SYNTHETIC SOURCES OF DRUGS

- A number of drugs synthesized in the laboratory are used most commonly.
- Even natural products such as hormones, antimicrobials etc. are also synthesized in the laboratory.

MICROBIAL SOURCE OF DRUGS

- Microbes provide an important source of drugs especially the antibiotics. All the antibiotics used against a variety of pathogens and also cancer are obtained from fungi, bacteria or actinomycetes. Some systemic drugs like ergot alkaloids (fungal source) are also obtained from microbes.
- Eg: Penicillin from Penicillium notatum
- Streptomycin, Tetracyclines, Chloramphenicol from Streptomyces sp.

4: PRINCIPLES OF DRUG ACTIVITY: PHARMACOKINETICS

Learning outcomes

After reading this module, the learner will be able to understand the different routes of drug administration and their relative advantages and disadvantages.

ROUTES OF ADMINISTRATION

- Routes of drug administration can be divided into three main classes as enteral, parenteral and topical.
    - *Enteral* administration refers to administration of drugs via the gut.
    - *Parenteral* (par – beyond, enteral - intestinal) administration covers intravenous, intramuscular, subcutaneous, intraperitoneal etc.
    - *Topical* application refers to application of drugs on the skin and mucous membrane.
- Factors governing the choice of route are:
    - Physical and chemical properties of the drug (solid/liquid/gas; solubility, stability, pH, irritancy)
    - Site of desired action – localized or generalized
    - Rate and extent of absorption of the drug from different routes
    - Effect of digestive juices and first pass metabolism of the drug
    - Rapidity with which the response is desired (routine treatment or emergency)
    - Accuracy of dosage required (intravenous and inhalation need fine tuning of dose)
    - Condition of the patient (unconscious, vomiting)

ORAL ADMINISTRATION

- Dosage forms available for oral use include
- *Liquids*: Aqueous solutions, suspension (dispersion of a solid in a liquid) and emulsion (dispersion of a liquid in liquid)
- *Solids*: Powders, tablet, enteric coated tablet, capsule, granules
- For tablets and capsules the factors that affect the actual amount of the drug absorbed or available include disintegration, coating, adjuvants used, compression, drug particle size – micronization, amount of the drug, chemical form (salt), physical state (amorphous or crystalline, solvated or anhydrous) and local pH of the absorptive area.

Advantages of oral route

- Generally the safest route
- Economical

- Convenient and relatively simple for owner
- No need for sterile equipment
- Systemic distribution can be achieved

Disadvantages

- Absorption may be variable
- Gastric irritation may cause vomiting
- Not useful if animal is vomiting
- Requires cooperation of patient, which is not usually forthcoming ina veterinary patient
- Drugs may be destroyed by gastric acidity, gut flora, mucosal enzymes and liver enzymes
- Onset of effect is usually slow
- Not generally preferred in ruminants since the drug gets diluted in the voluminous ruminal contents
- When antimicrobials are administered to ruminants orally for a longer duration of time, they may affect the microbial ecosystem of the rumen
- Presence of food and other drugs may alter the absorption pattern leading to unpredicatability in the desired action.

Enteric coated preparations

- Drugs that are destroyed by the gastric juice or that cause gastric irritation can be administered orally with a coating that prevents dissolution in the acidic gastric contents.
- They dissolve once they reach the duodenum and release the active drug. Onset of drug action can be delayed with enteric-coated tablets.

Sublingual tablets

- Drugs that are lipid soluble and non-irritating can be administered sublingually, so that absorption directly from the oral cavity is achieved when a rapid response is required, particularly when the drug is either unstable at gastric pH or rapidly metabolised by the liver. Eg. Glyceryl trinitrate.
- Drugs absorbed by mouth pass directly into the systemic circulation without entering the portal system and so escape the first-pass metabolism. This type of tablet is useful in the treatment of angina pectoris where the drug enters directly into the systemic circulation and provides immediate effect. Once the required effect has been achieved, the excess tablet can be spit off.

Timed release preparations

- Timed release preparations are designed to produce slow uniform release and absorption of the drug over a period of 8 hours or more. They are also known as spansules or timesules.
- *Advantages*
    - Less frequent administration
    - Lasts overnight
    - Drug levels are more constant and do not peak after each administration (less toxic effects)
    - Good for short-acting drugs
- *Disadvantages*
    - Marketed preparations are sometimes not reliable
    - Dissolution rates may be irregular
    - Not needed for long acting drugs
    - Not good for a brief therapeutic effect

Rectal administration

- This route of administration is useful when the animal is unconscious or vomiting.
- Rectal absorption is often incomplete and erratic.
- Drugs can be administered rectally in the form of enema or suppository.
- Irritant and unpleasant drugs can be administered per rectum. However, rectal inflammation may occur due to highly irritant drugs.

INTRAVENOUS ROUTE

Parenteral administration

- While considering parenteral administration, the points of importance include
  - Volume to be administered
  - Concentration of the drug
  - pH
  - Toxicity
  - Viscosity
  - Particle size, if suspension is used
  - Adjuvant used in the preparation
- In general, parenteral administration requires skill of injection and use of sterile equipment. Parenteral preparations are normally used as solutions or suspensions.

Intravenous administration

- *Advantages*
  - Extremely rapid onset of action
  - Initial absorption step is bypassed
  - Drug levels can be controlled more accurately
  - Suitable for irritant drugs
  - Suitable for large volumes of drugs
- *Disadvantages*
  - Most dangerous route as toxicity can easily occur
  - Drugs must be in aqueous solution
  - Must be performed slowly
  - Once injected, drug cannot be retrieved

Sites for venipuncture in different species

- Cattle, sheep and goat - At any point along the whole length of the jugular vein in the jugular furrow, on the venterolateral aspect of the neck on either side
- Horse - External jugular vein in the jugular furrow only in the cranial part of the neck.
- Pig - Auricular vein
- Dog - saphenous vein on the medial aspect of the leg or recurrent tarsal vein on the dorsal aspect of the leg.

SUBCUTANEOUS AND INTRAMUSCULAR ROUTES

Subcutaneous administration

- This route is useful when slow and continuous absorption is required. The formulation must be isotonic and at physiological pH.
- Certain drugs that are irritating can cause severe pain and necrosis. The rate of distribution of the drug is largely dependent on blood flow and hence, the rate of distribution can be slowed by including a vasoconstrictor.

- Warmth or vigorous massage will increase distribution. Addition of hyaluronidase can enhance drug dispersion. This enzyme hydrolyses the hyaluronic acid polymers that comprises the intercellular cement and thus facilitates diffusion through the tissues.
- Specialised subcutaneous preparations include *dermojet* and *pellet implantation*.
- Dermojet is a process where no needle is used. A high velocity jet of the drug solution is projected from a microfine orifice using a gun like implement. The solution passes through the superficial layer and gets deposited in the subcutaneous tissue. It is essentially painless and suitable for mass inoculation.
- Pellet implantation provides sustained release of the drug over weeks or months. The pellet impregnated with the drug is implanted in the subcutaneous tissue. Sialistic (non biodegradable) and biodegradable implants are used.
- Crystalline drug is packed in tubes made of suitable material and implanted under the skin. Constant blood levels can be maintained as the drug is released uniformly over a period of time. If non-biodegradable implant is used, it should be removed after the specified period of time.

Sites for subcutaneous injection in different species

- Cattle, sheep and goat - Fold of flank extending from the caudoventral abdominal wall to the craniomedial aspect of the thigh near stifle joint or loose skin on the lateral aspect of the neck.
- Horse - Loose skin on the lateral aspect of the neck. Normally subcutaneous injection is not preferred in horses.
- Dog - Fold of the flank

Intramuscular administration

- Drugs in aqueous solution are rapidly absorbed after intramuscular administration. However, very slow constant absorption occurs if the drug is administered in oil or suspended in other repository vehicles as depot preparations. It can be used for relatively irritant drugs and such drugs must be administered deep intramuscularly. Intramuscular injections are always painful and large volumes cannot be injected.
- A disadvantage of this route is the possibility of improper deposition in nerves, blood vessels, fat or between muscle bundles in connective tissue sheaths. Whenever drugs are administered intramuscularly, it is always advisable to confirm that the needle is not in the blood vessel.
- Sites for intramuscular injection in different species:
- Cattle, sheep and goat – 1. Hind limb a) Gluteal region covered by gluteal muscles and b) posterior aspect of thigh between the semimembranous and semitendinous. (In sheep and goat (b) is preferred).
- 2. Neck – In the heavy muscles on the caudodorsal aspect of the neck. Needle can pierce through the following structures – skin, fascia, trapezius, rhomboideus, splenius and complexus, depending upon the length of the needle and force applied. This site is preferred only in well built animals. Care should be taken to avoid vertebral column and the dorsal branch of the XI cranial nerve.
- In indigenous cattle with hump, hump is also preferred to administer intramuscularly.
- Horse - Neck region and brisket region (pectoral muscles)
- Dog - Hind limb between the semimembranosus and semitendinosus.

OTHER PARENTERAL ROUTES

Intraperitoneal administration

- This route is particularly useful in laboratory animal medicine and neonatal animals and for the administration of large volumes.
- There is a very large absorbing area and absorption is rapid. There is a danger of infection and peritoneal adhesions. Thus it is not used routinely. Peritoneal dialysis is becoming more frequently used in small animals with renal failure and renal insufficiency.

Intradermal administration

- This route is used mainly for diagnostic purposes eg. for Tuberculin and Johnin testing in cattle and also for hypersensitivity testing before administering some drugs known to induce hypersensitivity.

Intrathecal administration

- In this route the drug is administered through the membranes enclosing the central nervous system in the lumbar area or into the cisterna magna.
- It is occasionally used for radiographic examinations and chemotherapy of central nervous system infections and neoplasms.

Epidural administration

- This route is mainly used to anaethetise animals for surgery like parturition in cattle.
- The drug is administered between the first and second coccygeal vertebrae.

Intraarticular administration

- This route is used to administer anti-inflammatory agents into the joint capsule.
- The other parenteral routes of drug administration rarely used are intra- arterial, intramedullary, intratesticular, intracardiac etc.

LOCAL ADMINISTRATION OF DRUGS

- Local administration of drugs refers to external application or application to a localized site such as eye. ear. mucous membranes etc.
- Some of the local sites of administration include:
    - Skin: Application of drugs on to the skin such as powder, lotion, ointment etc.
    - Mucous membrane:
        - Mouth and pharynx: mouthwash, gargle, paint etc.
        - Eye, ear and nose: Drops, spray, irrigation
        - GI tract: non absorbable drugs such as kaolin, antacids, some antibiotics which are intended to remain within the GI tract and not absorbed
        - Bronchi and lungs: aerosol, inhalations
        - Vagina: Pessary, bolus, tablets
        - Rectum: Suppository, enema etc.
    - Tissues: Drugs can be administered to some of the tissue but are intended to act only on the site of absorption. eg. Intraauricular, intrathecal
    - Arterial: Some drugs are given intraarterially to act on the localized area supplied by the artery. Eg: angiography, anticancer drugs.

5: STRUCTURE OF BIOLOGICAL MEMBRANES

Learning outcomes

At the end of this module, the learner will be able to visualize the ultrastructure of a biological membrane, a vital structure through which all drugs have to pass through at various stages.