B.PHARMACY
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MODULE- 2ND

DRUG-INDUCED DISEASES

Drug-induced diseases are commonly encountered and described as adverse drug reactions i.e. an undesirable effect of drug treatment.

Drug-induced diseases are commonly encountered and described as adverse drug reactions i.e. an undesirable effect of drug treatment. There are two types of adverse drug reactions: Types A and B. A type A drug reaction is a predictable dose and/or time dependent exaggerated response related to the primary (desired) or secondary (unwanted) pharmacological activity of the drug administered. Lack of response caused by underdosing is also considered a type A drug reaction. A type B drug reaction is an unpredictable dose and/or time-independent unrelated response referred to as a cytotoxic adverse reaction as it generally causes damage to target cells. The parent drug and/or the production of potentially reactive metabolite(s) may be responsible for the cytotoxicity. Contrarily to Type A drug reactions, Type B reactions are largely unavoidable and include some drug allergies and all idiosyncrasies.

Organs most susceptible to Type A reactions are the highly perfused liver and kidneys as they are subjected to the highest concentration of and exposure to systemic drugs. Organs most susceptible to Type B reactions causing drug-induced allergies are organs that contain tissues acting as haptens such as skin and blood-forming units, and tissues that filter and trap immune complexes such as the glomerulus and joints.

The clinical manifestation of an adverse drug reaction will depend on the type of drug reaction (A or B) and the organ(s) involved. Allergic drug reactions, hepatotoxicity, nephrotoxicity, gastrointestinal irritation/toxicity, neurotoxicity, ototoxicity, dermatological manifestations, endocrine system reactions, haematological dyscrasias and pulmonary toxicity have all been identified for different drugs administered to companion animals. Fortunately, not all adverse drug reactions are clinically relevant; however, reporting suspected reactions is important in assuring safe and efficacious drug use in animals.

Allergic drug reactions

There are four types of drug-induced allergic reactions: Types I to IV. A Type I allergic drug reaction is IgE-mediated where drugs act as haptens. This immune-mediated response is immediate and causes anaphylaxis or anaphylactoid-like reactions. Species-specific "shock" organs for dogs are the liver and gastrointestinal tract, and the lungs for cats. Examples of drugs that may cause an anaphylactic reaction are β-lactams by directly causing a physiological response to the immune-mediated histamine release. Examples of drugs that may cause an anaphylactoid reaction are morphine, thiacetarsemide and amphotericin B by causing a non immune-mediated direct mast cell degranulation. The administration of a small test dose may help detect and avoid full-blown reactions. A Type II allergic drug reaction is cytotoxic. It occurs when antibody bound blood cells lyse due to direct binding by IgG and IgM, and are removed from circulation. Targeted cells are stem cells in the bone marrow and mature circulating cells such as RBC, WBC and platelets. This type of allergic reaction may be manifested as haemolytic anemia, agranulocytosis and leucopenia, thrombocytopenia or a combination thereof. A Type III

allergic drug reaction is an immune complex disease also called serum sickness. It is induced by the antigen-antibody complexes, mediated by IgG or IgM, and complement activation. Clinical signs will vary according to the affected organ but will usually include fever and lymphadenopathy. This type of reaction has been documented in dogs with the administration of sulphonamide antimicrobial drugs. Potentiated sulphonamide syndrome in dogs includes a variety of intrinsic toxicities such as blood dyscrasias (due to induced folate deficiency), renal tubular acidosis (due to induced crystalluria), nausea, vomiting, hypoglycemia, hypothyroidism, kerotoconjunctivitis sicca (KCS), and idiosyncratic disorders such as drug fever, dermatopathies, liver disease, meningitis, myocarditis, polyarthritis, interstitial nephritis and uveitis. A Type IV allergic drug reaction is cell-mediated and manifested as a delayed hypersensitivity that reflects a cellular response by lymphocytes and macrophages that infiltrate the site and cause mediator release perpetuating the inflammatory response, at the antigen site. Drug-induced allergic reactions may be mild to life-threatening. They are more likely to be life-threatening when they affect major organs such as the liver, kidneys, gastrointestinal tract, lungs and the central nervous system.

Hepatotoxicity

Both Type A and Type B adverse drug reactions can affect the liver. This organ is susceptible to toxic effects of drugs since it receives a large portion of the cardiac output (increased exposure to drugs), is a "portal of entry" for oral drugs, and is a major site of metabolism and excretion of drugs. The potential for hepatotoxicity in companion animals may be enhanced by dietary imbalances (high fat, low protein), by the presence of concomitantly administered drugs that alter the metabolizing enzymes or by altered hepatic blood flow. Documented examples of hepatotoxic drugs include glucocorticoids, anticonvulsant drugs, acetaminophen, carprofen, diazepam (cats), ketoconazole, some benzimidazoles, sulphonamides and thiacetarsamide.

Nephrotoxicity

The kidneys are also vulnerable to the undesirable effects of drugs as they also receive a significant amount of the total cardiac output (25%), are responsible for the reabsorption of salts and water, the passive reabsorption of certain drugs (progressive concentration of the drug in the filtrate), and is also a major site of metabolism and excretion. Furthermore, the kidneys are sensitive to extra-renal factors such as decreased blood flow and dehydration that may predispose them to or exacerbate drug-induced nephrotoxicity. Documented examples of nephrotoxic drugs include aminoglycosides, NSAIDs, ACE inhibitors, Amphotericin B, sulphonamides and thiacetarsamide.

Gastrointestinal irritation/toxicity

Most oral drugs and many intravenously administered drugs (especially if rapid administration) have the potential of causing gastrointestinal adverse drug reactions such as nausea and vomiting. Drugs that inhibit cell division are potentially toxic by impairing the rapid turnover of mucosal epithelial cells of the gastrointestinal tract, independent of the route of administration. This is particularly true for tetracyclines, chloramphenicol (chronic administration) and anticancer drugs. Drugs that affect the chemoreceptor trigger zone (CRTZ) will also cause

nausea and vomiting, also independently of the route of administration, namely digoxin, anticancer drugs and most opioids. Gastrointestinal irritation may also be caused by NSAIDs through inhibition of protective prostaglandins, or by alteration of the microflora caused by selected antimicrobial drugs or by drug-induced achlorhydria.

Neurotoxicity

The Central Nervous System (CNS) is particularly vulnerable to direct and indirect drug-induced toxicities due to the high metabolic rate of neurons, their marked need for external nutritional support, and their unique lack of a regenerative capacity leading to accumulated lesions and additive effects of toxic injuries. There is also the possibility of delayed manifestation of an adverse drug reaction when neuronal reserve can no longer compensate, which often makes it difficult to find a drug cause to effect relationship. A compromised blood-brain barrier (BBB) such as in pediatric patients, certain diseases and breed particularities may render the CNS particularly vulnerable to toxic effects of drugs which normally would not cause significant adverse effects when administered at therapeutic doses. Typical clinical signs of neurological drug-induced adverse reactions include emesis, diarrhea, salivation, fever, disorientation, ataxia, trembling, seizures, depression, coma and blindness. Documented examples of drugs associated with neurotoxicities in dogs and cats include ivermectin (Collies and Australian shepherds), phenothiazines, butyrophenones, metoclopramide, tricyclic antidepressants, metronidazole, fluoroquinolones, aminoglycosides (neuromuscular blockade) and amitraz.

Ototoxicity

Drug-induced adverse reactions may affect either the auditory system or the vestibular system or both. Vestibular damage is easier to detect in dogs and cats than auditory damage especially in older cognitively challenged patients. Ototoxic effects may be reversible or irreversible. Anticancer drugs such as vincristine, vinblastine and cisplatin are toxic to the hair cells of the organ of Corti thereby affecting the auditory system of the ear. Furosemide on its own, can cause cochlear damage, or enhance the ototoxicity of aminoglycosides when administerd concomitantly. Other examples of ototoxic drugs include fluoroquinolones, chlorhexidine and propylene glycol.

Dermatological manifestations

Both Type A and B adverse drug reactions are manifested in the skin either as an allergic reaction or an immune-mediated reaction such as lupus erythematosus, pemphigus or pemphigoid skin lesions. Similar to the liver and the kidneys, the skin has metabolizing enzymes which makes it susceptible to drug-induced reactions from the parent drug and/or metabolites. Alopecia or generalized exfoliation has been reported with the administration of anticancer drugs, hormonal therapy, glucocorticoids (cushinoid presentation), hetacillin (cats), and flea collar and lime-sulfur dips, respectively. Eczema or eczematous dermatitis has been associated with coal tar shampoo, diethylcarbamazine, 5-fluorocytosine, griseofulvin, topical neomycin, phenothiazine derivatives and sulphonamides. Pruritus has been associated with human recombinant erythropoietin (with skin or mucocutaneous lesions), KBr, methimazole and diethylcarbamazine; purpura or pemphigus has been reported with chloramphenicol and

thiabendazole, whereas urticaria and angioedema were associated with tetracyclines and Vitamin K.

Endocrine system reactions

The endocrine system offers several targets where drugs may interfere with important hormonal axes such as the thyroid and cortisol systems. Drug-induced decrease in hormonal concentration may include the suppression of hormone release, decreased hormone synthesis or altered peripheral metabolism of the hormone. Hypothyroidism may be caused by hepatic metabolizing inducers such as phenobarbital, rifampin and glucocorticoids, or by sulphonamides and antithyroid drugs. A decrease in the hypothalamus-pituitary-adrenal (HPA) axis has been documented in dogs with the use of glucocorticoids. The inhibitory effect of ketoconazole on testosterone and adrenal steroid production has been used to treat prostatic cancer, benign prostatic hypertrophy and hyperadrenocorticism.

Hematological dyscrasias

Drug-induced adverse reactions may affect the bone marrow and/or mature circulating cells. Both the parent drug and/or metabolite(s) may cause toxicity to the stem or mature hematological cells. Anemia, leucopenia or thrombocytopenia, or a combination of all of them (pancytopenia) can reflect drug damage to the bone marrow. Hematological disorders are assessed by cell count, time to onset after drug exposure, course of the reaction and time to resolution after discontinuation of the drug. Reactions may be immunological or non-immunological. Examples of non-immunological reactions include anticancer drugs, estrogen derivatives, phenobarbital (reversible) and chloramphenicol. Manifestation of anemia may be caused by NSAIDs and anticoagulants, due to their predictable pharmacological effect on platelets and coagulation cascade, and in cats by methimazole, propylthiouracil, acetaminophen or benzocaine due to the formation of methemoglobin.

Pulmonary toxicity

Drug toxicity to the lung may be caused by gaseous or particulate toxicants, or systemic exposure. As for the liver, kidneys, skin and hematological cells, lungs are susceptible to the parent drug and metabolite(s) as they possess Clara cells or type II alveolar cells which contain cytochrome P450 enzymes for local metabolism of drugs. Since the "shock" organ for the cat is lungs, Type I allergic drug reactions (Type B adverse drug reactions) are expected in this species, primarily manifested as acute respiratory difficulties.

Factors that may predispose a patient to the development of type A adverse drug reactions

- Pharmacological factors: pharmaceutical, PK and PD drug interactions
- Pathological factors: renal, hepatic, cardiac and endocrine diseases
- Physiological factors: age-induced differences, species/breed PK and PD differences and drug disposition (ADME)

Avoiding adverse drug reactions

Type A (predictable) adverse drug reactions

• Obtain a proper diagnosis and treat according to recommended protocols, using least toxic drug(s) as appropriate.

• Evaluate patient before and during drug treatment with emphasis on target organ of toxicity (using appropriate diagnostic tests) and remission of clinical signs.

• Minimize drug interactions.

• Educate client on the potential toxicities and associated clinical signs, and communicate frequently.

• Evaluate patient for remission of clinical signs, use the least amount of drug that will have therapeutic effect and discontinue (or wean off slowly) as soon as drug is no longer needed.

• Use of compounds that help prevent metabolite damage to liver: N-acetylcysteine (intracellular form of glutathione), ascorbic acid (oxygen radical scavenger) and S-adenosylmethionine (SAMe - contributor to a number of methylation reactions in the body).

Type B (unpredictable) adverse drug reactions:

• Keep abreast on knowledge of potential occurrence of this type of adverse reaction.

• Frequent patient monitoring is important to avoid potential disastrous situations.

Diagnosing a drug-induced disease

• Ideally, the offending drug should be discontinued and side effects should be allowed to subside, then a challenge with the same drug should show a similar undesirable pharmacological activity.

• Limitations include polypharmacy (i.e. difficult to determine which drug is the culprit) and ethical issues (especially when dealing with anaphylactic reactions or severe toxicity).

Although drugs are important tools for treatment of several diseases affecting cats and dogs, they also invariably come with potential predictable and unpredictable undesirable effects. It is not possible to list all possible drug-induced adverse reactions for all drugs in all species. It is thus important to be vigilant and maintain a good veterinarian-client-patient relationship in order to appropriately avoid these reactions or offer appropriate supportive treatment for our patients when needed, and finally, to keep abreast on knowledge of potential occurrence of adverse drug reactions.

Principles of toxicology

It is the science of the adverse effects of chemicals on-It is the science of the adverse effects of chemicals on living organisms.living organisms. A descriptive toxicologist performs toxicity tests toA descriptive toxicologist performs toxicity tests to obtain information that can be used to evaluate the riskobtain information that can be used to evaluate the risk of exposure to a chemical pose to human beings and theof exposure to a chemical pose to human beings and the enviroment.enviroment. Amechanistic toxicologist attempts to determine howAmechanistic toxicologist attempts to determine how chemicals exert deleterious effects on living organisms .chemicals exert deleterious effects on living organisms. A regulatory toxicologist judges whether or not a drug A regulatory toxicologist judges whether or not a drug or other chemicals has a low enough risk to justify makingor other chemicals has a low enough risk to justify making it available for its intended purpose .it available for its intended purpose .

An acceptable daily intake (ADI) is the input of a chemical that can be consumed over an entire life-time without any apprciable risk. A threshold limit value (TLV) is the maximum concentration of each chemical that does not harm the enviroment. Forensic toxicology that combines analytical chemistry and the fundimental toxicology in a medicolegal concept that assisst in postmorteum investigations to establish the cause of a stage of a crime up to the level of death crimes.

Clinical toxicology focuses on disease that are caused or are uniquely associated with toxic substances to help in diagnosis through new techniques and treatment of such intoxications.

Dose-response curve

It is crucially important as it is graded in individuals quantal in population .

Gradedd doses given to an individual may result in a greater reponse as it increases.

Quantal doses given to a population affect a larger percentage as they are raised . This is used to determine the median lethal dose (LD50) of drugs and other chemicals.

Risk and its assessment

• There is marked differences in LD50 of drugs , some may be harmful in a fraction of micrograms and others may be relatively less harmful in doses of several grams or even more.

• Inspite of the advanced technology , it is not easy to distinguish between toxic and non-toxic drugs.

Pracelsus statement" All substances are poisons , but the right dose differentiate the remedy from the poison" . In risk assessment one should consider the direct and indirect harmful effects of a chemical on the enviroment when used in the quantity and manner proposed. In a chemical delivered to humans and enviroment in association with food, one should be very careful. In those given as drugs , one should weigh the benefit vs harm.

Chemical forms of drugs that produce toxicity. Deleterious effects of any drug are due to the chemical structure of the parent drug and its metabolites that are produced by enzymes , light and reactive oxygen species.

Toxic metabolites

Chemical metabolites of drugs are mainly the cause of their toxicities.

• Unstable metabolites are called reactive metabolites.

• Both stable and unsatble metabolites are more toxic in cases where CYP450 is increased.

Phototoxic and photoallergic reactions

• Many chemicals are biotransformed into their toxic metabolite by hepatic enzymes.
• Some chemicals are activated in the skin by ultraviolet &/or visible radiation.
• Inphotoallergy, drugs may absorp the light ,then converted to a product that is more potent as an allergen than the parent drug.
• Drugs on reaching the skin , either locallyor systemically, may undergo photochemical reactions within the skin to induce directly photosensitivity or enhance the usual sunlight effects.

Reactive oxygen species

• Paraquat and its metabolites lose one electron paired in electron donation with oxygen forming a reactive oxygen species leading to severe lung injury.

Spectrum of undesired effects

• A drug may produce many types of effects, but only one remains the goal of treatment.
• Side effects of a drug are usually non- deleterious.
• Undesirable toxic effects include most of the other effects.

Types of toxic reactions

• Toxic effects are either pharmacological, pathological or genotoxic.
• Depending on the concentration of the chemical ,toxic effects are usually reversible.
• Pharmacological effects discontinue due to biotransformation,while pathological and genotoxic effects need repair

Local versus systemic toxicity

• Local toxicity occurs at the site of first contact between the toxicant and the biological system.
• Systemic toxicity requires absorption and distribution of the toxicant.
• A toxicant may produce both effects .
• Severity of local toxicity depends on the portal of entry.

Reverible and irreversible toxic effects

• Prohibitively toxic drugs cause irreversible toxicity.
• Ability of the tissue to reverse the drug toxicity depends on the tissue capacity to regenerate.

Delayed toxicity

• Most toxic drug effects occur at predictable time.
• Aplastic anemia occur after weeks of chloramphenicol treatment stops.
• Carcinogenic effects of chemicals are also delayed type of toxicity.

Chemical carcinogens

• Either genotoxic or non-genotoxic.
• Most gentoxic carcinogen are inactive which turn in the body into the primary or ultimate ones by drug metabolizing to reactive electron defficient intermediates (electrophiles) .
• These electrophiles interact with electron-rich centers in DNA to produce mutation.
• DNA can reverse this effects if DNA repair mechanism are normal .
• Nongenotoxic carcinogen are promoters that do not produce a tumor alone, but can potentiate the effects of genotoxic carcinogens by facilitation of the growth and development of dormant or latent tumor cells.

Laboratory tests

i/ Mutagenicity testing of the carcinogens using Ames test of Salmonella typhimurium for genotoxic carcinogens.

ii/ Using laboratory animals feeding with the carcinogen for the entire life-span , then do autopsies and histopathological testing comparing with control animals. This test is for genotoxic and promotor carcinogens.

Allergic reactions

• An adverse reaction that result from previous exposure to a particular chemical or to one that is structurally similar.

• Hapten + endogenous protien antigen complex + antibody complex subsequent eposure {allergy}

Idiosyncratic reactions

• Are the genetically determined abnormal reactivity to a test.

• This response could be in a form of extreme sensitivity to low doses or increased insensitivity to high doses of a chemical.

• These genetic polymorphisms can be due to inter-individual differences in drug pharmacokinetics or pharmacodynamics .

• This knowledge is used toindividulize dosages in a science known as pharmacogenomics.

Interactions between chemicals

•Concurrent exposure to more than one chemical may alter the pharmaacokinetics of one or both interacting drugs.

•The pharmacodynamics of drugs may be altered due to the competition on receptors.

•Functional non-receptor drug interaction occur when two drugs have different mechanisms of action.

•The combined toxicant therapy may be equql to,less than or greater than the sum of effects of the individual agents.

Classification of chemical interations between drugs

• Additive effect= combined effects of two chemicals is equal to the effect of each toxican if given alone.

• Potentiation= increased effect of a toxicant acting simultaneously with a non-toxic one. • Antagonism=interferance of one chemical with the action of another (antagonistic agent = antidote).

Descriptive toxicity tests in animals

• Principles: -When followed properly the application to human beings. -Exposure of lab. Animals to toxic agents in much lower dose than expected in humans.

• Experimental animals are tested for:

i Acute toxicity by estimating the LD50 in two different animal species by two different routes of adminstration, death number in two weeks are recorded, signs of intoxications,lethergy, behavioural modifications and morbidity.

ii Subacute is then tested for 90 days by using laboratory species in the same route intende to be used by humans (3 doses) ,detect the needed parameters and test organs by a pathologist.

iii Chronicity is tested for short term drugs for 6 month and for long term drugs for two years.

Incidence of acute poisoning

• Incidence of acute poisoningecreased highly due to good packing of drugs,drain cleaners,turpentine and other house hold chemicals,improved medical training and care and increased public awareness of potential poisons.

• Although the most common causes are house hold cleaners and cosmetics ,drugs are the most common causes of death.

• Most of death cases occurs intentionally in adults and accidentally in kids. • Accidental poisoning in kids accounts to 53% of the incidence of poisoning.

Sources of information on poisoning

i. Books.
ii. Computerized sources.
iii. Poison centers.

Prevention & treatment of poisoning

• Many acute poisoning incidences by common sense advice from a physician.

• Toxic agents are either having specific antidote or not .The majority of toxicants do not have antidote ,so :

-Maintain respiration and circulation.

-Do serial measurements of vitalsigns and reflexes. -Observe response to therapy and need for additional treatment.

• In acute poisoning treatment you maintain vital functions, keep the concentration of toxicants in tissue as low as possible by decreasing its absorption and enhancing its elimination, then combat toxicological signs at effecter sites.

Prevention of further absorption

i. Emesis : this used for oral poisoning .It is contraindicated in case of case of corrosives for the fear of gastric perforation and further necrosis of the oesophagus, aspiration in cases of coma, delirium or stupor ,in case of ingestion of CNS stimulants for the fear of convulsion and in case of ingestion of petrolium distellates for the fear of peritonitis.It is indicated in case of dangerous chemicals like pesticides.
ii. Gastric lavage is the administration of a tube into the stomach to wash it with water ,normal saline or half normal saline before the absorption of poisons.This need experts for the fear of gastric injury, but its contraindications are similar to those of emesis.
iii. Chemical adsorption of many chemicals to the surface of activated charcoal avidyl to reduce the enterohepatic circulation of the drug and enhance its excretion.

•Chemical inactivation is the changeof the chemical nature of a poison rendering it less toxic or decrease its absorption.This needs time and the use of neutralizing agents is contraversal.

•Purgation : The rashionale for using osmotic harmless cathratic is to minimize absorption by hastening the passage of toxicants through the GIT, usually after the ingestion of enteric coated tablets by more than one hour.

DRUG INTERACTION

DRUGS USED IN PREGNANCY