Tissue binding

Some tissue or specific tissue constituents such as proteins, phospholipids, mucoproteins accumulate in significant quantities of drugs in higher concentrations than plasma. For example amidarone which acts as an antidysrhythmic drug. Griseofulvin is keratin precursor cells and may persists in keratin is on this basis that drug elicit its therapeutic effect and therapeutic value.

Tetracycline has binding potential to organelle the mitochondria, the quinapyramine and homidium has affinity for D.N.A of the trypanosome and heavy metals to mucopolysaccharides of connective tissue. Tissue binding of drugs is generally reversible.

Dicophane (DDT) can persist in body fat for several months.

Barriers of Compartments and tissues

The barriers that exist in particular tissues tend to retard the movement of all or certain classes of the drug into them. The placenta acts as a barrier to some drugs that could be toxic to a foetus and permits the passage of others. Anesthetics that do not excessively depress a foetus are chosen when carry out cesarean section.

The so-called blood-brain barrier (BBB) has been identified in individual in several dog breeds including Old English sheepdogs, Australian shepherds and English shepherd to have p-glycoprotein defect which is a drug transporter.

The BBB is relatively impermeable to many drugs but when there is inflammation the drug could pass.

The eye has a barrier that impedes some drugs from diffusing into the tissue.

Disease Processes and interference with drug distribution

Antibiotics usually do not diffuse well into abscesses or Heart failure and shock can reduce normal blood flow to tissue and thus impedes drug distribution kidney failure (uremia) can alter

the plasma binding of some drugs such as furosemide and phenylbutazone liver failure can cause a reduction in amount of protein (albumin) available for protein binding.

Ionization and pH

- If a drug is a weak acid it would not readily ionize in acid environment that is it would be in non ionic form. Thus, it would be readily absorbed or be distributed readily
- If a drug is in its ionic form it would be trapped in a barrier (compartment) so it would have low solubility and its volume of distribution would be low.
- The degree of ionization of drug would determine whether or not it would have a large volume of distribution. This is in analogy with the rate of absorption of a non-ionized or ionized drug.

ADVERSE DRUG REACTIONS AND INTERACTIONS

Overview

- 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.

Mechanisms and types of allergy: Hypersensitivity reactions are divided into two classes –

Humoral (or immediate) reactions

Cell-mediated (or delayed hypersensitivity) reactions.

The immediate reactions consist of anaphylaxis (the classical type 1 reaction), antibody-mediated cytotoxicity (type II), and immune complex damage (type III).

Delayed hypersensitivity is classified as type IV.

Immediate (or humoral) reactions

Type I reactions (anaphylaxis) - Tissue-fixing antibodies, chiefly IgE, are produced and get fixed to mast cells. Subsequent exposure of these sensitized cells to specific antigen results in reaction between the cell-attached antibody and the antigen. Release of histamine and other mediators of inflammatory reactions, then cause the clinical signs characteristic of allergic reactions; hypotension, angioedema, urticaria, erythema, pruritus, pharyngeal and laryngeal oedema, bronchospasm, cardic dysrhythmias vomiting, colic, but often death does not take place for hours. The manifestations occur quickly after challenge and are thus called immediate hypersensitivity reactions. In horses, cattle and rabbits, the chief shock organ is the lung, and obstruction to respiration caused mainly by contraction of the pulmonary arterioles is the main symptom. There is sometimes an associated rash or urticaria. Examples of type I reactions are pollen allergy in dogs, equine respiratory allergies, food allergies in various species, vaccine and drug allergies, or allergy to external parasites (such as ticks and fleas).

Type II (cytolytic) reactions - These are the autoimmune reactions. Drugs and components of specific tissue cell act as antigen. The resulting antibodies (IgG, IgM) bind to the target cells. On exposure, antigen/antibody reaction takes place on the surface of these cells, complement is activated and cytolysis occurs, e.g haemolysis, aplastic anaemia, thrombocytopaenia, agranulocytosis, organ damage (liver, kidney, muscle). Examples of these reactions are canine polyarthritis, systemic lupus erythematosus and acquired hemolytic anaemia of dogs. Also, antibodies may react against tissue that have been damaged during the course of an infection thereby prolonging the disease, as may possibly occur in canine nephrits and the late demyelinating encephalitis of distemper.

Type III (immune complex mediated) reactions - These are mediated by circulating antibodies (predominantly IgG, in cats IgM tends to be more common). Antigen-antibody complexes bind complement and precipitate on red blood cell membrane or vascular endothelium;

polymorphonuclear leukocytes accumulate, giving rise to inflammatory response. The reaction may be localized as in Arthus reaction pneumonitis (or farmers lungs), or may be systemic as in serum sickness. The reaction usually subsides in 1-2 weeks.

Cell-mediated reactions

Type IV (delayed hypersensitivity) reactions - These are mediated through production of sensitized T-lymphocytes carrying receptors for the antigen. On contact with the antigen, these T-cells produce macrophage aggregation factors (or activating factors, known collectively as lymphokines). Lymphokines attract large numbers of non-sensitized mononuclear cells (macrophages) which accumulate at the site of the reaction and generate an inflammatory response. Antibody plays no role; this is the basis of cell-medicated immunity. Examples are allergic contact (or chemical) dermatitis; tuberculin, Johnin and Mallein diagnostic tests; transplanted tissue rejection; photosensitization and allergic responses to arthropods (e.g tick, mites).

Treatment of hypersensitivity reaction

Immediate reactions are treated with adrenaline and an antihistamine (eg, chlorpheniramine) to prevent the physiologic response to released chemical mediators. All severe reaction including cell-mediated reactions should in addition receive a glucocorticoid (eg, hydrocortisone or prednisolone). Glucocorticoids suppress the events that take place subsequently i.e., inflammatory reaction and cellular infiltration which histamine release normally causes. Of recent, various cytotoxic drugs have proved useful in controlling immune-mediated disease. Those most frequently used include the alkylating agent cyclophosphamide; the antimetabolite mercaptopurine and azathiprine, and the folic acid antagonist methotrexate. The anthelmintic, levamisole can stimulate immune response by increasing the activity of macrophages, but can also act as an immunosuppressant. In addition to these drugs, ionizing radiation, antilymphocyte serum and removal of lymphoid tissue (thymectomy, splenectomy and in birds, removal of bursa of Fabricius) also produce immunosuppression. Renal transplantation, for instance, has been greatly aided by antilymphocyte serum.

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.