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Drug-induced (or iatrogenic) disease is caused by drugs, which persist even after the offending drugs have been withdrawn and largely eliminated.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).