COURSE CODE:	VPC 302
COURSE TITLE:	Introductory Veterinary Pharmacology
NUMBER OF UNITS:	3 UNITS
COURSE DURATION:	TWO HOURS PER WEEK

COURSE DETAILS:

Course Coordinator:	**Dr. Olubukola Tolulope Adenubi D.V.M., M.Sc.**
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Other Lecturers:	**Prof. R.O.A. Arowolo, Dr. J.O. Olukunle, Dr. K.T. Biobaku**

COURSE CONTENT:

Introduction to the evolution and principles of veterinary pharmacology and toxicology, sources, nomenclature and presentation of drugs, routes of drug administration, pharmacokinetics and pharmacodynamics; adverse drug reactions and interactions, introduction to neuropharmacology, introductory toxicology.

COURSE REQUIREMENTS:

This is a compulsory course for all veterinary medical students in the University. In view of this, students are expected to participate in all the course activities and have minimum of 75% attendance to be able to write the final examination.

READING LIST:

Aliu, Y.O (2007). Veterinary Pharmacology (1st edition).

Boothes M. (2001). Veterinary Pharmacology and Therapeutics for small animals.

Nicholas H.B. (1988). Veterinary Pharmacology and Therapeutics. IOWA University Press.

Wanamaker B.P and Kathy L.M (2009). Applied Pharmacology for Veterinary Technicians 333 -335.

LECTURE NOTES

HISTORICAL DEVELOPMENT OF PHARMACOLOGY

- Ever since it was realized that a large number of diseases that afflict animals and man were caused by bacteria, scientists have been looking for substances that would kill the bacteria but leave the infected subject unharmed.
- The evolution of pharmacology can be traced through 3 distinct periods; a pre-Ehrlich era before 1891; the period of Paul Ehrlich (1854-1915), and the period after 1935 highlighted by the discovery of sulphonamides and antibiotics.
- **Pre-Ehrlich era:** The Chinese were aware, over 3,500 years ago, of the therapeutic properties of moldy curd of soybean. They applied this material as standard treatment for carbuncles, boils and similar infections.
- The powdered bark of cinchona has been used since 1630 to treat malaria.
- In 1877, Louis Pasteur and Joubert first described the concept of antibiosis. They noted that the anthrax bacilli grew rapidly when inoculated into sterile urine, but failed to multiply and soon died if one of the 'common' bacteria of the air was introduced into the urine culture at the same time.
- **Ehrlich era:** Towards the end of the 19^{th} century, a German bacteriologist, Paul Ehrlich (1854-1915), observed that certain vital dyes like methylene blue specifically killed and stained certain bacterial cells. He reasoned that chemical substances might be produced that could unite with and destroy parasitic agents of diseases without injuring the host cells. He aptly called these chemical substances 'magic bullets'. In 1891, he demonstrated the efficacy of methylene blue in the treatment of human malaria.
- The first real step forward was the preparation of arsphenamine, an organic arsenical by Ehrlich and co-workers in 1900. This substance was of value in treating syphilis and trypanosomosis. Ehrlich is regarded as the father of modern antimicrobial chemotherapy; he was awarded a Noble prize in 1908 with a Russian bacteriologist, Elli Metchnikoff.
- Little progress was made in the next thirty years. But there were many antiseptics and disinfectants introduced that could eradicate infections when applied

topically; their systemic use was precluded by their toxic reactions or tissue injury.

- **Post Ehrlich era:** In 1929, Alexander Fleming of St Mary's Hospital, London, whilst studying variants of *Staphylococcus* found one of his culture plates contaminated with a fungus (later identified as *Penicillum notatum*); the fungus destroyed surrounding bacterial colonies. His efforts to extract the bacteriolytic substances failed.
- In 1935, Gerhard Domaqk reported that the red azo dye, prontosil protected mice against infection by certain bacteria. Bovet, Nitti and Trefoues proved that prontosil owed its therapeutic efficacy to its conversion in the body to sulphanilamide. This was a milestone in the history of pharmacology.
- In 1940, Chain, Falk and Florey of Oxford succeeded in producing significant quantities of the first penicillins from culture of *Penicillin notatum.*
- In 1944, after more than 10,000 microorganisms had been screened, Waksman and his colleagues reported the isolation of streptomycin from *Streptomycin griseus,* found in a diagnostic culture from a chicken's throat. Waksman also first defined the term 'antibiotic' as a chemical substance produced by microorganisms (bacteria, fungi, and actinomycetes) having the property of destroying other micro-organisms or inhibiting their growth in high dilution.

NOMENCLATURE AND PRESENTATION OF DRUGS,

All drugs have at least three names:

a. Chemical name
b. Non- proprietary/ Generic name
c. Proprietary/ Trade/ Brand name

Drugs are presented as solid, semi-solid, liquid, aerosol or gaseous forms.

Immediate Release Drug Formulations

Solid Dosage Forms:

Tablets

- A mixture of active drug and inert binding materials or excipients, usually in powder form, pressed or compacted into a solid.

- Some tablets are in the shape of capsules, and are called “caplets”

Wettable Powder

- Drug dosage form in fine particles.
- Could be sprinkled on feed or dissolved in drinking water.
- It is commonly used in poultry.

Suppository

- Inserted as a solid into the rectum (rectal suppository), vagina (vaginal suppository) or urethra (urethral suppository), where it dissolves inside the body to deliver the drug.
- Used to deliver both systemically-acting and locally-acting medications.

Capsule

- Hard gelatin e.g ampicillin capsule for dry, powdered ingredients or miniature pellets.
- Soft gelatin e.g garlic capsule.
- Primarily used for oils and for active ingredients that are dissolved or suspended in oil.

Semi solid Dosage Forms:

- Examples are ointments, creams and gels commonly used to treat dermatological diseases.
- Ointments are homogeneous, viscous, semi-solid, greasy, thick oil, intended for external application to the skin or mucous membranes.

Liquid Dosage Forms:

Suspension

- Formulation of two-phase system composed of a finely divided solid that is dispersed in a liquid phase, which is usually water.
- Suspensions are common as oral drug preparations.
- **Never administer intravenously.**

Emulsion

- Aqueous suspension of insoluble liquid substance usually with emulsifying agent to stabilize the preparation.

- Usually administered orally or topically.

Solutions

- Oral Solution: Aqueous preparation of drug for oral use. The drug is in true solution.
- Parenteral Solution: Sterile and pyrogen free aqueous preparation for injection. Drugs may also be dissolved in oil for prolonged absorption.
- Ophthalmic Solution: Sterile hypotonic aqueous solution of drug for administration into the eye.

Tinctures

- Tinctures vary in strength. Examples are tincture of iodine, opium, belladonna and digitalis.

Liniment

- Liquid preparation of a drug in which the drug is dissolved or suspended in dilute alcohol or water. They often contain dissolved or emulsified oils and are applied to the skin by rubbing or massage.

Lotion

- Usually an oil in water base which contains insoluble medicinal agents in suspension and is applied to the skin without rubbing following which the solvent evaporates leaving a film of drug.

Aerosol

- The drug exists as liquid or solid particles so small as to remain suspended in air for long periods.
- Aerosol generators may produce particles in 1-5μm ranges.
- For therapeutic purpose, aerosols are introduced in the body by inhalation.

Controlled-Release Drug Delivery Systems

Synonyms: Sustained; Modified; Prolonged; Slow; Gradual and Extended Forms

- Provide an initial therapeutic dose immediately following administration and subsequently followed by a gradual release of the drug over a prolonged period of time.

- Extend the duration of pharmacological response compared to the conventional single dose formulation.
- They produce therapeutic blood level quickly and maintain such levels without the usual "peak –and-valley" effect of a normal dosage form.
- Examples: enteric coated tablets, sub dermal implants, depot antibiotics etc.

ROUTES OF DRUG ADMINISTRATION

Enteral: Oral and rectal

Parenteral: intramuscular, intravenous, subcutaneous, intrammamary, intrathecal etc

PHARMACOKINETICS

DRUG ABSORPTION

The passage of drug from its site of non-intravascular administration into the blood.

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 GI tract
- Interaction with other medications.

1. **Mechanism of absorption**:-

Drugs pass across cellular membranes through three common methods.

a) Passive transport

b) The drug may pass through pores

c) Active transport

2. 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.

3. 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.

4. 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. Drugs are absorbed faster in the muscles than subcutaneously.

5. Solubility of the drug:

The lipid (fat) solubility of a drug tends to be directly proportional to the degree of drug non-ionization. The degree of lipid solubility of a drug often is expressed as its lipid partition co-efficient.

6. Drug absorption and formulation of the drug:

The absorption of a 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 the formulation

dissolve. Drug depot and patches are associated with prolonged or sustained – release formulation in veterinary medicine.

7. 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 extent of drug absorption. Factors such as degree of intestinal motility, emptying time of the stomach, irritation or inflammation of mucosa etc can affect the rate and extent of absorption of medications.

DRUG DISTRIBUTION:

The process by which a drug is carried from its site of absorption to its site of action. Highly lipid soluble drugs e.g. 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 muscles, fat, visceral take up the drug, plasma concentration falls and the drug is then withdrawn from the highly vascularized 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 causes 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) does 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.

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

Apparent volume of distribution:

Basic drugs (e.g. amphetamine) are 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.

ADVERSE DRUG REACTIONS AND INTERACTIONS

- No useful drug produces just a single effect. Both desirable and undesirable additional effects occur, and so whenever a drug is given, a risk is taken.
- Adverse drug effect or reaction is any undesirable or unintended consequence of drug administration.
- The severity of adverse reactions has been graded as –
- Mild/ minor adverse reactions: requires no antidote, therapy, nor is prolongation of hospitalization necessary.
- Moderate adverse reactions: this requires a change in drug therapy or dosage regimen, although not necessarily cessation of the drug.

- Severe adverse reactions: potentially life-threatening, causes permanent damage, requires discontinuation of the drug and specific treatment of the adverse reaction.
- Lethal adverse reactions: directly or indirectly contributes to the death of the patient.

Prevention of adverse drug reactions

Adverse drug reactions can be minimized but not altogether eliminated by observing the following practices;

- Avoiding all inappropriate use of drugs in the context of patient's clinical condition.
- Using appropriate dose, route and frequency of drug administration based on patient's specific variables.
- Taking into consideration previous history of drug reactions including allergic diseases.
- Ruling out possibility of drug interactions when more than one drug is prescribed,
- Carrying out appropriate laboratory monitoring (e.g prothrombin time with warfarin).

Predictable, dose-related drug reactions

Although animals show considerable species and individual variation in their response to drugs, most drug toxicity is related to the amount of drug administered, and can occur as side-effects, secondary-effects or over-dosage toxicity.

Side-effects: These are unwanted, but often unavoidable drug effects that are predictable from the drug's pharmacological effects, and occur within therapeutic doses. For example, atropine is used in peptic ulcer for its anti-secretory action, and produces dryness of the mouth as a side-effect. This makes atropine useful in pre-anaesthetic medication to dry salivary and bronchiolar secretions. A side-effect may be based on a different phase of action, e.g, the antihistamine, promethazine produces sedation (drowsiness) which is unrelated to its anti-allergic action, but makes antihistamines useful in motion sickness. Thus, an effect may be therapeutic in one context but be a side-effect in another. Oestrogens used in anal adenoma in male dogs can be expected to have a feminizing effect, and this is unrelated to their anti-ovulatory action.

Many drugs have been developed from observation of side-effects, e.g, sulphonamides used as antimicrobial were found to produce hypoglycaemia, copious urine flow and acidosis as side-effects. This directed research resulting in the development of oral hypoglycaemic sulphonylureas (e.g tolbutamide) and the carbonic anhydrase inhibitor, acetazolamide.

Secondary-effects: These are direct consequences of a primary action of the drug, e.g suppression of gastrointestinal bacterial flora by oral tetracyclines resulting in diarrhoea. This paves the way for superinfection with yeasts and fungi. Also chronic corticosteroid therapy weakens host defense mechanisms so that the animal becomes more susceptible to infection.

Over-dosage toxicity: This is predictable toxic effect that occurs with dosage in excess of the therapeutic range. Some over-dosage toxicity may occur because of drug accumulation caused by the patient's ineffective renal excretion or hepatic metabolism.
Lethal dose 50 (LD_{50}): This is a dose that kills 50% of the animals.
Effective dose 50 (ED_{50}): A dose that produces the desired effect in 50% of the subjects is termed the ED50.
The therapeutic index (or margin of safety): The ratio of LD_{50} to ED_{50} and is a guide to the drug's safety. It is desirable that the therapeutic index (TI) be large. With most drugs, the TI is high (e.g, isometamidium in rats has a TI of 23), but with some drugs, this value may be small. For example, digoxin has TI values of 2-2.5 in dogs.
Unpredictable, non-dose-related drug reactions

Allergic (or hypersensitivity) reactions: These are immune-mediated, unexpected reactions to a drug that are unrelated to the pharmacological actions of the drug and are largely independent of dosage. Allergic reactions do not appear to have a high incidence in veterinary medicine (perhaps <10% of all drug-related adverse effects). Nevertheless, hypersensitivity reactions to some drugs can lead to serious and even fatal consequences. They occur in a small percentage of the animals or human population exposed to the drug and cannot be produced in others at any dose. Prior sensitization is needed and a latent period of at least 1-2 weeks is required after the first exposure. The drug or its metabolite

acts as an antigen or more commonly hapten and induce production of antibody/sensitized lymphocytes. Following subsequent injection of the drug (e.g, penicillins, cephalosporins, phenothiazines, immune sera) with its antigenic properties, a violent antigen-antibody reaction occurs with widespread release of histamine and other chemical mediators of inflammation (serotonin, leukotrienes especially LT-C4, D4,) dopamine, heparin, plasma kinins and prostaglandins). Active immunization is almost free from this risk.

Idiosyncratic reaction

This is a genetically determined abnormal reactivity to a chemical. It is largely restricted to certain patients with a particular genotype. For example, thin-skinned or white-skinned horses may exhibit exaggerated cholinergic response (panting, profuse salivation, sweating, urination, defaecation, muscle tremors, abdominal discomfort and prostration) to an injection of imidocarb. Although these reactions are inevitable, when they occur unexpectedly for the first time, they may be circumvented by injecting atropine prior to the treatment of such horses with imidocarb. In addition, certain uncharacteristic or bizarre drug effects due to peculiarities of an individual animal or species occur and for which no genotype has been described. For example, the phenothazine cause prolapse of the penis in the horse, which may persist for several days. A related but distinct effect (priapism) has been reported for acepromazine in horses. Priapism, involving persistent engorgement and turgidity of the penis has been described, with turgidity and oedema lasting several days.

Photosensitization

This is a cutaneous disorder resulting from drug-induced sensitization of the skin to sunlight (UV radiation). The reactions are of two types: phototoxic and photoallergic.

In phototoxic reaction, drug or its metabolite accumulates in the skin, absorbs light and undergoes a photochemical reaction followed by a photobiological reaction. This results in local tissue damage (sunburn-like erythema, oedema, blister, hyperpigmentation and desquamation). Drugs involved in acute phototoxic reactions include tetracyclines

(especially demeclocycline) and tar products. Drugs causing chronic and low-grade sensitization include nalidixic acid, flouroquinolones, thiazides, and phenothiazines. In cattle, photosensitization has been observed with the sulphoxide metabolite of phenothiazine. It occurs 2-3 days post-treatment with the anthelmintic, and when the cattle are exposed to bright sunlight. The affected animals usually show keratitis and corneal ulceration.

Photoallergic reaction: The drug or its metabolite induces a cell-mediated immune response. The reaction takes the form of an immediate flare and wheal on exposure to sun. Drugs involved include sulphonamides, sulphonylureas, griseofulvin, and chlorpromazine.

Target organ toxicity

Local irritation: This may manifest as pain, tissue necrosis or damage caused at the site of administration of the drug. Aqueous solution of diminazene aceturate injected in combination with phenazone as Berenil ® causes severe pain at intramuscular site of administration, while isometamidium can induce severe tissue necrosis if injected subcutaneously, or a dose higher than 0.8 mg/kg is given by deep intramuscular injection. Local gastric irritation with vomiting is encountered when aspirin is administered orally to dogs.

Specific organotoxicity: When a drug is concentrated in any site, the chances of localized toxicity are increased. This can occur in the kidney, where the excreted drug is rapidly concentrated by reabsorption of water from the proximal tubule. Degenerative change in the renal tubule has been recorded following the use of many drugs such as mercurial diuretics, antibiotics (e.g, aminoglycosides, amphotericin B, bacitracin) and antiprotozoal agents (eg, imidocarb). Acetylated metabolities of sulphonomides are liable to precipitate in the urinary tract and cause crystalluria, particularly in hot weather or where water intake is low. The liver is a second very common site of damage because it receives drugs in high concentration via the portal vein and also due to its role in drug metabolism. Carbon tetrachloride causes centrilobular fatty change in the sheep even after a recommended dose.

Medullary depression or myocardial sensitization to adrenaline is common among the anaesthetics; CNS stimulation, even leading to convulsions, is a feature of local anaesthetic (eg procaine) toxicity. Occasionally, the use of a drug is followed by disturbances of the formed elements of blood, either as they circulate or by bone-marrow depression. In cats, long-term exposure to chloramphenicol has produced bone marrow depression.

Drug-induced (iatrogenic) illness

Drug-induced (or iatrogenic) disease is caused by drugs, which persist even after the offending drugs have been withdrawn and largely eliminated. Examples of iatrogenic diseases include peptic ulcer induced by salicylates and corticosteroids; Parkinsonism caused by phenothiazine and other antipsychotics, and hepatitis caused by isoniazid.

Teratogenicity

This refers to capacity of a drug to cause a derangement in foetal development (i.e a dsymorphorgenic effect) when administered to a pregnant animal. The placenta does not strictly constitute a strong barrier and any drug can cross it to a greater or lesser extent. The embryo is one of the most dynamic biological systems, and in contrast to mature animals, drug effects are often irreversible. The thalidomide disaster in Europe (1958-61) focused attention on this type of adverse effect. Thalidomide was introduced in Europe in 1857 and, based on animal tests, was promoted as a “safe and effective sedative”. It was prescribed to pregnant women for giving relief from morning sickness (nausea and vomiting). In 1961, the first reports were published suggesting that thalidomide produced a rare birth defect called phocomelia (shortening or seal-like limbs) or amelia (complete absence of the limbs), when taken between the 24^{th} and 36^{th} day of pregnancy. Chemically induced teratogenic and/or embryotoxic effects have been described in domestic animals. Cats fed high levels of griseofulvin throughout pregnancy have delivered kittens with micro-opththalmia. Parbendazole is reported to be teratogenic in sheep when given between days 16 and 24 of pregnancy producing arthrogryposis and other limb distortions. In domestic animals, the foetus is most likely to be affected by the

induction of abortion due to drugs administered in late pregnancy (e.g, purgatives, corticosteroids, prostaglandins) administered in late pregnancy.

Carcinogenicity

Carcinogenicity refers to the capacity of a drug to induce or promote neoplastic change. Chemical carcinogenesis is well recognized but generally takes several years (10-40) to develop. For example, oestrogens administered to pregnant women have induced vaginal adenocarcinoma in their daughters some 25 years later. Griseofulvin fed at high levels (0.5-2.5% of the diet) for 400 days produced liver tumours in mice. Anticancer drugs (e.g cyclophosphamide) have been implicated in chemical carcinogenesis.

Mutagenicity

Many carcinogens can damage somatic and germ cells to cause chromosome aberrations to appear in the progeny. Therefore, mutagenicity testing, which is more rapid and cheaper than conventional carcinogenicity testing, has been developed to detect genetic (ie, mutagenic) changes in cells or organisms. Many anticancer agents including alkylating agents (eg cyclophosphamide) and purine analogues (eg, 6-mercaptopurine) have been shown to elicit mutagenic changes.

Benefit-to-Risk Ratio

In every therapeutic endeavour, risks must be weighed against benefits for each particular clinical situation. Drug therapy is justified only if the possible benefits outweigh the possible risk after considering the qualitative and quantitative impact of using a drug and the likely outcome if the drug is withheld. This is the benefit-to-risk assessment. Phenylbutazone, for example, occasionally causes death in horses, but is this sufficiently frequent to discourage its use in the treatment or prevention of trauma? Diethylstiboestrol is a useful growth promoter, but its use has been banned in European countries because of reports of its ability to induce cancer in man and animals. Oxytetracycline has caused fatal colitis in horses, yet it is a broad-spectrum antibiotic of long half-life. The value of the animal would surely be sufficient to sway the clinician to an alternative remedy, unless the infection is life threatening and is known to be sensitive only to

oxytetracycline. If the veterinary clinician decides in favour of therapy, he has also to make a cost-benefit decision in the case of food-producing animals.

Preclinical safety and toxicity testing

While no chemical can be certified as completely "safe" (or free of risk), it is possible to estimate the risk associated with exposure to the chemical under specified conditions if appropriate tests are performed.

Acute toxicity study: Large single doses are given to enable determination of median lethal dose, maximum tolerated dose, the toxic symptoms developed in the test animals, and the time they appear. At least 3 species of animals (one not a rodent), and administration is usually more than once.

Subacute and chronic toxicity study: Effects of daily doses varying from the expected therapeutic doses to levels high enough to produce toxicity in susceptible organs. These studies usually last for 90 days (subchronic toxicity), or the lifetime of the test animal (i.e 2 years in a rodent or longer in non-rodents). At the end of the study, the animals are sacrificed and pathologic examinations are conducted to determine target organ toxicity; effects on reproductive functions in rats and rabbits, including mating behaviour, fertility, parturition, teratology, perinatal and postnatal effects, lactation, etc, immunotoxic, mutagenic, carcinogenic or teratogenic potential and an assessment of the drug's irritant and sensitizing properties.

In vitro toxicity tests: There is a growing interest in in vitro toxicity tests that provide a more rapid, cost-effective predictive test for drug toxicity. The greatest emphasis has been in the area of mutagenicity, with the most popular test being the Ames bioassay. A chemical shown to be a mutagen would also have the potential to be a carcinogen in mammalian experimentation.

Clinical evaluation: Clinical evaluation (or target animal studies) of new drugs is conducted in 4 phases.

Phase 1: the effects of the new drug as a function of dosage are established in healthy target animals.

Phase 2: the drug is studied in target animal patients to determine its efficacy in the treatment of, or prophylaxis against, the disease or symptoms for which the drug is intended.

Phase 3: more widespread clinical trials that may move from the realm of clinical investigators to practicing clinicians are carried out to establish efficacy and safety in disease animals.

Phase 4: is the study of the actual use of the drug in veterinary practice.

DRUG INTERACTIONS

Drug interactions are said to occur when the pharmacologic response to one drug is altered by the presence of a second drug. The expected response may be increased or decreased or result in adverse reactions as a result of the interaction. There are several mechanisms by which drugs may interact in vivo.

Drug interactions may be classified as

- Pharmacokinetic drug interactions - plasma or tissue levels of a drug are altered by the presence of another drug.
- Pharmacodynamic drug interactions - the action or effect of one drug is altered by a second drug.
- Pharmaceutical interactions (or drug incompatibilities) result from chemical or physical reactions of drugs mixed in vitro.

Direct drug interactions: Direct interaction result from chemical or physical incompatibility, and may occur in vivo or in vitro. In the treatment of excessive bleeding

evoked by heparin (an acid drug) with intravenous injection of protamine sulphate (a strong base), the protamine combines with heparin to form a stable salt that prevents any

further anticoagulant activity of heparin. Gentamicin is inactivated by carbenicillin when the two are mixed together in vitro for intravenous infusion. Because of the possibility of this type of drug interaction, it is generally considered poor practice to mix drugs or vehicles in the same syringe.

Interactions affecting absorption: Because a large number of drugs are administered orally, the rate or extent of absorption of drug from the gastrointestinal tract may be altered by drugs that increase gastric motility (eg, metoclopramide), or conversely by drugs that delay gastric emptying (eg, anticholinergic drugs such as atropine). Tetracyclines can combine with polyvalent ions such as calcium, magnesium, aluminium and iron to form complexes that are poorly absorbed. Milk and milk products, and numerous antacids can markedly reduce the absorption of tetracyclines, and should not be co-administered orally. Antidiarrhoeal preparations are capable of adsorbing co-administered drugs. For example, a kaolin (hydrated aluminium silicate) pectin mixture can produce erratic absorption of lincomycin when the two are given simultaneously. The bioavailability of diminazene aceturate following intramuscular administration alone as Ganaseg® is 95% when administered in combination with phenazone (a pain killer) as Berenil ®, its bioavailability is reduced to 50%.

Interactions affecting distribution: Drugs may compete for binding sites on the plasma or tissue proteins, or may displace previously bound drug. Displacement from plasma or tissue binding site would tend to increase the blood concentration of the displaced drug. Phenylbutazone (an anti-inflammatory agent) may compete with phenytoin for binding to albumin. Similarly, phenylbutazone is able to displace warfarin (an anticoagulant) from its binding site and enhance the free circulating concentration of the anticoagulant. The displacement is responsible for many cases of warfarin poisoning. Sulphonamides (chemotherapeutic agents) are able to displace sulphonylureas (oral antidiabetic agents) and cause severe hypoglycaemia. Such a mechanism may contribute to the elevation of serum digoxin concentration by concurrent quinidine therapy.

Interactions at drug receptor sites: Drugs may interact at receptor sites in a competitive manner, eg, morphine-naloxone, or by interference with the pathway to the receptor site.

Some of the most commonly recognized interactions (both therapeutically useful and potentially dangerous), come into this group. For example, aminoglycoside antibiotics (streptomycin, neomycin, gentamicin) produce skeletal neuromuscular blockade, similar to that which occurs with tubocurarine or gallamine. The mechanism involves competition with acetylcholine for its receptors at the skeletal neuromuscular junction. Thus, combinations of aminoglycosides and non-depolarizing neuromuscular blockers can lead to excessive muscle relaxation. Cardiac glycosides act by inhibiting the enzyme transporter Na+/K+-ATPase that regulates the transport of Na+ and K+ across the myocardial cell membrane. The inhibition of the pump results in decrease in the concentration of intracellular K+. This effect is likely to be responsible, at least in part, for the increased toxic effects of glycosides to patients also receiving diuretics. It is generally recommended that potassium supplement be considered for all, especially congestive heart failure patients being treated with cardiac glycosides.

Interactions altering metabolism: Some drugs are able to stimulate the production of drug-metabolizing enzymes. Drug interactions, usually involving a loss of therapeutic activity, may result from the consequent increase in the rate of metabolism. This type of interaction is particularly important when the drugs are involved in the maintenance of vital functions, such as control of blood pressure, clotting or sugar levels. Phenobarbitone is one of the most well known enzyme-inducing drugs. Clinically significant interaction can occur when it is used in combination with phenytoin in the treatment of epilepsy. Adjustment of phenytoin dosage in these circumstances may be required to avoid therapeutic failure. Phenobarbitone has also been shown to reduce the therapeutic efficacy of concurrent administration of phenylbutazone or phenytoin.

Drug metabolism may be inhibited by the presence of other drugs. This would result in prolonging of the biological half-life of the drug and an increase in therapeutic efficacy. Of course, potentiation of toxicity is also possible. Drugs that are most likely to be involved in clinically important interactions of this type are these with a low therapeutic index, where inhibition of metabolism is likely to cause toxic effects. Chloramphenicol is a potent inhibitor of microsomal protein synthesis. Thus, other drugs administered concurrently show marked increases in potency. For example, the duration of

pentobarbitone-induced anaesthesia in cats and dogs is greatly prolonged following chloramphenicol therapy. The potentiation effect can still be seen 3 weeks after cessation of chloramphenicol administration in dogs.

Interactions affecting renal excretion: The renal excretion of drugs can be altered by concurrent drug therapy. Drugs that alter blood flow to the kidney modify the renal clearance of other drugs. For example, water or osmotic diuresis increases drug excretion rates. Also, since only free drug is filtered at the glomerulus, drugs that displace others from protein-binding sites may increase the rate of renal excretion of the displaced drug. Furthermore, competition for tubular transport carries will also alter the excretion of competing drugs. For example, probenecid interferes with active tubular secretion of penicillin, thereby prolonging its duration of action. Drugs that alter urinary pH can alter the extent of tubular reabsorption of ionisable drugs. Drugs that acidify the urine such as ascorbic acid or ammonium chloride increase the urinary excretion of weak bases (e.g amphetamine, diazepam).

INTRODUCTION TO NEUROPHARMACOLOGY

The Nervous System is divided into two anatomical divisions:

- The Central Nervous System (C.N.S) - the brain and spinal cord
- The Peripheral Nervous System (P.N.S) - the neurons located outside the brain and spinal cord, that is, any nerve that enters or leaves the C.N.S. The PNS is further divided into the efferent nerves that carry signals away from the brain and spinal cord to the peripheral tissues and the afferent division, whose neurons bring information from the periphery to C.N.S.
- The efferent division of the P.N.S. can be further divided into two major functional subdivisions: The Somatic and the Autonomic Nervous System.
- The Somatic efferents are involved in voluntarily controlled body functions such as contraction of skeletal muscles in locomotion or posture.

- The Autonomic Nervous System (ANS) functions involuntarily to regulate essential body functions.

The Autonomic Nervous System (ANS)

The ANS is composed primarily of visceral motor (efferent) neurons that innervate smooth muscles of the viscera, cardiac muscles, vasculature, and the exocrine glands.

The Autonomic Efferent Neurons

The efferent neurons of the ANS are anatomically divided into two namely:

1. Sympathetic (or thoracolumbar).
2. Parasympathetic (or Craniosacral)

Both the sympathetic and the parasympathetic neurones emerge from the brain stem or spinal cord and terminate in the motor ganglia. The function of the ganglia is that it relays information between the preganglionic neurone and the postganglionic neuron. The preganglionic fibres of the sympathetic nervous system are short. They end in ganglia adjacent to the spinal cord. *The only exception is the adrenal medulla's preganglionic fibre which is analogous to a postganglionic fibre,* because it releases epinephrine and norepinephrine directly. These neurotransmitters are released into the blood stream when stimulated by preganglionic fibers. **It is important to note that the postganglionic sympathetic fibres are long like the preganglionic fibers of the Parasympathetic Nervous System which are generally long,** while the postganglionic fibres are short. The physiologic functions of the two systems usually oppose one another to bring about a state of balance. When the balance is disrupted, drug therapy may be indicated to restore the original balance necessary for homeostasis.

The Sympathetic (adrenergic) Nervous System Receptors

The receptors are divided into

1. Alpha-1
2. Alpha-2
3. Beta-1
4. Beta-2
5. Dopaminergic

Generally the alpha-1 and alpha-2 are stimulatory and the beta receptors are inhibitory.

The Parasympathetic Nervous System Receptors

The Parasympathetic **(**cholinergic) Nervous System receptors are **nicotinic** and **muscarinic** receptors.

Neurotransmitters:

The primary neurotransmitters of the adrenergic sites are **norepinerphrine, epinerphrine, and dopamine.** Epinephrine stimulates the alpha and beta receptors and is a potent stimulator of the heart and a powerful dilator of the bronchioles.

Acetylcholine is the neurotransmitter at the sympathetic postganglionic fibre of the sweat glands and blood vessels. The neurotransmitter for cholinergic sites is acetylcholine.

Acetylcholine combines with both nicotinic and muscarinic receptors.

Cholinergic sites are found in both the *sympathetic and parasympathetic nervous* Systems. **The nicotinic receptors are found in all the *Autonomic ganglia*, in the *Adrenal medulla* and at the neuromuscular junction of the somatic nervous system. The muscarinic receptors are found at the synapse of postganglionic fibres of the parasympathetic nervous system and at few of the sympathetic postganglionic fibres.**

How Drugs Affect the Autonomic Nervous System

1. Mimicking neurotransmitters
2. Interfering with neurotransmitter release
3. Interfering with the breakdown or reuptake of neurotransmitters at the synapse
4. Blocking the attachment of neurotransmitters to receptors.

Classes of Autonomic Nervous System Agents

Cholinergic agents are drugs that stimulate receptors sites mediated by acetylcholine. This is achieved by the drug mimicking the action of acetylcholine. This could be done in two ways:

1) The drug might have a direct action
2) The drug might have an indirect action on the receptors

The drug is said to have a direct action on the receptors when it sensitizes the receptor by mimicking acetylcholine. The drug is said to be indirectly acting when it inhibits the breakdown of acetylcholine. The cholinergic drugs (agents) are also called parasympathomimetic drugs.

Clinical Uses

1. Aids in diagnosis of myasthenia gravis
2. Reduce the intraocular pressure of the glaucoma
3. Stimulate GI motility
4. Treat urinary retention
5. Control vomiting
6. Act as an antidote for neuromuscular blockers.

Examples of Direct-acting Cholinergic Agents

1. **Carbamylcholine:-** It had been used to treat atony of the gastrointestinal tract and to stimulate uterine contraction in swine.
2. **Bethanechol (urecholine):-** Used in G.I and urinary tract atony.
3. **Pilocarpine:-** It is used to treat glaucoma by reducing the intraocular pressure.
4. **Metoclopramide:-** It is used to control vomiting.

Indirect-acting Cholinergic (Anticholinesterase) Agents

1. **Endophonium:** Is used to diagnose myasthenia gravis.
2. **Neostigmine:** These products are used to treat urinary retention, GI atony and as antidote to neuro-muscular blocking agents.
3. **Organophophate Compounds:** These are commonly used as insecticide dips and may result in toxicity if not appropriately used.
4. **Demecarium:** This is used in the preventive management of glaucoma.

Side effects of cholinergic drugs

Bradycardia, hypotension, lacrimation, diarrhoea, vomiting.

Cholinergic Blocking Agents (Anticholinergics)

Cholinergic blocking agents are drugs that oppose the effect of acetylcholine and this group of drugs elicit their effect at the muscarinic receptors of the Parasympathetic Nervous System.

Examples:

1. Atropine: It is used as a pre-anaesthetic drug to dry secretions and prevent bradycardia. It is also used to treat organophosphate poisoning.

2. Scopolamine: This is used in anti diarrhea medication.

3. Methscopolamine: Similar to the effect of Scopolamine.

4. Glycopyrrolate: Is a quaternary ammonium compound with action similar to atropine, but has provides longer action than atropine and is used as a preanaesthetic agent.

5. Aminopentamide: Is used to control diarrhea in dogs and cats.

6. Pralidoxime (2-PAM): A cholinesterase reactivator used to treat organophosphate intoxication.

Side effects:

Drowsiness, disorientation, tachycardia, photophobia, constipation, anxiety, burning at site of injection.

Adrenergic (Sympathomimetic Agents)

Adrenergic agents are agents that mimick the action of epinephrine or norepinephrine**.** Adrenergic agents are classified as catecholamines or non-catecholamines and either of these categories can be classified according to the specific receptor types activated namely:

1. Alpha -1
2. Alpha -2
3. Beta -1
4. Beta -2

Examples

1. **Epinephrine (Adrenaline):** Used to increase heart rate and cardiac output and constriction of the blood vessels in the skin.

2. **Norepinephrine:** Stimulates alpha receptors. It influences vasopressor effect and raises the blood pressure.
3. **Isoproterenol: I**t is a beta stimulator it is used as a bronchodilator.
4. **Dopamine:** Dopamine is a precursor of epinephrine and norephinephrine. It is dose dependent and to treat shock and congestive heart failure.
5. **Ephedrine, Terbutaline**, **Albuterol:** these are beta agonists and are brochodilators.
6. **Phenylpropanolamine (prolamine):** Is used to treat urinary incontinence in dogs.

Side effects:

- Tachycardia, hypertension, nervousness, cardiac arrhythmias, pulmonary oedema.

Adrenergic Blocking Agents

Adrenergic blocking agents are used to disrupt the activity of sympathetic nervous system. The adrenergic blocking agents are classified as:

a) Alpha blockers
b) Beta blockers
c) Ganglionic blockers

Alpha Blockers

- Alpha blockers have limited use in veterinary medicine
- The most frequently used in veterinary medicine is **Phenoxybenzamine**

1) Phenoxybenzamine could be used in

a) Laminitis treatment in horses
b) Urethral obstruction in cats.

2) Tranquilizers (acepromazine, droperidol) - These tranquilizers act as alpha blockers and cause vasodilation.

3) Prazosin:- is used as an hypotensive agent.

4) Yohimbine:- used to treat xylazine toxicity.

5) Atipamezole:- this is a reversal agent of medetomidine

Side effects of alpha receptor blockers

- Hypotension, tachycardia, muscle tremors (phenoxybenzamine), seizures (acepromazine).

Beta blockers

Used to treat glaucoma, arrhythmias, and hypertrophic cardiomyopathy.

Examples

1. **Propranolol:-** is used to treat cardiac arrhythmia and hypertrophic cardiomyopathy.
2. **Timolol:-** is an ophthalmic preparation that is to treat glaucoma.
3. **Atenolol:-** used in a similar way to propranolol.

Side effects of B-Blockers

Bradycardia, hypotension, worsening heart failure, bronchoconstriction.

INTRODUCTORY TOXICOLOGY; SOURCES AND TYPES OF POISON, ANTIDOTAL THERAPY

Definitions:

- Toxicology: It is the science or study of poisons on biologic systems, including their properties, actions and effects. Also their detection and identification, the treatment and prevention of the conditions produced by them.
- Toxicant: Any poisonous agent

- Toxins/Biotoxins: Poisons produced by biologic sources e.g venom, plant toxins.
- Toxicosis/ Poisoning/ Intoxication: Any disease produced by a toxicant
- Acute toxicosis: Effects during the first 24 hours
- Chronic toxicosis: Effects produced by prolonged exposure (> 3months)
- Toxicity: Refers to the amount of a toxicant necessary to produce a detrimental effect.
- Hazard: Describes the likelihood of poisoning under conditions of use.
- Toxicant accumulation/ biomagnifications: Occurs when absorption exceeds the ability of the body to destroy or excrete a xenobiotic compound.
- Ecotoxicology: The study of the relationship of potentially toxic chemicals in living organisms and their environment.
- Tolerance: The ability of an organism to show less response to a specific dose of a chemical than it demonstrated on a previous exposure; refers to acquired and not innate resistance.
- LD_{50}: The dose that is lethal to 50% of a test sample or population. Expression of toxicant concentrations are in ppb or ppm in feedstuff, water, air, tissue etc. Other expressions of dose are maximum nontoxic dose, maximum tolerated dose, approximate lethal dose.

Toxicology as a discipline

- It is a multifaceted science
- It contributes to, and draws from fields such as chemistry, pharmacology, pathology, psychology, clinical medicine, botany etc.
- ***Is toxicology a chemical or biological science?***

Who are toxicologists?

- Toxicologists are persons trained in the knowledge of poisons.
- They may have been trained solely in this specialty or more often than not, they were trained as veterinarians, physicians, chemists, physiologists, pharmacologists, entomologists, botanists, agronomists and some other specialties.

- The common factor is an interest in learning more about the undesirable effects of substances and energies on living organisms and their environment.

Veterinary Toxicologist

- A person having special knowledge of the poisons affecting the animals and birds in which man is interested for his economic gain or pleasure, and of those substances which, when present in animal products, could injure the health of the people consuming them.
- He is also concerned with the determination of the safety of drugs, chemicals and energies intended for direct use by people (the best qualified to evaluate the results of animal experiment action which usually preceed human usage).

Environmental Toxicology

- Chemicals released into the environment abound there to elicit their deleterious effects on the ecology where man, animals and other organisms interact.
- The delicate interactions is altered by these chemicals with devastating effects on man and animals.

Factors affecting the activity of poisons

Exposure-related, biologic or chemical factors regulate absorption, metabolism and elimination and accordingly, influence the clinical consequences.

Factors related to exposure:

- Dose
- Duration and frequency of exposure
- Route of exposure
- Time of exposure
- Environmental factors e.g temperature, humidity etc

Biologic factors:

- Species of animal
- Age and size of animal
- Sex and hormonal factor of animal
- Nutritional and dietary factor
- Health status

Chemical factors:

- Chemical nature of the toxicant
- Vehicle/Carrier

Diagnosis

- History
- Clinical signs
- P/M lesions
- Laboratory examinations
- Bioassay/ Animal inoculation

Treatment of Poisoning

General Considerations:

- Each clinical case of poisoning presents individual problems
- More often than not, approach to treatment is determined by
  i. Nature of poison involved
  ii. Condition of the patient

Principles of therapy:

1. Prevention of further absorption
2. Supportive or symptomatic treatment
3. Specific antidote

Prevention of further absorption:

- Remove the source of poison or remove the animals from the area in which the poison exist.

- Limit the absorption of material already in or on the animal for topical chemicals.

Wash the animal or remove contaminated hair or wool.

- For ingested toxicants**:**

- Induce vomiting eg apomorphine
- Gastric lavage is useful in smaller animals
- Rumenotomy in ruminants
- Purgation when slow-acting poisons are involved.
- Activated charcoal serves to adsorb poison in the stomach

Supportive Therapy:

- Control of seizures
- Maintenance of respiration
- Treatment for shock
- Correction of electrolyte and fluid balance
- Control of cardiac function
- Alleviation of pain

Specific Treatment (Antidotal therapy):

- This is application of drugs to reverse or neutralize the effect of the poison.
- Specific antidotes for the treatment of poisoning are highly desirable but rather rare.
- Some antidotes form complexes with the toxicant (e.g the oximes bind with organophosphates), others block or compete for receptor sites e.g vitamin K competes with the receptor for coumarin anticoagulants such as warfarin and a few affect metabolism of the toxicant e.g ferric to ferrous reduction with methylene blue in nitrate poisoning.