General Pharmacology
(Pharmacokinetic III)
Principles of Pharmacology
(PP VII)

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• **References:**
  
  • Basic & clinical pharmacology by Katzung
  • Lippincott’s illustrated reviews by Finkel, Cubeddu & Clark
  • Clinical pharmacology by Laurence
Learning Objectives
At the end of pharmacokinetic lectures you should be able to

1. Describe the terms ‘therapeutic window’ and ‘therapeutic range.’

2. Describe the relationship between plasma level and therapeutic response.

3. List three reasons why there may be no simple relationship between plasma level of parent drug and magnitude of the therapeutic response.

4. Define the terms ‘clearance’ (CL), half-life \((t\frac{1}{2})\), volume of distribution \((V)\), and ‘area under the curve’ \((AUC)\) as they relate to drug kinetic.
5. State that: CL = Clrenal + Clhepatic, and be able to predict the consequence of change in either component on the plasma drug concentrations.

6. Predict the concentration of a drug immediately after i.v. administration, given an apparent V in litres from a text.

7. Draw a graph to depict the plasma level profile of a drug given by i.v. infusion, and identify the factors that determine the shape of this graph.

8. State that at steady state: Administration Rate = Elimination Rate
9. Define the term ‘bioavailability’ (F), state the use of AUC values to calculate F.

10. Explain the basis underlying zero-order and first-order kinetics of drug elimination from plasma. Give examples of drugs which are metabolized according to these kinetics.

11. Describe the relationship between pH, pKa, and degree of ionisation of acidic and basic drugs, and use this relationship to predict movements of drugs across membranes at various sites of the body.

12. List the factors that influence drug absorption from the skin, lungs, and muscle.
13. List the factors that determine the rate and extent of distribution of a drug.

14. Predict the distribution of a drug, given its volume of distribution.

15. Describe the 1- and 2-compartment models of drug distribution.

16. Describe the processes involved in reversible and irreversible binding of drugs to lipids, tissue proteins, and plasma proteins. Describe the effect of plasma and tissue binding of drugs on their distribution in the body.

17. Describe the mechanisms underlying placental transfer of drugs.

18. Describe the mechanisms underlying transfer of drugs across the blood-brain barrier.
19. Outline, with examples, the principal routes by which drugs may be metabolized.

20. Describe the physico-chemical consequences of drug metabolism.

21. Describe the pharmacological consequences of drug metabolism.

22. List, with examples, the factors that may modify the level of metabolism of a drug.

23. Describe the processes involved in biliary excretion of drugs, and give examples of drugs excreted principally by this route.

24. Define the term ‘enterohepatic recirculation’ of drugs, and indicate its possible consequences on pharmacological action.

Give examples of drugs eliminated in the expired air and milk.
25. Describe the processes involved in the excretion of drugs in the urine.

26. Indicate how knowledge of the renal clearance of a drug may help in elucidating the renal handling of that drug.

27. Indicate the basis for determining modification of drug dosage in renal failure.

List the possible causes for inter-individual variation in drug response.

28. Describe, with examples, the pharmacokinetic and pharmacodynamic bases underlying drug-drug interactions.
30. Describe the phenomenon of genetic polymorphism as it relates to drug treatment

31. Describe the mechanisms underlying the genetic polymorphism in the metabolism and effects of suxamethonium, isoniazid, and CYP2D6 substrates

32. Describe the mechanism underlying the genetic polymorphism in erythrocyte glucose-6-phosphate dehydrogenase activity as it relates to oxidant drugs

33. Describe the phenomenon of drug-induced malignant hyperthermia
• **DRUG METABOLISM**

• Drugs are treated as foreign substances and so they are subjected to various mechanisms to get rid of them.

• Water soluble drugs are eliminated unchanged by the kidneys, while lipid soluble drugs are going to undergo structural modification, the structure is changed by enzymes and metabolized into more water soluble metabolites and then eliminated by the kidneys.
• So **METABOLISM**: is defined as the process of chemical transformation within the body to change drugs, by two major ways:

• **1) Reducing lipid solubility**: in this case, lipid soluble drugs (water insoluble) are changed into lipid insoluble (water soluble) and then excreted by the kidneys without reabsorption.

• **2) Reducing biological activity**: in most cases, active drugs are changed into inactive metabolites.

• So in rare cases, active drugs are changed into active metabolites and sometimes inactive drugs are changed into active metabolites. e.g. cortisone (inactive) is changed by metabolism into hydrocortisone (active).
• **REACTION OF DRUG METABOLISM:**

• **1- Phase I**: phase I reaction converts lipophilic molecules into more polar molecules by introducing or unmasking a polar group, e.g. OH, -NH$_2$

• This phase may increase or decrease or leave unaltered the drug's pharmacological activity.

• **A) Phase I reaction utilizing CP450 system**, reaction of this phase involved in drug metabolism are catalyzed by CP450 system.

• **B) Phase I reaction not involved modified CP450 system**, such as amine oxidation (oxidation of histamine, alcohol) and proca. inamide.

• Drug + O$_2$ + NADPH + H$^+$ $\rightarrow$ drug + H$_2$O + NADP$^+$
BIOCHEMICAL REACTION OF METABOLISM:

1) Non-synthetic (non-conjugative) reaction:
   a) Oxidation: the most important reaction taking place in CP450 of the liver (the major site for metabolism).
   b) Reduction: by cytoplasmic microsomes.
   c) Hydrolysis: by enzymes such as esterases and amidases
2) **Synthetic (conjugation) reactions:**

a) Glucuronide synthesis.
b) Glycine synthesis.
c) Sulfate conjugation.
d) Acetylation.
e) Methylation.
FACTORS THAT DELAY METABOLISM OF DRUGS:

1- **Protein-binding**: the higher the percentage of protein binding, the less the amount of drug metabolized.

2- **Localization of a drug in the adipose tissue**: e.g. thiopental (localized in adipose tissue) quinacrine (localized in the liver). The localization will protect these drugs against metabolic degeneration.

Thiopental: used as general anesthetics (barbiturates) “IV”
Quinacrine: used as anti malarial agent.
3- **Disease** of liver and immaturity of the drug metabolizing enzymes:

as in (neonatal) newborn are incapable of metabolizing drugs, this will interfere with metabolism of some drugs that are metabolized by liver enzymes.

4- **Presence of other drugs:** one drug may inhibit the metabolism of another drug and this will prolong and intensify its action.
• **ENZYME INDUCTION:**

• It is an absolute increase in an enzyme amount and therefore an increase in its activity as a result of continuous exposure to particular chemicals. Enzyme induction is accompanied by a hypertrophy of the liver cell endoplasmic reticulum which contains most drug metabolizing enzymes.
• Enzyme induction develops and depends on its time of exposure to an agent such as a drug or tobacco smoke. Some substances also cause enzymatic induction such as barbecued meat/barbiturates, DDT (an insecticide), ethanol and phenytoin.

• Induction results in an acceleration of metabolism and usually in a decrease in the pharmacological action of the inducer and also of co-administered drugs. In case of drugs metabolically transformed to reactive intermediates, the enzyme induction may exacerbate drug mediated tissue toxicity.
ENZYME INHIBITION:

Some drugs may inhibit the action of cytochrome P450 enzyme such as proadifen. This agent binds to the cytochrome molecules and competitively inhibits the metabolism of potential substrates.

Cimetidine, ketoconazole bind tightly cytochrome P450 through competitive inhibition and reduce the metabolism of endogenous substrates (testosterone) and other drugs through competitive inhibition.
• **First pass metabolism**: also called first pass elimination or presystemic elimination, it refers to the metabolism of a drug that occurs in route from the gut lumen to the systemic circulation.

• Some drugs as chlorpromazine, morphine and propanolol are metabolized in the gut wall, but in most cases, the first pass metabolism occurs in the liver. The first pass metabolism is so complete for certain drugs such as lignocaine (a local anesthetic) that the bioavailability following drugs administration of that drug is zero. However, in case of a drug given orally, the drug can have a first pass metabolism up to 80% such as propanolol.
ELIMINATION OF DRUGS AND TERMINATION OF DRUG EFFECT:

- This process depends (sometimes) mainly on the excretion from the body, but mostly is the result of biotransformation to "inactive" products that are excreted.

- Few drugs are given in a "Pharmacologically inactive form", these are named "PRODRUGS" which has to be metabolized to an active form.
MAJOR ORGANS OF DRUG ELIMINATION: According to importance...

1) THE KIDNEY: drugs excretion may be achieved by:

a) Glomerular Filtration: it's the passive diffusion which will remove drug molecules up to the size of a small protein. Drugs that bound to plasma proteins are poorly filtered; while unbound drugs are filtered clear fairly quickly.

Some drugs are actively secreted by special mechanisms which are located in the segment of proximal convoluted tubules (PCT), for example: weak acids as "diuretics".
b) Through **tubular secretion**: in this case, highly lipid soluble molecules are rapidly reabsorbed from the tubular urine, and so they have to be metabolized to a water soluble form in order to be excreted.

But in case of water soluble drug molecules, they can be excreted easily without metabolism.

Metabolism of many drugs will result in a less but not completely lipid soluble form, such metabolites are less likely to be absorbed from the tubular lumen that the parent drug.
2) **THE LIVER**: it's the most important organ of drug "metabolism", few drugs are actively secreted into the bile, through which they reach the duodenum and are reabsorbed from the intestinal lumen again, this is called "Entrohepatic Recycling". This process increases the concentration of the drug and the half-life ($t_{1/2}$).

3) **GIT**: it has a large surface area (as large as a soccer field). This is represented by the lipid membranes of the stomach cells and the intestine. Across this surface area, drugs can be transported from the lumen to the blood, however certain drugs can return across these membranes to the lumen of GIT.

   This mechanism is only occasional and is especially important in weak-basic drugs.

   These drugs should be also in high concentration in order to diffuse back through the GIT membranes into the lumen.
4) **THE LUNGS:** are only important in one case → "Gaseous Anesthetics". In other cases it's of no importance as an organ of elimination.

5) **MINOR ROUTES:** include: sweat, salivary and mammary glands.
• **CLEARANCE**: has two definitions,
  • Special Definition: it's the rate of elimination of a drug in urine relative to its concentration in plasma.
  • General Definition: it's the rate of elimination by all routes of elimination relative to the concentration of a drug in any biological fluid.

• Clearance = Rate of Elimination / Concentration

  It's either blood Clearance (CL\textsubscript{b}), plasma Clearance (CL\textsubscript{p}) or unbound (free) drug Clearance (CL\textsubscript{u}) depending on the concentration measured.

  • If the blood concentration is used to defined clearance, then the maximum possible clearance is equal to the sum of the blood flows to the various organs of elimination by the liver the clearance is equal to the blood flow only to the liver.
PROLONGATION OF DRUG ACTION:

1) Using a large dose but sometimes this method is not feasible (not practical). It's possible only with drugs of wide therapeutic window.

2) By inducing vasoconstriction to reduce the blood flow to the site of injection. For example: Adrenaline is given with local anesthetic to maintain the local anesthetic at the site of injection by inducing vasoconstriction.

3) Slowing the metabolism of a drug i.e. by reducing its rate of metabolism) such as "Carbidopa" which makes metabolism of LDopa slower (L-Dopa is given to Parkinson's patients) so Carbidopa prolongs its action.
4) By delaying the excretion of a drug (this method is possible but not practicable) because it's dangerous.

5) By the use of the special pharmaceutical formulation, this has same concentration per unit time as well as prolonged action.

This achieved by the manipulating the formulation of drug by:

a) By the so called "Sustained-Release Oral Preparations".

b) By "Depot Injectable" means one injection lasts for weeks or months like "Contraceptives" last for 3 months.
• **INTOLERANCE:**

  • It means a **LOW** threshold to the normal pharmacological action of drug.

  • This **means**: a normal dose produces more response in intolerant people than that of normal people.
As shown above; 95.5% of population would respond within the median range of doses.

Few people (2.25%) on the left are called "INTOLERANT", those people respond to small doses and are called "HYPERSENSITIVE".

The other 2.25% on the right are called "NATURAL TOLERANT PEOPLE", they only respond to high doses.
THE CAUSES OF INTOLERANCE MIGHT BE:

1) Biological Variation: for example the number of receptors.

2) Disease: may increase or decrease the response.

3) The presence of other drugs: for example Bronchial Asthmatic patients that are sensitive to Histamine lead to Vasoconstriction and Bronchial Spasm.
TACHYPHYLAXIS:
It's a rapid loss of activity (development of tolerance), that's specially observed in laboratory experiments due to "depletion of transmitters" such as Histamine in tissues and others.

ACCUMULATION OR CUMULATION:
It's the accumulation of a drug in the body. This may lead to toxic effects. The causes of Accumulation:
1) Frequent Dosing more than supposed to be taken
2) Renal Failure this will reduce the elimination of a drug
3) Hepatic Failure or Liver Disease in this case the drug is not metabolized by the liver
IDIOSYNCRACY or idiosyncrasy:
It's a drug reaction that's qualitatively different from the usual effect obtained in the majority of patients due to Genetic Causes (abnormalities).
SIDE EFFECTS:
They are "unwanted" effects occurring during therapy. For example: Vomiting and Nausea in case of Morphine usage. Also Diarrhea due to Ampicillin administration.

SECONDARY EFFECTS:
They are the "indirect results" occurring during drug therapy. For example destruction of intestinal flora by Tetracycline (antibiotic).

TOXIC EFFECT:
They are caused normally by large doses and sometimes by small doses too. The small doses may cause toxic effect in patients with liver and kidney failure for example.
DRUGS INTERACTION:
They're either:

1) **Synergism:** Divided into:
   
   A) **Potentiation:** in this case one drug may potentiate the effect of another.
   The final response is greater than what it would be if the two drugs were working separately (without interaction)
   
   
   \[ 1 + 1 = x, \text{where } x \text{ is greater than two}. \]

   B) **Summation:** in this case the effect of one drug is added to that of another drug.
   
   \[ 1 + 1 = 2. \]

2) **Indifference:**
This means there isn't any interaction between drugs.
PHARMACOGENETICS:
It's the science concerned with drug responses that are governed by "heredity". Inherited factors causing different response to drugs are commonly biochemical because single gene governs the production of enzymes.
Inherited abnormal response to a drug mediated by a single gene is called (Idiosyncracy),
A) **HERITABLE CONDITION CAUSING INCREASED OR TOXIC DRUG RESPONSE**

This includes:

1) **Acetylator Status:**

Acetylate is important in drug metabolism especially in drugs possessing the NH$_2$ group.

In case of slow acetylators i.e. individuals with a slow Acetylation processes, for example "Isonizide" (used for TB) will cause "Peripheral Neuropathy",

While in rapid acetylators, the same drug will cause "Hepatocellular Necrosis" (more hepatic metabolism),
2) Defective Carbone Oxidation: in this case there're either extensive or poor oxidation i.e. individuals who can oxidize carbon rapidly or slowly, Poor oxidizers are especially at risk with standard doses of drugs such as "Metaprolol" due to increased f3-Blocking, which will lead to "Hypotension".
3) Glucose 6-P Dehydrogenase (G6PDH) deficiency:

this enzyme is very important to the activity of RBC if it's deficient, then there will be hemolysis of RBC, if they were exposed to certain drugs such as oxidant drugs, these drugs are about so in number and the patient with G6PDH deficiency will be at risk with each one.

Some of these drugs are: Dapsone (antibiotic used to treat leprosy and certain types of skin diseases), Primaquine (for treating malaria) and Aspirin.
4) **Pseudo cholinesterase deficiency**: as you may know, Cholinesterase hydrolyses the acetylcholine at N-ending, while other tissues and plasma contain other non-specific, hence called "Pseudo cholinesterase".

This enzyme is responsible for terminating the neuromuscular blocking action of "Suxamethazone" (muscle relaxant). Affected individuals form so little pseudo cholinesterase so metabolism of cholinesterase is seriously reduced.

The deficiency appears when the patient fails to breath, assisted breath (ventilation) may have to be taken for hours.
B) HERITABLE CONDITIONS CAUSING DECREASE IN DRUG RESPONSE:

1) Resistance to Coumarin (anti-coagulant): Patients affected possess a variety of enzymes that converts vit.K to its reduced and active form.
   The normal enzyme responsible for this function is inhibited by Coumarin. In case of the variant enzyme, the patient affected needs 20 times or more of usual dose to obtain the normal response.

2) Resistance to Suxamethanium:
   This condition is due to increased Pseudo Cholinesterase activity and failure of the normal doses of Suxamethanium to produce the response i.e. muscular relaxation.
3) Resistance to vit. D

Patients develop rickets and respond only to doses of vit. D that may reach 1000 times the normal doses.

4) Bacterial resistance to drugs:

It's genetically controlled and of great importance
Thank you