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Medi Quest BRS Hospital

A monthly News letter from BRS Hospital

Pharmacokinetics and Pharmacodynamics for the Practitioner

Part 2 - Pharmacokinetics and Pharmacodynamics

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Pediatrician BRS Hospital

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20.What do you mean by steady state concentration of a drug ?

The steady state concentration is reached when the dosage amount given (by any route) is equivalent to the amount of the drug leaving the body by whatever route it is eliminated. The time it takes to reach this "steady state" is related to the half-life of the drug by the following:

Percent of final Steady state achieved	Time in terms of the half-life of the drug
50.0 %	1
75.0 %	2
87.5 %	3
93.75 %	4
96.88 %	5

From the above, it can be seen that after five t½'s of a drug you will reach ≈ 97% of the final Steady state concentration if the drug is given prior to its complete elimination (prior to 5 times the half life of the drug). Fluctuations about the steady state or mean plateau concentration will obviously depend upon the dosing interval - being greatest as you increase the interval in relation to the half-life of the drug and being smallest as you decrease the dosing interval. Thus, the smallest fluctuation would occur with an i.v. infusion

Please note that even with a constant infusion it will still take 5 times the half-life of the drug to reach the maximum plateau concentration or steady state level.

Important point to note: Whatever the dose and whatever the dosing interval the time taken to reach steady state concentration for a drug remains the same.

21. What are the clinical applications of half life ?

a.If a drug has a short half life say minutes then it has to be given as a constant infusion, Example Dopamine

a. Drugs with longer half lifes can be given once a day ,example Phenobarbitone, digoxin, diazepam , amitriptyline.

b. Drug dosing intervals should be equal or close to the half life of a drug in order to quickly achieve steady state therapeutic levels and avoid wide fluctuations between doses.

c. In clinical practice in deciding the dosing intervals we have to compromise between

of minimizing the between dose variations of effectiveness and patient inconvenience leading to poor compliance due to frequent doses.

22. What do you mean by efficacy half life ?

Drugs whose effects or efficacy or actions outlast their plasma concentration form a very

significant group and introduce the term

"efficacy half-life". This is defined as that time it would take for a drug to lose half of it's effectiveness or efficacy.
What usually happens is that it is noticed that a dug with a relatively short half-life is still able to produce an effect long after it is supposedly eliminated (which would be 5 times the plasma half-life). It is presumed that the drug is acting intracellularly and either remains partly bound to the receptor long after most of the extracellular drug has been eliminated or the drug is a "hit-and -run" type which alters a receptor such that the effect remains long after the drug is gone. The reason it is important to always be on the lookout for this phenomenon is that it is far easier for patients to take a drug once or twice a day than three of four times a day.
Agents of note where this concept is operational include the following:

Agent/drug	Plasma t½	Acceptable dosing interval
Propranolol	3.3 hours	once or twice a day (for BP)
Prednisone	3.5 hours	once a day
Colchicine	20 minutes	once a day
Allopurinol	2 hours	once a day or longer

23. What are the routes by which a drug is eliminated by the body ?
Removal of a drug occurs via a number of routes **the most important being through the kidney into the urine.** Other routes include bile, intestine , lung or breast milk in nursing mothers.

24. How would you Describe the interplay between drugs and the kidney with reference to the drug elimination ?
One should remember three factors in renal elimination of a drug
A. Glomerular filtration: Drugs enter the kidney through renal glomeruli, in the glomerular filtrate. Lipid solubility , ionisation and pH do not influence the passage of drugs into the glomerular filtrate.
B. Proximal tubular secretion: Drugs which were not transferred by the glomerular filtrate reaches the tubular lumen by Secretion of drugs by proximal tubules by active transport.Each of these transport systems shows a low specificity and can transport many compounds ; hence competition between drugs for carriers can occur , for example Probenecid blocks the tubular secretion of penicillin and was used to increase levels of the antibiotic.
C. Distal tubular reabsorbtion: As the drug moves towards the DCT the concentration of the drug increases above that present in the perivascular space and if the drug is lipid soluble and non ionised it diffuses back . Manipulating the pH of the urine can prevent reabsorbtion . For example , a patient presenting with phenobarbitol overdose can be given bicarbonate , which alkanizes the urine ,keeps the drug ionized , thereby decreasing its reabsorbtion.

The amount of drug excreted is the sum of the amounts filtered and secreted minus the amount reabsorbed.

25. In the elimination of a drug what are Phase I and Phase II reactions
The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal tubules.
Therefore lipid soluble drugs must first be metabolised in the liver using 2 general sets of reactions Phase I and Phase II
a) Phase I reaction :
Phase I reaction converts Lipophilic molecules to more polar ie water soluble molecules. Phase I reaction is mostly catalyzed by cyto chrome P 450 system
Phase I metabolism may increase, decrease or leave unaltered the drug`s pharmacologic activity

b) Phase II reaction :
The Phase II reaction consist of conjugate reaction with an endogenous substrate which produces a more water soluble compound then Phase I reaction, that is readily excreted. Glucuronidation is the most common and the most important conjugation reaction.

Pharmacodynamics

1.What is Pharmacodynamics

Pharmacodynamics deals with the effect of drugs on biologic systems(body)
i e what the drug does to the body

2.What are drug receptors

Receptors are the specific molecules in a biologic system with which drugs interact to produce that effect. The interaction of a drug with its receptor is the fundamental event that initiates the activity of the drug

3.What is the modern concept of drug receptors

Modern concepts of drug receptor interactions consider the receptor to have at least 2 states
Active (RA) and inactive (R1)
Many receptor system exhibit some activity the absence of ligand suggesting that some receptors are in the activated state. Activity in the absence of ligand is called constitutional activity

4. What are agonists – Full agonists and partial agonists

A full agonist (Full) : Drug capable of fully activating the effector system when it binds to the receptor

A partial agonist (Half) : Produces less than full effect, even when it has saturated the Receptors

5.What are the different classes of Antagonists :

Competitive antagonists : These drugs bind to receptor in a reversible way without activating the effector system can be displaced by high doses of agonist

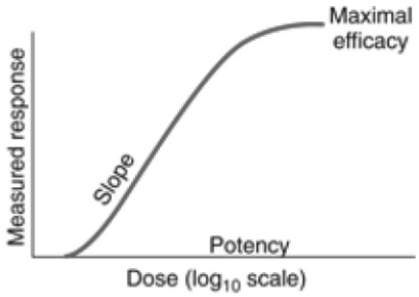
Irreversible antagonists : The effects cannot be over come by addition of higher dose of Agonist

Physiologic Antagonists: Binds to a different receptor molecule produces an effect opposite to that produced by the drug it antagonizes.

Chemical Antagonist : Interacts directly with the drug being antagonised to remove it or to prevent it from binding to its target.

6. What is graded dose response curve

A graph plotted with increasing doses of drug or its concentration on the X axis and the response it produces on the Y axis
Dose Response curve



7. What are the uses of a graded dose response curve

This graph informs the efficacy and potency of a drug

8. What do the terms EC50 and EC Max denote

EC 50 is the dose or concentration at which effect is half maximal. EC Max is the dose or concentration at which effect is maximal

9.What you mean by Potency and Efficacy of a drug

Potency refers to the amount of drug needed to produce a given effect. For instance if 5mg of drug A relieves pain as effective as 10mg of drug B, drug A is twice as potent as drug B.

In graded dose response curve smaller the EC 50 greater the potency of the drug

In a graded dose response curve the effect chosen is 50% of maximal effect i e EC 50.

Efficacy refers to the maximal therapeutic that a drug can produce regardless of the dose.

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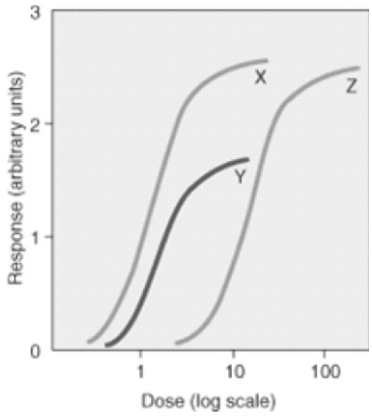
Comparision of Dose Response curves of Three drugs X,Y,Z to understand the concept of Potency and Efficacy



Interpretation:

Drug X and Z have more efficacy ie Maximal Therapeutic response than drug Y

Drugs X and Z have same efficacy but with Drug X it is achieved at a lower dose , hence drug X is more potent than Drug Z

Drug Y is more potent than Drug Z but its efficacy is lower

(Graphs Reproduced From Merck Manual Online for Health Care Professionals)

10. What is Therapeutic index

Therapeutic index of a drug is the ratio of the dose that produces toxicity to the dose that produces a clinically desired effect or response in a population of individuals

Therapeutic index = Toxic dose / Effective dose

Larger the therapeutic index safer the drug.

11. What is Therapeutic range

It is clinically more useful, it describes the dosage between minimal effective therapeutic concentration and minimum toxic concentration or dose

Wider the differences between effective and toxic doses safer the drug and vice versa.

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