Primary Cast Episode 27 - Pharmacology General Principles

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Pharmacodynamics

1. **Agonists**

   In the context of drug-receptor interactions, what is the difference between a full agonist and a partial agonist?
   High concentrations of full agonists can evoke a maximal response, whereas partial agonists cannot evoke a maximal response at any concentration

   Under what circumstances can a partial agonist act as an antagonist?
   In the presence of a full agonist, a partial agonist can act as an antagonist. Buprenorphine is an example of this.

   In relation to drug responses, what is the EC50?
   The concentration at which an agonist produces half of its maximal effect

   What are spare receptors?
   The concentration of agonist producing the maximal response may not result in occupancy of a full complement of receptors
   These receptors are said to be “spare”

   What are the 2 main mechanisms of receptors becoming spare?
   Temporal spares - the receptor triggers a prolonged response after transient binding
   Numerical spares - limited substrate with excess receptors

   What is the significance of spare receptors?
   Increasing the number of receptors coupled to an effector can allow a lower concentration of agonist to still produce a given proportion of maximal response. This means the tissue is more sensitive.

2. **Antagonists**

   What is an antagonist?
   Receptor antagonists bind to receptors but to not activate them. The primary action of antagonists is to prevent agonists from activating receptors

   What is the difference between competitive and non-competitive antagonist?
   Competitive - competes with the agonist for the active site by binding at the same place as the agonist. Increasing concentration of agonist will produce the given effect.

   Non-competitive or irreversible can bind in such a way that the receptor is no longer available for binding, either by modifying the active site or by binding with stronger bonds. In this case, the duration of effect depends on the turnover of receptor-antagonist molecules and the effect cannot be overcome by increasing concentrations of agonist.

What type of antagonist is naloxone?
Competitive

What other antagonists can you list?
Flumazenil
Propranolol
Mono-amine-oxidase inhibitors

What effect does a competitive antagonist have on the concentration-effect curve?
Shifts the curve to the right, because higher concentrations of agonist can overcome a competitive antagonist. The EC50 is increased.

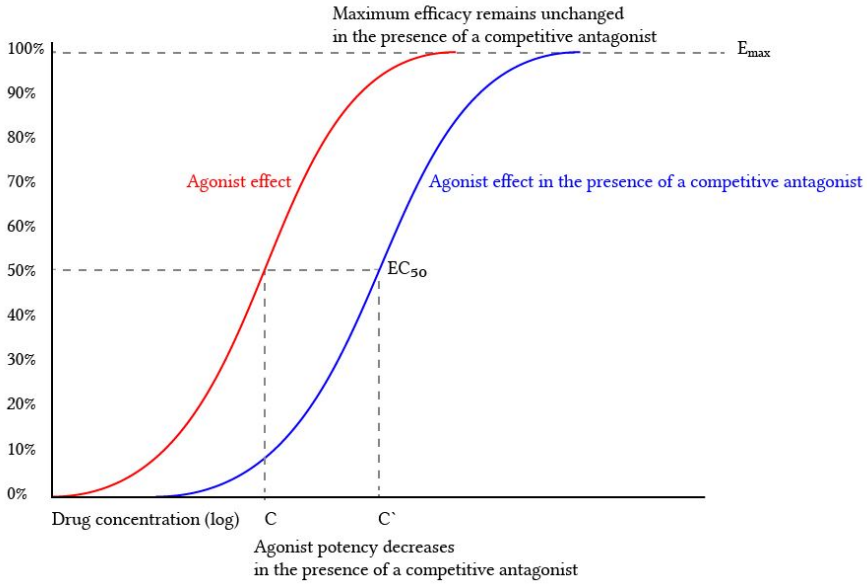
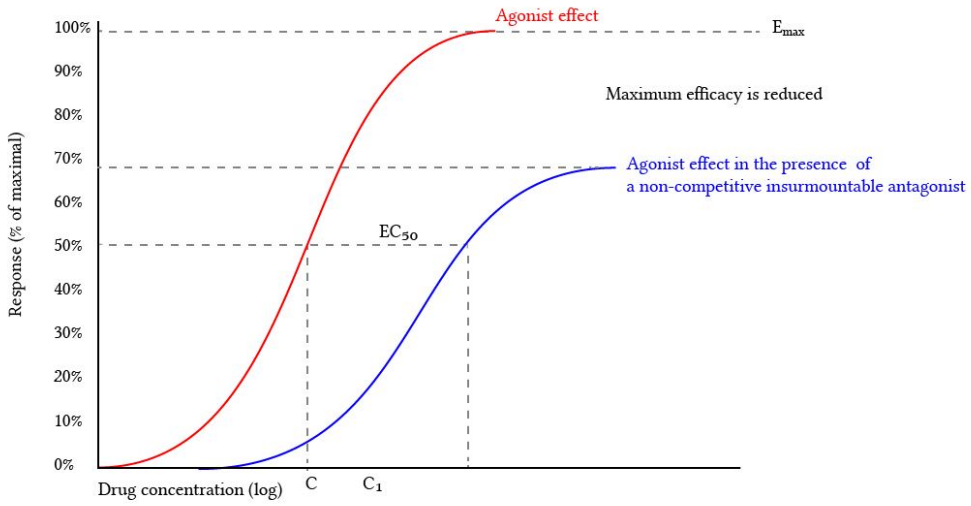


Image from
https://derangedphysiology.com/main/cicm-primary-exam/required-reading/pharmacodynamics/Chapter%20418/competitive-and-non-competitive-antagonists
(Deranged physiology is a great page for primary study!)

What effect does an irreversible antagonist have on the concentration-effect curve?
Reduced maximal effect
The EC50 may be the same or different



This image also from Deranged Physiology

3. **Potency and Efficacy**

Can you define potency?

- Potency refers to the affinity or attraction between an agonist and its receptor and the amount of a drug required to produce an effect of a certain intensity
- Refers to the concentration (EC50) or the dose (ED50) of a drug required to produce 50% of that drugs maximal effect.
- Dependent on affinity of a drug for its receptor and the number of receptors available

Can you define efficacy?

- Efficacy is the maximal effect a drug (agonist) can produce (Emax) when all receptors are occupied, irrespective of the concentration or dose required to produce that response
- Determined by the drugs mode of interactions with receptors or by characteristics of the receptor-effector system involved

Can you please show the difference between efficacy and potency by drawing dose response curves

- Graph has dose on the x-axis and response on the y- axis
- Curves are sigmoid or S-shaped
- A curve that is further to the left will have greater potency because less of the drug is required for the effect
- A curve that is the tallest (or has the greatest y-value) has a greater efficacy because the y-axis measures the response, regardless of dose required to get there

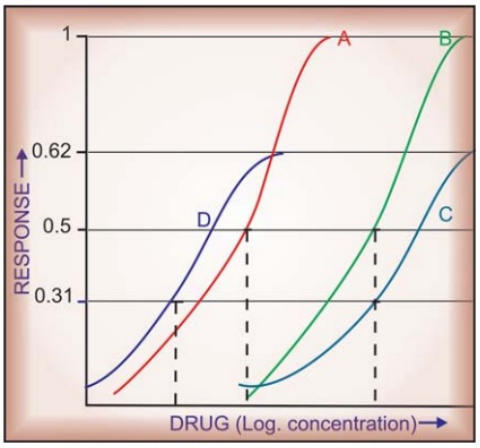


Fig. 4.12: Illustration of drug potency and drug efficacy. Dose-response curve of four drugs producing the same qualitative effect
Note:
Drug B is less potent but equally efficacious as drug A.
Drug C is less potent and less efficacious than drug A
Drug D is more potent than drugs A, B, & C, but less efficacious than drugs A & B, and equally efficacious as drug C

Image from: https://www.pharmacy180.com/article/drug-potency-and-efficacy-884/

Compare the potency of morphine and fentanyl
Fentanyl is 100 times more potent than morphine - 0.1mg of fentanyl is equivalent to 10mg morphine

What factors affect a drugs efficacy?

- Affinity of receptor for drug
- Drug/receptor interaction
- Route of administration, absorption, distribution through the body and the clearance of the drug from the blood or site of action

4. **Secondary Messengers**

In reference to drug action, what is a second messenger?
A second messenger is a method of transmembrane signalling. It is an intracellular substance which has its concentration altered by a process that is initiated by an extracellular ligand. The second messenger then acts to facilitate an intracellular process

What are the steps in action of a drug via a second messenger?

- The drug binds to a receptor on the extracellular side of the plasma membrane
- Triggers the activation of G protein on cytoplasmic side
- Activated G protein changes an enzyme ion channel
- This changes the concentration of intracellular second messenger which mediates the response

Can you give an example of a second messenger and the type of response it produces?

cAMP - via adenylate cyclase, causes:

- Mobilisation of fat and carbohydrates
- Conservation of water by the kidney
- Increased rate and contractility of the heart
- Calcium regulation
- Adrenal hormone regulation
- Relaxation of smooth muscle

Other second messengers include:

- Calcium and phosphoinositides (which is the name for a family of acidic phospholipids in cell membranes)
- cGMP - via transmembrane guanylyl cyclase

Can you give and example of a drug that acts via this second messenger system?
Beta agonists - which act via Gs proteins attached to B-adrenoreceptor and cause increased intracellular cAMP
Other examples include glucagon, thyrotropin, histamine, serotonin, acetylcholine and opioids

Pharmacokinetics

5. **Absorption**

What variables influence the extent and rate which a drug is absorbed?

- Route of administration
- Nature of the absorbing surface including the cell membrane i.e. single epithelial layer in the GIT va layers of skin cells, and the surface area of absorption in the stomach/small intestine etc
- Blood flow to the area of absorption
- Drug solubility i.e. lipid solubility
- Drug formulation - i.e. the presence of enteric coating

Explain why aspirin absorption is enhanced by low pH in the stomach?
Aspirin is an acidic drug with a low pKA, which means it is relatively un-ionised in the stomach and therefore more soluble here so is absorbed more readily here.

How does the ionisation of a drug affect its solubility?
Drugs exist as weak acids or weak bases and in the body they are either ionised or un-ionised. Ionised are water soluble and un-ionized are more lipid soluble,

What are the disadvantages of rectal drug administration ?

- Erratic absorption due to contents in the rectum
- 50% first pass metabolism
- Local irritation
- Uncertainty of drug retention

6. **Bioavailability**

What is bioavailability?

The fraction of unchanged drug reaching the systemic circulation following administration by any route.

What factors affect bioavailability?

- Extent of absorption - drug properties, reverse transporters, gut wall metabolism
- First pass metabolism - where drug is removed by the liver
- Rate of absorption - determined by site of administration and drug formulation

What is first pass metabolism?

- After the absorption of orally ingested drug, the portal blood delivers the drug to the liver
- It can be metabolised in the liver, in the gut and in the portal system before reaching the systemic circulation
- This reduces the bioavailability of the drug

Can you increase a drug's bioavailability? Give an example.

- Change the route of administration - IV, IM, SC, SL, inhalational or transdermal can avoid first pass metabolism. PR administration can still have 50% first pass metabolism
- Change the drugs properties - to increase the absorption by making it more hydrophilic or lipophilic, using a prodrug
- Increase the dose

What is the bioavailability of ibuprofen?

It is high. Ibuprofen is a weak organic acid, well absorbed orally and has minimal first pass metabolism.

(Note: usually if we give things orally all the time the bioavail is relatively high!)

7. **Distribution**

Define the volume of distribution of a drug

Defined as the volume in which the amount of drug in the body would need to be uniformly distributed to produced the observed concentration in blood, plasma or water

What factors affect the Vd?

- Drug properties - lipid solubility, pKa, pH, protein binding
- Patient factors - age, sex, disease state, body composition, blood flow

How is it possible for a drug to have a Vd of 2500L in an adult?

Higher concentration in extravascular tissues than in the blood - example being lipid soluble medications that are not homogeneously distributed

Give some examples of drugs with high and low volumes of distribution

High - morphine, digoxin, clonidine, beta blockers, diazepam
Low (approx TBW) - aspirin, frusemide, most antibiotics, warfarin

What is the relevance of Vd in overdose?
Drugs with a high Vd cannot be dialysed off because most has left the circulation. Those with a low Vd (i.e. lithium) can be

8. **Metabolism & biotransformation**

What factors are responsible for differences in drug metabolism between individuals?

- Genetic - enzyme deficiencies or super metabolisers
- Diet & environmental - exposure to enzyme inducers
- Age and sex - men have an increased metabolic rate, extremes of age have decreased enzyme activity
- Drug interactions - enzyme induction or inhibition
- Disease states - liver function, thyroid state

What is drug biotransformation?
The process of drug metabolism which allows drugs to become inactive or increases excretion by making them more hydrophilic or by metabolising them to a less active agent.

What are the main sites of biotransformation?

- Liver
- GIT
- Skin
- Kidneys

What is the role of the cytochrome P450 enzymes?

- These are part of the biotransformation system to detoxify drugs/substrates.
- They act by oxidation (phase 1 reaction) and make substances easier to conjugate
- Located on the smooth ER

Describe phase 1 and phase 2 reactions

- Phase 1 - unmasking the sunctional group (-OH, -NH2, -SH) to become a more polar metabolite, induced oxidation, deamination, hydrolysis, reductions
- Phase 2 - conjugation with endogenous substrate to become highly polar

Note - phase 1 and 2 can occur alone, sequentially or simultaneously. The metabolites can be more active or toxic then the parent drugs.

How is suxamethonium metabolised?

Rapid phase 1 hydrolysis by butyryl-cholinesterase and pseudocholinesterase in the liver and plasma

Why might a patient have a prolonged paralysis following sux use?
Patients who have a genetic deficiency in butyryl-cholinesterase have a slower metabolism

What is meant by the term enzyme induction ?
Drugs can cause an increased rate of synthesis or decreased rate of degradation of some enzymes leading to accelerated substrate metabolism. This can lead to decreased pharmacological action of the co-administered drug.

9. Clearance

What is drug clearance?
Measure of the availability of the body to eliminate a drug. Rate of elimination in relation to the concentration of the drug or volume of plasma cleared of the drug per unit time.

*Note: elimination and clearance can be referred to as the same thing but there are different questions in the past papers for these topics. Elimination of a drug is used to describe the "**irreversible removal of the drug from the body"** and clearance is defined as above, being the **"volume of fluid cleared of drug per unit time"***

What factors affect clearance?

- Concentration - which depends on the dose/bioavailability
- Elimination - which depends on specific organ function, blood flow, protein binding. Major sites of elimination are the kidneys and liver - therefore factors that affect these organs function and blood flow will have the most effect

What is the difference between capacity limited and flow dependent drug elimination?

- *Capacity limited* - is saturable (zero order) where clearance varies depending on the drug concentration. E.g. aspirin, phenytoin, ethanol
- *Flow dependent -* is not saturable (1st order) - where most of the drug is cleared by the 1st pass of blood through an organ so elimination depends on the rate of drug delivery to the organ and thus on blood flow. Plasma protein binding may also have a small role. E.g amitriptyline, labetalol, morphine, verapamil, lignocaine

What factors affect renal clearance?

- Renal function
- Renal blood flow
- Plasma protein binding

What are some drugs that are predominantly cleared by the kidneys?
Gentamicin (the main one to mention), vancomycin, digoxin, ampicillin

10. Elimination

Define elimination half life
The time taken to change the amount of drug in the body by half during elimination
T1/2 = 0.7 x Vd/Clearance

How does knowing a drugs half life help us clinically?
Aids in dosing regimen planning, identifies timelines in overdose and can help establish time to steady state after dose change

What disease states can affect the elimination half life?
Liver, renal, cardiac disease

What is first order elimination kinetics?
A constant fraction or percentage of the drug is eliminated per unit time. Rate of elimination is proportional to the amount of drug in the body. Half life remains constant. Most drugs are eliminated this way.

How does this differ to zero order kinetics?
With zero order, a constant amount of drug is eliminated per unit time, rate of elimination is constant and is independent of drug concentration. In overdose the half life will be prolonged. Examples - ethanol, phenytoin, salicylates