VPC 302- INTRODUCTORY VETERINARY PHARMACOLOGY

DRUG ABSORPTION

Before drugs can reach their site of action, they must pass across a series of cellular membranes that make up the absorptive surfaces of the sites of administration. The degree to which a drug is absorbed and reaches the general circulation is called bioavailability

Drug absorption:- is the passage of drug from its site of non-intravascular administration into the plasma.

The factors that may affect the absorption process include the following:

- Mechanism of absorption
- pH and ionization status of the drug
- Absorptive surface area
- Blood supply to the area

- Solubility of the drug
- Dosage form
- Status of the Gl tract (motility permeability and thickness of the mucosal epithelium).
- Interaction with other medications.

1. **Mechanism of absorption** :- Drug pass across cellular membranes through three common methods.

a) Passive absorption (transportation)

- This occurs by simple diffusion.
- The drug moves from the area of high concentration to area of lower concentration on the other sides.
- This requires no energy expenditure.

b) **The drug may pass through pores**

- The drug may pass through the pores of the cell membrane
- The drug would pass form one side of the membrane to the other or it may dissolve into the cell membrane
- A tablet or capsule disintegrates this result in high concentration of the drug in the Gl
- The concentration then passes through the cell membrane of the intestinal villi and adjacent capillaries, it appears in small concentration in the blood stream.
- The drug may cross a membrane passively with the help of a carrier.

Some small drug molecules such as electrolytes may simply move with fluid through pores in cell membranes. Active transport of drugs across cell membranes move from lower concentration to an area of high concentration this requires an expenditure of energy. This is the

usual mechanism for the absorption of Sodium, Potassium, and other electrolytes. In pinocytosis, a third method of passive transport, cells engulf drug molecules by invaginating their cell membrane to form a vesicle that then breaks off from the membrane in the interior of the cell.

pH and ionization status of the drug.

- Many drugs can pass through a cell membrane only if they are non-ionized (not positively or negatively charged).
- Most drugs exist either as ionized or non-ionized
- The pH of the drug and the pH of the area in which the drug is located can determine the degree to which a drug becomes ionized and thus is absorbed.
- Weakly acidic drugs do not ionize readily in acidic environment.
- Similarly a weakly alkaline drug would not ionize readily in alkaline environment.
- Therefore, an acidic drug would be absorbed better in an acidic environment and alkaline drug would be absorbed readily in an alkaline environment.

Conversely, if a drug is acidic in an alkaline environment the drug would be ionized readily hence it would be ionized readily hence it would not be absorbed easily. The drug thus, would be trapped in that environment.

Absorptive surface of the area.

As the absorptive surface of the area of drug placement increases, so does the rate of absorption. One of the largest absorptive surfaces in the body is found in the small intestine, because of the efficient design of the villi that maximizes the surface area.

Blood supply to the area.

The rate of absorption of the drug is dependent on the perfusion rate to that area. Therefore, if the perfusion rate is high it means the rate of absorption of the drug is low. The drug for example is absorbed faster in the muscles faster than subcutaneously. Initiating the fight-or-flight response increases the blood supply to the muscles and compromises the supply to the intestine. Heat and massage also increases blood flow to an area. Cardiac failure or shock would result to poor circulation.

Solubility of the drug.

The lipid (fat) solubility of a drug tends to be directly proportional to the degree of drug non-ionization. As was stated previously, the non-ionized form is the one that usually absorbed. The degree of lipid solubility of a drug often is expressed as its lipid partition co-efficient.

Drug absorption and formulation of the drug.

The absorption of drug depends on the formulation of the drug. Various inert ingredients such as: carriers (vehicles), binding agents. And coatings are used to prepare dosage forms. These substances have major effect on the rate at which formulation dissolve. Drug depot and patches are associated with prolonged or sustained – release formulation in veterinary medicine. Subcutaneous implants that contain growth stimulants that break down slowly and release their products over prolonged periods are used in some situation.

Status of the gastrointestinal tract.

When drugs are orally administered the condition of the gastrointestinal tract can have a major influence on the rate and extend of drug absorption. Factors such as degree of intestinal motility, emptying time of the stomach, irritation or inflammation of mucosa (e.g. gastritis enteritis), damage to the villi of loss of the villi (e.g. viral diseases), composition and amount of good

materials, and changes in intestinal micro-organisms can affect the rate and extent of absorbance of medications. Another consideration regarding drugs that are absorbed from the G.I. tract is the first pass effect. This refers to the fact that substances are absorbed from G.I. tract into the portal venous system which delivers the drug to the liver before it enters the general circulation. In some instances, a drug then is inactivated or less active.

The process of combining some drugs with other drugs or with certain food can negatively affect drug absorption. Example is tetracycline is reduced if it is administered with milk products. Antacids may reduce the absorption of phenylbutazone or iron products.

Methods for delaying drug absorption.

- It may be desirable for a therapist to achieve delay absorption of adrenaline to local anaesthesia (lidocaine)
- Another method of delaying absorption from (poorly soluble salt, ester or complex, injected either as an aqueous suspension or an oily solution. Penicillin G Procaine is poorly soluble salt penicillin). This result in 'slow release'
- Physical characteristics of the drug may also influence its rate of absorption.

Insulin zinc suspensions.

- Solid implantation of pellets subcutaneous for example estradiol a steroidal hormone. The rate of absorption is proportional to the surface area of the implant.

DRUG DISTRIBUTION.

Drug distribution: is the process by which a drug is carried from its site of absorption to its site of action.

Drug redistribution:

Highly lipid soluble drugs e.g. (Thiopentone, halothane) given by intravenous injection or by inhalation respectively, initially get distributed to organs with high blood flow (e.g. brain, heart, kidney). Later, less vascular but more bulky tissue (Like muscle fat visceral) take up the drug, plasma concentration falls and the drug is then withdrawn from the highly vacularized sites into the blood stream. If the site of action of the drug was in one of the highly perfused organs (e.g. brain) redistribution results in its termination of action. For example, thiopentone results to an unconsciousness in 10-20 seconds after administration and consciousness returns in 20-30 minutes.

Volume of distribution:

The volume of distribution of a drug (V_d) is the volume of the body fluid compartment in which it appears to distribute with a concentration equal to that of the plasma.

A drug that is water soluble (e.g. penicillin sodium) do not enter cells and are therefore restricted in distribution, while drugs that are lipid soluble have wide range of distribution e.g. xylazine can pass freely into all the fluids compartments thus, its wider distribution.

- Other examples such as warfarin are bound to the protein in the plasma namely albumin but have a small volume of distribution 0.1-0.2L/kg.

Apparent volume of distribution:

The concept of the apparent volume of distribution could be introduced in an instance of basic drugs (e.g. amphetamine) they avidly readily taken up by tissues and thus, have volume of distribution larger than volume of the entire body, hence the term apparent volume of distribution.

The factors that affect distribution of a drug are as follows

- Drug lipid solubility

- Degree of ionization at physiologic pH
- Extent of binding to plasma and tissue protein and extents of blood perfusion from one place to the other.
- Barriers of tissues or compartment.

The ways of exploring distribution of drug to its site of action

- Liposome encapsulation.
- Antibody tagging
- Permeability enhancers

Drug lipid solubility :- Using the basic chemistry as inference if a drug is lipid soluble either as an organophosphate or organic lipophilic drug. It would have high affinity for lipids and thus, could beat through many cell membrane barrier ,since it could dissolve or pass through the phospholipids bi-layer of the mosaic layer of the cell membrane. Therefore such a drug would have a large volume of distribution. Where as for non lipid soluble drugs the volume of distribution or the extend of distribution of drug would small because the polar nature of the drug molecules would result to trapping of the molecules in particular barrier bounded compartment such barriers that the drug molecules could not beat through the membranes or bound would not be able to penetrate through would end up resulting to minimal extent of distribution, thus a limited volume of drug distribution.

Plasma protein binding

Most drugs possess physiochemical affinity for plasma proteins and are transported in the blood stream partly in plasma water (as free drug), and partly bound to plasma protein (as protein-bound drug). Binding to albumin is the most common, but B-globulin and an acid glycoprotein may also bind drugs.

Acidic drugs (eg salicylates, benzodiazepines) generally bind to plasma albumin, and basic drugs (e.g quinidine, lidocaine) bind to xi-acid glycoprotein. Drug-protein binding is usually reversible, and is achieved by various forces between the molecules of the drugs and the receptors or sites involved in bounding with plasma proteins. The forces involved Vander Waals, hydrogen bonding, as well as electrostatic respectively. The drug molecules bounded to the protein of the plasma acts as the reservoir of the drug that is not bound. However the free and bound drug fractions are in constant equilibrium, and the free drug removed from the plasma by metabolism or excretion is replaced by drug released from the bound fraction. For example a single dose of suramin can offer protection against trypanosomosis for 3months because it is bound to plasma extensively.

Drugs that are bound to plasma proteins may be displaced from their binding sites by other drugs that are more strongly bound, so-raising the free (and pharmacologically active) Concentration of the first drug for example Phenylbutazone and Salicylates displaces tolbutamide producing severe hypoglycaemia. Indomethacin and phenylbutazone displace warfarin, which may result in warfarin toxicity. Sulphonamides and Vitamin K displace bilirubin and this is useful in treating kernicterus (increased blood bilirubin level.) in human neonates.