PHARMACOKINETICS

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INTRODUCTION

- Pharmacokinetics is the study of drug disposition and focuses on the changes in drug plasma concentrations
- Plasma drug concentration of any drug will change i.e. either rise or fall depending on the following processes;

a) Absorption
b) Distribution
c) Elimination
   - Metabolism (Biotransformation)
   - Excretion

- Metabolism involves the breaking down of the parent drug into one or more metabolites, mostly done by the liver while Excretion parent drug or metabolites is primarily done by the kidney

ABSORPTION

- This involves the passage of drug molecules from the site of administration into the systemic circulation
- This applies to all routes except the topical and IV routes
- Drugs administered topically are directly applied on the target tissue while drugs administered through the IV route are directly delivered into the circulation
- Orally administered drugs have been found to face a greater barrier than the parenteral route

Absorption process

- Absorption is dependent on three major forms of transport;

i. Passive diffusion
ii. Active transport
iii. Facilitated diffusion

Passive diffusion

- Passive diffusion across the biological barrier is the process by which most drugs are absorbed
- This is accomplished either through lipid diffusion or aqueous diffusion
- Lipid diffusion involves the dissolving of drug in the lipid components of the cell membrane thereby, making lipid solubility an important facilitator of the process
- Aqueous diffusion involves the absorption of the drug molecules through the aqueous pores (aquaporins) of the cell membrane
- Aqueous diffusion is restricted by molecular weight of drugs and thus many drugs are too large to be absorbed by this process

FICKS LAW: states that the rate of absorption is proportional to the concentration gradient across the barrier and the surface area available for absorption at the site

Active transport

- This requires a carrier molecule and energy provided through the high energy phosphate bond of adenosine triphosphate (ATP)
- Drugs can be transported against the concentration gradient e.g. 5-fluouracil an antineoplastic drug

Facilitated diffusion

- This needs the carrier molecule but no energy is needed
- This process cannot transport drugs against concentration gradient but diffusion is enhanced than when the carrier molecule is absent
- Cephalosporines like cephalexin undergo facilitated diffusion by an oligopeptide transport protein in intestinal epithelial tissues

Effects of pH on absorption

- Generally, many drugs exist as acids or bases, both existing as either ionized form or non ionized form
- The non-ionized form of drugs are sufficiently soluble in membrane lipid to cross cell membranes and the ratio of the concentration of the ionized to the non ionized at a particular site influences the rate of absorption
- In the stomach with a pH of 1, non-ionized form of weak acids (pKa = 3.5 – 5) and ionized weak bases (pKa = 8 – 10) will dominate but weak acids will be more readily absorbed than weak bases
- In the intestines with pH 7, weak bases are mostly ionized but much less so compared to the stomach and hence weak bases are more readily absorbed from the intestine than the stomach
- Weak acids can also be readily absorbed from the intestines than from the stomach despite their greater ionization because of increased surface area

Henderson-Hasselbalch equation

- The Henderson-Hasselbalch equation is useful for estimating the pH of a buffer solution and finding the equilibrium pH in an acid-base reaction.

- Weak acids (HA) donate a proton(H+) to form anions (A-) while weak bases accept a proton to form cations

DRUG DISTRIBUTION

- Drugs are distributed to the body organs and tissues through circulation and diffusion into interstitial fluid and cells
- A good number of drugs are not uniformly distributed through out total body water
- Other drugs are restricted to the extracellular fluid or plasma concentration
- Drugs with sufficient lipid solubility easily diffuse into cells through membranes
- Drugs can also be actively transported into cells e.g. drugs' transportation into hepatic cells where they may undergo biotransformation

Effects countering drug distribution

- Drug distribution is some way opposed by a number of ATP driven efflux pumps known as ABC transporters (ABC being an acronym of ATP binding cassette)
- The most notable or widely studied ABC is the P-glycoprotein(Pgp), also called permeability glycoprotein which is expressed on the luminal side of intestines, brain capillaries etc.
- Pgp excludes drugs from various tissues acts as a detoxifying mechanism but can lead to therapeutic challenges like the exclusion of cancer drugs from tumours which can cause chemotherapeutic drug resistance
- Drugs like amiodarone, erythromycin, propranolol inhibit Pgp and hence help in increasing tissue levels of these drugs and thereby augmenting their pharmacological effects

Factors affecting distribution

i. Organ blood flow

- Drug distribution is highly affected by the cardiac output received by the organ

- High perfused tissues like the brain, heart, liver and kidneys experience the rapid distribution and thus enabling a rapid onset of action

- There is lower drug distribution of Less perfused tissues like the skin, bones, skeletal muscle

ii. Plasma protein binding

- Almost all drugs are reversibly bound to plasma proteins, primarily albumin while others are lipoproteins, glycoproteins and β-globurins
- The extent of binding depends on the drug's affinity for the protein binding site which ranges from 10 – 99% of the plasma concentration
- Plasma protein binding is saturable and a drug can be displaced by another drug with the higher affinity for such sites
- However the doses at which many drugs are given are not enough to occupy the vast number of protein binding sites

iii. Molecular size

- This affects the distribution of extremely large molecules e.g. anticoagulant heparin
- Heparin is largely confined to the plasma compartment though it also goes through biotransformation in the liver

iv. Lipid Solubility

- This is the major factor affecting the rate of drug distribution
- In the brain, the blood brain barrier (BBB) restricts the penetration of polar and ionized drug molecules
- This barrier is formed by tight junctions between the capillary endothelial cells and the glial cells (astrocytes) that surround the capillaries which inhibit the penetration of polar molecules into the brain neurons

BIO-TRANSFORMATION

- Drug biotransformation or metabolism is the enzyme catalyzed conversion of drugs to their metabolites
- Biotransformation mostly take place in the liver but the metabolizing enzymes are also found in other tissues like the gut, brain, kidney, lungs and skin
- Drug biotransformation and excretion are the two processes responsible for the decline of plasma drug concentration over time
- Both of these processes are involved in drug elimination
- **Clearance** is a measure of the rate of elimination of the drug

Role of drug biotransformation

- The fundamental role of biotransformation is to inactivate drugs and other foreign compounds that can harm the body
- It acts as the natural detoxifying process
- Drug metabolites are usually more water soluble than their parent drugs hence they are usually excreted by the kidneys
- Some drug metabolites are active while others are inactive
- Generally, many drugs undergo attachment to polar groups, a process called conjugation
- The general rule suggests that most of these conjugated drugs are inactive except with a few exceptions

Formation of active metabolites

- Many pharmacologically active drugs such as sedatives like diazepam are converted to their active metabolites

- **Prodrugs** are pharmaceutically formulated inactive drug compounds which are biotransformed into active metabolites after having been administered which subsequently give the desired pharmacological effect

- Enalapril an antihypertensive drug is a prodrug as it is inactive in nature and is usually converted to enalaprilat, its active metabolite

First pass effect

- Drugs absorbed through the gut reach the liver through the hepatic portal vein before entering the systemic circulation

- Many drugs like extensively converted to inactive metabolites through the gut wall and the liver and have low bioavailability after oral administration

Process of metabolism

- Drug biotransformation is divided into two phases each carried out by unique sets of metabolic enzymes
- These are Phase I and Phase II
- Phase I enzymatic reaction create or unmask a chemical group required for Phase II reaction
- In some cases however, drugs bypass Phase I biotransformation and go directly to Phase II
- While some Phase I drug metabolites are pharmacologically active, most phase II drug metabolites are inactive

Phase I

- This involves oxidative, hydrolytic, deamination and reductive reactions

Oxidative reaction

- This is the most common type of phase I biotransformation which is catalyzed by enzymes isolated by the microsomal fraction of the liver
- The microsomal Cytochrome P450 (CYP) mono-oxygenase system is a family of enzymes that catalyzes the biotransformation of drugs with a wide range of chemical structure
- CYP exist in different families as CYP1, CYP2, CYP3 which are likely related by gene duplication
- Each family is divided into subfamilies with a related homologous protein sequence of which CYP3A catalyzes more than half of microsomal drug oxidation

Drugs affecting the Microsomal CYP system

- There are a number of drugs that affect the metabolism of drugs by either inducing or inhibiting the CYP enzymes

CYP450 enzyme Inducers

- CYP inducers causes the increase in the enzyme secretion
- If given concomitantly with another drug whose metabolism is dependent on the CYP enzyme, the other drug is metabolized at an increased rate
- This may affect the therapeutic effect because of the reduced bioavailability of the other drug
- Examples of CYP enzyme inducers are rifampicin, phenobarbitone, carbamazepine, phenytoin (**RPPC**) – **SMOKING & DRINKING IN BARB'S CAR RIFS HER PHEN**

CYP450 enzyme inhibitors

- Inhibitors on the other hand, will cause the reduction in the secretion of the enzyme
- This will lead to the accumulation of the other drug whose metabolism is dependent on the CYP enzymes because of reduced clearance
- This eventually will lead to toxicity
- Examples of CYP enzyme inhibitors are erythromycin, ciprofloxacin, cimetidine (**CEC**)

Cytoplasmic enzymes

- A few drugs are oxidized by cytoplasmic enzymes
- Alcohol is metabolized to aldehyde by alcohol dehydrogenase
- Caffeine and theophylline a bronchodilator are metabolized by another enzymes called xanthine oxidase

Hydrolytic reactions

- Amides and esters are hydrolyzed by a variety of enzymes including cholinesterases which inactivate choline esters
- These inactivate choline esters, local anaesthetics and esmolol a drug used for treatment of tachycardia

Reductive reactions

- This is less common compared to oxidative and hydrolytic reactions
- Chloramphenicol, an antimicrobial agent is metabolized by nitro reductase with also an involvement of CYP enzymes
- Nitroglycerine, a vasodilator undergoes reductive hydrolysis catalyzed by glutathione organic nitrate reductase

Phase II metabolic reaction

- In phase II biotransformation, drug molecules undergo conjugation reactions with an endogenous substance such as gluconate, acetate, sulfate or glycine
- Conjugation enzymes present in the liver and other tissues join various drugs with one endogenous substances to form water soluble metabolites
- These water soluble metabolites are more easily excreted
- Most conjugated drug metabolites are pharmacologically inactive

Glucuronide formation

- Conjugation of a parent drug and a gluconate molecule mostly uses glucuronosyl transferases

Acetylation

- This is accomplished by N-Acetyl transferase enzymes using the acetyl coenzyme A(Acetyl coA) as a source of the acetyl group

Sulfation

- In this process, sulfotransferases catalyze the conjugation of several drugs which include minoxidil a vasodilator and a triamterene a potassium sparing diuretic

PHARMACOGENOMICS

- The completion of the Human Genome Project has led to the understanding of the great degree of individual variation in gene coding for drug metabolizing enzymes

- This is called **Polymorphism**

- Modern genetic studies were triggered by rare fatalities in children who were being treated for leukemia using thioupurine agent 6 mercaptopurine

- The discovery was that children died because of drug toxicity due to expression of faulty variant of thiopurine methyltransferase, the enzyme that metabolize 6 mercaptopurine

Examples of variations

Variations in Acetyltransferases activity

- Two classes of people exist i.e. fast acetylator and slow acetylators
- Slow acetylators were first identified amongst patients receiving Isoniazid a drug for treatment of tuberculosis who were found to have developed peripheral neuropathy the very reason why currently pyridoxine (Vitamin B 6) is given as prophylaxis
- Distribution of these phenotypes varies from population to population with 15% of Asians, 50% of Caucasians and Africans, more than 80% of mid east populations falling within the slow acetylator phenotype
- Drugs like sulphonamides, procainamide an anti arrhythmic drug and hydralazine an antihypertensive can also cause toxicity among slow acetylators

Variation in CYP2D6 and CYP2C19

- Genetic polymorphism of CYP2D6 and CYP2C19 are well characterized with human population of extensive and poor metabolizers having been identified
- These differences are caused by 70 identified variants in the CYP2D6 gene and 25 variants of the CYP2C19 gene
- Most individuals are extensive metabolizers of CYP2D6 substrates while only 10% and a smaller fraction of Asians and Africans are slow metabolizers
- Higher rates of adverse drug reactions are reported among psychiatric patients who are slow metabolizer due to increased psychotropic drug plasma concentration
- Poor metabolizers of CYP2C19 substrates have higher levels of proton pump inhibitors like omeprazole while higher metabolizers may need higher doses of omeprazole to treat peptic ulcers

Potential remedy against polymorphism

- In both Phase I and Phase II enzymes, a number of polymorphisms are recorded
- This can be connected to having more than 30 families of drug metabolizing enzymes, all with genetic variants
- With polymorphism in mind, individual tailoring of drug and dose based on patient's genomic identity will bring about major development in pharmacotherapy

DRUG EXCRETION

- Excretion is the removal of drug from the body fluids and it primarily takes place through urine

- Other routes of excretion include the bile, sweat, saliva, tears, faeces, breast milk and exhaled air

- Like any endogenous substance going through the kidney, drugs undergo

  - Glomerular filtration

  - Active tubular secretion

  - Passive tubular reabsorption

Glomerular filtration

- This is the first step in renal excretion
- The free drug enters the renal tubule as a dissolved solute in the plasma filtrate
- Drugs which have a larger fraction bound to plasma protein like warfarin, an anticoagulant will have a low glomerular filtration

Active tubular secretion

- Drugs, particularly weak acids and bases undergo tubular secretion by tubular system in the proximal tubular cells
- The process is competitively inhibited by other drugs of the same chemical class e.g. secretion of penicillins and other weak acids is inhibited by probenecid, an agent used to treat gout
- Active tubular secretion is not affected by plasma protein
- This is due to equilibrium of free drug and the bound drugs in that while the free drug is actively transported across the renal tubule, this fraction of free drug is replaced by a fraction that dissociates from the protein

Passive tubular reabsorption

- The extent to which a drug undergoes passive reabsorption across the renal tubular cells into the circulation depends on the lipid solubility of the drugs
- Drug biotransformation facilitates drug elimination by forming polar drug metabolites that are easily eliminated compared to their less polar parent drugs which are easily reabsorbed
- Most non electrolytes including ethanol are passively reabsorbed across the renal tubular cells
- Ionized weak acids and bases are not reabsorbed and they are rapidly excreted in the urine than nonionized drugs
- The proportion of nonionized and ionized drugs is affected by the PH which can be modified to increase excretion of a drug after a drug overdose

Biliary excretion and enterohepatic cycling

- Many drugs are excreted in the bile as the parent drug or metabolite
- Compounds with molecular weight higher than 300 with both polar and lipophilic groups are favored in biliary excretion
- Smaller molecules are excreted only in negligible amounts while conjugates especially the gluconate increases biliary excretion
- Excreted conjugated drugs can be hydrolyzed back to the parent drug and can end up being reabsorbed into circulation and eventually return to the liver
- This is referred to as enterohepatic cycling
- Thus biliary excretion is only as successful as the extent to which enterohepatic secretion is not complete

Other routes of excretion

- Sweat and saliva are minor routes of excretion for some drugs

- In pharmacokinetics studies , saliva measurements are sometimes used because the saliva concentration of a drug often reflects the intracellular concentration of the drug in target tissues

Quantitative Pharmacokinetics

- To derive and use expressions of pharmacokinetic parameter, the first step is to establish a mathematical model

- This helps to accurately relate the plasma drug concentration to the rates of absorption, distribution and elimination

- The two compartmental models are;
  - First compartmental model
  - Two compartmental model

First compartmental model

- This is the simplest model

- The drug undergoes absorption into the blood according to the absorption rate constant (K_a) and also undergoes elimination from the blood with the rate constant (K_e)

Two compartment model

- This is the more accurate model and drug is absorbed in the central compartment (Blood), distributed to peripheral compartments (Tissues) and eliminated from the central compartment

- Regardless of the model used, rate constants can be determined for each process and can also be used to derive other pharmacokinetic parameters like elimination half life ($t_{1/2}$) of the drug

Bioavailability

- The fraction of the administered dose of the drug that reaches the systemic circulation in an active form
- Bioavailability is expressed as a fraction, the maximum of which is 1 (100%) which drugs administered through I.V give
- Bioavailability of orally administered drugs is of great concern as it is affected by many pharmaceutical and biological factors
- Pharmaceutical factors include the rate and extent of tablet disintegration, dissolution
- Biological factors include food which can inactivate or sequester the, gastric acid which inactivate the drug, gut and liver enzymes which can start drug metabolism and first pass effect

Volume of Distribution ($Vd=Dose/c_0$)

- This is the volume of the fluid in which a dose of the drug will need to be dissolved to have the same concentration as it does in the plasma
- This does not represent the volume in any particular fluid compartment but it is simply an apparent volume representing the relationship between the dose of the drug and the resulting plasma concentration
- Vd provides a measure of the extent of distribution of a drug
- Low Vd indicates that the distribution of the drug is restricted to a particular compartment e.g plasma or extracellular fluid
- When the Vd is equivalent to total body water (40L) as occurs with ethanol, it indicates that the drug has also reached the intracellular fluid as well

Clearance (Cl)

- This is the volume of the body fluid (blood) from which drug is removed per unit of time

Renal clearance

- Drugs that undergo tubular secretion with little re absorption will have a renal clearance equal to that of creatinine normally about 100ml/min
- Those whose clearance is lower than creatinine will be indicative that the drug is highly protein bound or undergoes passive reabsorption

Hepatic clearance

- Hepatic clearance is more difficult to determine than renal clearance because it include biotransformation and biliary excretion of parent compound
- Hepatic clearance is done by multiplying hepatic blood flow by arteriovenous drug concentration difference

First order kinetics

- In the first order kinetics, the rate of drug elimination (amount of drug per unit time) is proportional to the plasma concentration
- A drug's rate of elimination is equal to the plasma drug concentration multiplied by the drug clearance
- The plasma drug concentration can be determined from the dose of the drug and its clearance
- Because the plasma concentration is often correlated with the magnitude of a drug's effect, determination and adjustment of dose to achieve desired effect can be done using pharmacokinetic expression

Elimination half life ($t_{1/2}$)

- Elimination half life is the time required to reduce the plasma concentration by 50%
- It can be determined from the elimination rate constant
- Drug's clearance and volume of distribution are also used to express the $t_{1/2}$
- Disease, age and other physiological variables can alter drug clearance and distribution and can thus change the $t_{1/2}$

Zero order kinetic

- In zero order kinetics, the rate of drug elimination is constant
- The elimination half life is proportional to plasma concentration and inversely proportional to the drug concentration
- Small increase in dose will result in a disproportionate increase in plasma concentration
- Drug elimination is constant because the elimination processes becomes saturable e.g. alcohol, aspirin, phenytoin

Continuous Dose and drug accumulation kinetics

Steady state

- When a drug that follows first order kinetics is first administered, the drug will accumulate until it reaches the plateau concentration
- The first time the drug is administered, the rate of administration is higher than the rate of elimination as plasma concentration is very low
- As administration is continued, the rate of drug elimination gradually increases while the rate of administration remains constant
- Eventually as the plasma concentration become sufficient, the rate of elimination equals the rate of administration
- This is called the steady state equilibrium of which it takes five half lives for the drug to reach the steady state

Dose Calculation

Loading dose (Priming dose)

- This is given to rapidly establish a therapeutic drug plasma concentration
- This is determined by multiplying the volume distribution by the desired plasma concentration
- **$LD=[P] \times V_d$**
- This dose is either given as a single dose or divided dose
- A divided loading dose is desirable when giving more toxic drug like cardiac glycosides like digoxin

Maintenance dose

- This is given to establish or maintain a desired steady state plasma concentration
- The maintenance dose is the one that is administered regularly
- The maintenance dose is given based on the principle that at steady state, the rate of drug elimination equals the rate of administration

END