represented by the maximal height reached by a curve.

Dose response curves

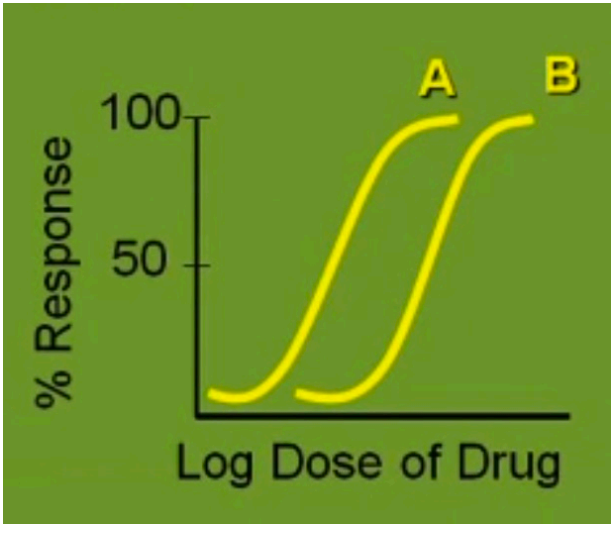
The graphs plot dose vs response.
They can be linear or Logarithmic, the latter is preferred.
The graphs allow us to visualise drug information like affinity, potency and efficacy.

In order to compare the **affinity** of the two drugs, the two curves must be parallel and have the same slope.

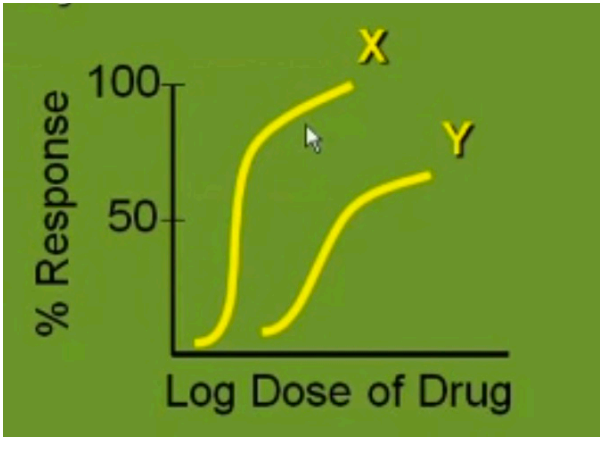
In the image to the right, the two curves are parallel and have the same slope.

The curve closer to the Y axis has the higher affinity.

Curve A has a higher affinity



In order to compare **Potency** of two drugs the curves should not intersect. It is not an absolute rule. This will be explained soon.
The curve closer to the Y axis has the higher affinity.



Any two curves can have their **efficacies** compared.
The curve with the higher Y value will have the higher efficacy
Note the Y value is a % out of 100 so if they both are at 100 it means they both activate the receptor maximally.

Curve X and Y do not have the same slope thus we cannot compare affinity.
But Efficacy and Potency can be compared.
Curve X has higher Potency and Efficacy.

More Definitions

Full agonist*

Produces a maximal efficacy (100%)

*Typically we don't use the term full agonist we just use the word agonist and the "Full" is implied.

Partial agonist.

Essentially the name designated to agonists which are not full agonists.

As previously stated, it is not recommended to compare the potencies of two curves which intersect. But it is not impossible to do so.

If we look at red point we see drug A, is exhibiting 30% response. What is the response of drug B at this dose? Zero since its plot hasn't started yet. At the dose represented by the red dot, drug B shows zero response.

But what if we looked at a point after the crossing of the two curves lets say at blue point. We will notice that the response of B has a higher Y axis then that of A which has plateaued. So after a certain dose, drug B has a higher potency than drug A and this certain dose is after the curves intersect.