Pharmacology 101 (Part 2) The Basics

How drugs work

Pharmacokinetic Phase

Pharmacokinetics is the study of how a drug enters and distributes in the body and how the body metabolises and eliminates the drug over a period of time.

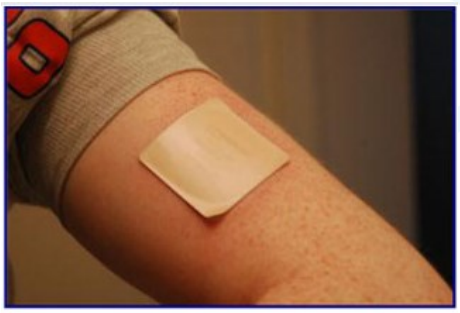
There are four pharmacokinetic processes to which drugs are subject to in the body.

These are:

1. **Absorption** (depending on the route of administration - intavenous drugs do not need to be absorbed as they are introduced directly into the circulation)
2. **Distribution**
3. **Metabolism**
4. **Excretion**

Routes of Drug Administration

Depending on the route of administration and mechanism of action of the drug being administered, drugs can either act locally or systemically. The term locally in essence means that the drug is confined to a specific area following administration. In order for a drug to have a systemic effect, it needs to enter the lymphatic or cardiovascular systems for distribution to target tissues and organs.



Transdermal Patch

Generally, drugs that are administered via the topical route (applied to body surfaces) provide a local effect. I say generally, because there are also numerous drugs that are applied topically and achieve a systemic effect. Transdermal patches for nicotine replacement, birth control and to treat angina have become widely available and used

Drugs are commonly administered via the enteral (along the gastrointestinal tract) or parenteral (taken into the body in a manner other than through the gastrointestinal tract) routes to achieve a systemic effect.

The enteral route of administration includes drugs administered via oral, sub-lingual (drug placed under tongue), buccal (drug placed between teeth and mucous membranes of cheek) and rectal routes.

The selection of which enteral route to use is largely dependant on the properties of the drug and how much of the drug is required at the target tissue/ organ to be effective.

Drugs administered orally are exposed to what is called the First Pass Effect. In essence, this means that after the drug is swallowed, it is absorbed by the digestive system and is transported to the liver via the portal vein. The liver metabolises the drug, sometimes to such an extent, that only a small percentage of the active drug is made available to the systemic circulation.

This is why drugs such as Glyceryl Trinitrate (to treat angina) are administered via the sub-lingual route, to avoid the First Pass Effect. If Glyceryl Trinitrate was swallowed it would simply result in an insufficient concentration of the drug following First Pass Metabolism, rendering it ineffective.

Sub-lingual Route

The parenteral route includes drugs administered via the intravenous (into a vein), intra-muscular (into skeletal muscle), subcutaneous (below the skin), intra-thecal (into the

subarachnoid space), Intraosseous (into bone marrow) and intra-articular (into a joint) routes.

The intravenous route introduces the drug directly into the circulatory system and therefore bypasses absorption and results in the fastest action. This is extremely useful in emergency situations where time vs. patient outcome plays a crucial role in the resuscitative process.

Absorption

Absorption is the process whereby drug molecules move from its site of administration into the circulatory or lymphatic systems. There are several variables that influence absorption, including, the nature of the absorbing surface, the blood flow to the site of administration, the solubility of the drug, the pH of the absorbing environment, the concentration of the drug and the drug dosage.

In order for a drug (besides intravenous drugs) to be absorbed and enter the circulatory system, it has to pass through several lipid cell membranes.

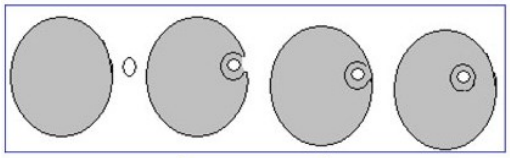
There are four main transport mechanisms which facilitate this process:

Passive Diffusion
is the most common and the most important transport mechanism and there is no energy expended during this process. If a drug?s concentration is higher in the gastrointestinal tract than in the blood, a concentration gradient will exist. As a result, drug molecules in the gastrointestinal tract (higher concentration) will diffuse across the lipid cell membrane into the blood (lower concentration). The drug will continue diffusing until it reaches equilibrium (balance) on either side of the lipid cell membrane. The concentration gradient thus transports the drug into the circulatory system.

Facilated Diffusion
allows for low lipid soluble drugs to be transported across the cell membrane by combining with a carrier molecule. The direction of transport is dependant on a concentration gradient and no energy is expended.

Active Transport
is used by drugs which closely resemble natural body substances. The process works against a concentration gradient (from low to high) and for this reason, requires energy to be expended.

Pinocytosis
is not a very common method for drug absorption and requires a great deal of energy expenditure. In pinocytosis, the cell membrane invaginates (folded back on itself to form a cavity or pouch), encloses the particles or fluid, then fuses again to form a vesicle that later detaches and moves into the interior of the cell.



Pinocytosis

Drug Distribution

Following absorption, the drug is then distributed to its target site.

There are several factors that influence how a drug is distributed and depending on circumstances, whether the drug is distributed to its target site at all.

Blood Flow
Distribution is greatly influenced by tissue perfusion (the amount of blood that flows through a unit quantity of tissue). Highly vascular organs such as the heart, liver and kidneys will usually acquire a drug quite rapidly. Structures such as fat, bone, muscle and skin may take longer to acquire a drug because they have less vasculature. The patient?s level of activity and skin temperature may also influence how drugs are

distributed to muscles and the skin. Decreased body temperature will result in constriction of peripheral blood vessels with resultant decreased blood flow.

Plasma Protein Binding
In the circulation, a drug can either be bound to plasma proteins or free in an unbound state. Albumin is the plasma protein most involved in the binding of drugs.

When a drug is bound to a plasma protein it is considered to be in an inactive state and can thus not exert a pharmacological action. Only unbound drugs can cause an effect. When unbound drug molecules leave the circulatory system, more drug molecules are released from plasma proteins in order to maintain a balance between bound (inactive) and unbound (active) drug molecules.

Plasma protein binding tends to be competitive and non-specific and this means that plasma proteins will bind with many different drugs. In addition, these drugs will compete with each other for binding sites on the plasma proteins. As such, the displacement of one drug by another may cause serious consequences.

Blood Brain Barrier
is a selective membrane which lacks the usual channels found in most other parts of the body. As a result lipid soluble drugs such as Diazepam will pass fairly readily into the Central Nervous System, whereas lipid insoluble drugs will have little or no effect because they will be blocked by the barrier.

Placental Barrier
permits the passage of lipid-soluble, non-ionised compounds between the mother and foetus, but prevents the entrance of those substances that are poorly lipid-soluble.

Sites of Drug Storage
Fatty tissues will act as storage sites for lipid-soluble drugs, such as Warfarin (anticoagulant). Drugs that have accumulated in fatty tissues may remain there for quite some time and not be released until after the administration of the drug has stopped.

Calcium containing structures such as teeth and bone can accumulate drugs that are calcium bound, such as Tetracycline (broad spectrum antibiotic).

Drug Metabolism
Drug metabolism or biotransformation involves the altering or modifying of the chemical composition of the drug. The products formed from metabolism are called metabolites and are more polar and far less lipid-soluble, thereby promoting their excretion from the body.

Drugs can undergo one of four potential biotransformation processes: Active Drug to Inactive Metabolite, Active Drug to Active Metabolite, Inactive Drug to Active Metabolite, and Active Drug to Toxic Metabolite.

Most drugs are metabolised in the liver where liver enzymes catalyse various reactions, however drugs can also be metabolised in the intestinal mucosa, lungs, plasma, kidneys and placenta.

Drug metabolism takes place in two processes, phase 1 and phase 2. In phase 1, the reactions attempt to metabolise the drug into a more polar metabolite. In phase 2, drugs or metabolites from phase 1 reactions which are not sufficiently polarised for excretion by the kidneys are made more hydrophilic (in other words more "water liking"). The resulting compounds are then readily excreted by the kidneys.

There are several factors that influence a patient's ability to metabolise drugs. These factors should always be considered when administering medications. These factors include:

The Age of the Patient
the older patient may have a significantly reduced First Pass Metabolism, resulting in a higher bioavailability of a drug. In addition, the slower production and delayed elimination of active metabolites may lengthen drug action. One therefore needs to consider reducing drug dosages in the older patient.

Underlying disease
acute or chronic liver disease could affect drug metabolism. In addition, a reduced liver blood flow due to

shock or heart failure may also reduce the metabolism of a drug in the liver.

Genetic Differences
the enzyme systems which control the metabolism of drugs are genetically determined. Some patient's may show an exaggerated or prolonged response to drugs which are extensively metabolised in the liver.

Drug Excretion
Filtration through the kidneys accounts for the majority of drug excretion. This however only applies to unbound drugs. Drugs that are bound to plasma proteins remain in the circulation.

Nearly all water and a large percentage of electrolytes are reabsorbed from the renal tubules back into the circulatory system. Polar compounds, which make up the majority of drug metabolites cannot diffuse back into the circulation and are subsequently excreted.

Several factors may influence the rate at which a drug is excreted by the kidneys. These include: a decrease in blood flow through the kidneys, pH of the urine, the presence of underlying kidney disease and the concentration of the drug in the plasma.

Some drugs and their metabolites are also excreted in bile. These then enter the duodenum via the common bile duct and are transported through the small intestine. Some of these drugs are reabsorbed back into the circulation and return to the liver via the enterohepatic circulation. The drug then undergoes further metabolism and is secreted back into the bile. Ultimately, drugs secreted into bile will pass through the large intestine and be excreted in faeces.

Well, that's pharmacokinetics in a nutshell. The pharmacology saga continues in next month's edition of The Responder where we will take a look at pharamacodynamics and the action of drugs at the receptor site.

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