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Review Article

Special considerations in veterinary formulation design

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Summary

This review gives insight into the many considerations necessary in developing a drug and its delivery system for use in veterinary medicine. Aspects such as geographical location, feeding techniques, dietary habit, the physiology of the gastrointestinal tract, drug distribution, metabolism, excretion, skin type, endocrinology, animal behavior, age of the animal, disease state, methods of dosing, product stability and tissue residue and their relevance to correct drug delivery system development are discussed.

Introduction

Formulation and design of veterinary drug delivery systems in recent years have taken new precedence. Realization of the necessity for more economical production of world food supplies and the interest of the western world in companion animals has given impetus to sophistication in drug action and formulation design. The future of innovation in the animal health area is bright. Different species and different disease states provide an exciting challenge that is being taken up with fervent interest.

To develop a drug and its delivery system for use in veterinary medicine requires special considerations not normally encountered in human medical drug delivery design.

One of the first considerations is whether the drug should be developed at all for use in a particular country. For example, companion animal products, i.e. products for pet care, will occupy a small but active part of the animal health care market in the western world. However, even with the public health risk through zoonoses, development of the pet care market in lesser developed countries would be futile.

If it is believed that the drug is worthy of development (efficacious and economically feasible) for a particular country, the type of drug delivery system has to be considered carefully. In the northern hemisphere there is intensive stock husbandry, hence confinement feeding is a major production technique. The northern hemisphere market structure is thus characterized by a high feed additive segment (55%) and by only 35% pharmaceuticals and 10% biologicals (Marsboom, 1980). The southern hemisphere, however, is based upon extensive stock husbandry. Therefore, the market structure is characterized by a low feed additive segment (10–15%) and either a high consumption of pharmaceutical products rising to over 80% in Australia and South Africa, based upon anthelmintics and acaricides; or a high usage of biological-type products in Latin America, based on foot and mouth disease vaccine (Marsboom, 1980).

Once the utility of developing a drug and drug formulation has been established, the following should be considered: (1) to which animal species is the drug to be administered; and (2) will the drug be given to more than one species of animal.

The animal species to which the drug is to be administered will markedly influence the route of administration, the dose size, dose frequency, the type of delivery system chosen, the bioavailability of the drug, etc. These differences between species occur because of differences in their size, body fat distribution and percent, their gastrointestinal tract, the activity of drug-metabolizing enzymes, urinary pH reaction, and the receptor sensitivity to different drugs. These factors and how they affect the drug and delivery system performance will each be discussed in turn.

Dietary habit

Dietary habit provides a broad basis for grouping domestic animal species; that is, they may be grouped as herbivores (horse and ruminants), omnivores (pig), and carnivores (dog and cat). In terms of physiological function, the digestive system is the principal distinguishing feature between herbivorous and omnivorous species. Other distinguishing features, which could be considered as allied to dietary habit, are the activity of the hepatic microsomal enzymes and the urinary pH reaction. Renal function in carnivorous and omnivorous animals shows considerable adaptability to diet (Gans and Mercer, 1977). The urinary pH reaction is certainly influenced (determined) by the diet. The carnivorous species excrete acidic urine while the herbivorous species excrete alkaline urine. The urinary pH reaction of the pig may vary depending on the diet.

Based on the limited available information, it appears that the half-lives of drugs which undergo extensive hepatic metabolism are considerably shorter in herbivorous species than in the carnivorous species. In pigs, the half-lives of these drugs can be either short or long, so that a pattern which would allow prediction of half-life based on the species of animal cannot be established (Gans and Mercer, 1977).

Gastrointestinal tract

The characteristic feature which distinguishes ruminants from other animals is that the alimentary tract is expanded anteriorly to the true stomach (abomasum) into a series of chambers (rumen, reticulum and omasum). In these, particularly the ruminoreticulum, vigorous microbial fermentation takes place under nearly anaerobic conditions.

The indigenous microflora of the ruminoreticulum may inactivate certain drugs by metabolic transformations of a hydrolytic or reductive nature. For example, chloramphenicol, when administered intraruminally at 50 mg/kg body weight to adult sheep, produced no detectable serum levels, whereas in two-week old lambs (rumination has not started; the oesophageal groove is closed in the young suckling animal such that the ruminoreticulum is bypassed), a peak of 15 μg/ml of serum was obtained within 2 h. Intra-abomasally in adult sheep, it produced high blood levels within 1 h after administration. Rapid degradation by ruminal contents in vitro was also evident (Theodorides et al., 1968). In ruminants, the antibiotic was inactivated by reduction of the nitro group in the ruminal environment (Davis et al., 1972; Theodorides et al., 1968; de Corte-Baeten and M. Debackere, 1978). Many other examples such as parathion, cyanogenic glucosides, cardiac glucosides, gossypol, caffeic acid, inorganic salts (for example, selenite is reduced to selenide and elemental selenium), etc., have been reviewed by Pope (1975).

Not only will fermentation processes affect the performance of a drug, but also the large volume and pH reaction of the contents of the gastrointestinal tract are responsible for the wide variation in drug distribution often found between herbivorous and carnivorous species. Table 1 shows comparisons of the gastrointestinal tract volume in different species. Because, in the typical cow, the first two stomachs contain a total volume of some 100–150 liters of ingesta and fluid, there is a relatively small area : volume-of-contents ratio. Hence the absorption of orally administered compounds from ruminant species may be slower than from simple-stomached animals. For example, aspirin was shown to be fast and relatively completely absorbed in the pig, dog and cat, variable in both rate and extent in the horse, and takes place slowly in ruminant species (Davis and Westfall, 1972). This slow absorption in the ruminant may also be due to the pH at the first site of absorption. Aspirin, a weak acid, would be highly ionized in the pH 5.33–6.73 of the

TABLE 1

SIZE AND RELATIVE CONTENTS (% OF LIVE WEIGHT) OF THE GASTROINTESTINAL TRACT OF SEVERAL SPECIES OF ANIMAL (ADAPTED FROM POPE AND BAGGOT, IN PRESS)

Organ	Ox	Goat	Horse	Dog	Man
Gastrointestinal tract	3.8	6.4	5.8	3.9	1.7
Gastrointestinal content	18.4	13.9	12.7	0.72	1.4

rumen, hence would be much more slowly absorbed than the unionized species found in the stomach of the simple-stomached animals.

Additional differences in gastrointestinal tracts and the effects these have on drug absorption have been reviewed by Pope and Baggot (in press).

The difference in the physiological make-up of the ruminant gastrointestinal tract as compared to simple-stomached animals can be used by the formulator of prolonged-release delivery systems as follows: an oral formulation or device may be made to lodge in the ruminoreticulum for an extended period by formulating for zero buoyancy and retainment by size. Passage through the ruminoreticulum is prevented by ensuring that the formulation does not disintegrate as there appears to be a limiting size of particle that can pass the neck of the omasum. Regurgitation is prevented by designing the formulation such that due to zero buoyancy, it lodges in the reticulum, and if dense enough, it remains there. Devices are retained by a special constructural configuration which allows an increase in size once administered into the rumen (Laby, 1974; Brewer and Griffin, 1980). Other formulation and size retainment considerations have been reviewed by Pope (1978).

Metabolism

Most drugs are eliminated by a combination of biotransformation, mainly hepatic metabolism and renal excretion. From a knowledge of the functional group in a compound, probable pathways for biotransformation can be predicted (Mandel, 1971). For example, an aromatic carboxyl may biotransform by ring hydroxylation, glucuronic acid conjugation, and/or by glycine conjugation. However, even though pathways may be predicted, biotransformation rates may vary between species and hence will govern the rates of elimination (Williams, 1971; Baggot, 1971). For example, the metabolic half-life of hexobarbital in the mouse, rabbit and dog is 19, 60 and 260 min, respectively. For antipyrine it is 11, 63 and 107 min, respectively (Quinn et al., 1958). Xylazine, a non-narcotic sedative analgesic, has been found to be a most useful drug for alleviating moderate pain in ruminant animals. Based on size of the intramuscular dose that is required to produce a useful clinical effect, the ruminant species appear to be 10 times more 'sensitive' to this drug than are the horse, dog and cat (Hopkins, 1972). Also, dose levels of xylazine for the pig are reported to be 20–30 times greater than those required in cattle. Compounds such as aspirin and phenols appear to be more toxic in cats than in other species. This is due to the relatively slow formation of glucuronide conjugates in the feline species (Robinson and William, 1958; Penny et al., 1967; Davis and Westfall, 1972). Other examples have been cited by Pope and Baggot (in press).

In addition to the fact that the rates of biotransformation may vary between species, these biotransformation rates may also determine the principal pathway for metabolism. That is, some species exhibit completely different mechanisms for biotransformation. For example, acetylation of aromatic amino groups is a reaction which is widely distributed among species (Smith, 1968), but does not occur in the dog and fox (Williams, 1967). Metabolism of the anticoagulant ethyl biscoumacetate

is by hydroxylation in man, whereas the rabbit hydrolyzes the ester to the free acid. In the dog, ethyl biscoumacetate is metabolized at a rate of about 3% per hour compared to about 20% per hour but by different mechanisms in man and rabbit (Burns et al., 1953).

Renal excretion

When a significant fraction of the dose is eliminated by renal excretion, the urinary pH reaction will influence the excretion rate of a weak organic electrolyte. Urinary pH will affect the rate of excretion of weak acids as elucidated by the pH partition hypothesis which relates dissociation constant, lipid solubility and the pH at the absorption site with the absorption characteristics at that site (Shore et al., 1957; Schanker et al., 1957, 1958; Hogben et al., 1957, 1959).

Herbivorous species excrete a slightly alkaline urine, pH 7.0–8.0; and carnivores, a slightly acid urine, pH 5.5–7.0. In any species, however, urinary pH depends mainly upon diet, e.g. suckling and milk-fed animals generally excrete an acid urine, even if when mature they excrete alkaline urine. Also, carnivores have in general a higher rate of glomerular filtration than herbivores. This may explain the shorter half-life of kanamycin in dogs than in horses (Baggot, 1977).

Biliary excretion

Polar compounds of molecular weight greater than 300, which may be glucuronide conjugates of drugs or endogenous substances, are excreted mainly in the bile. Species may be grouped together as 'good' (rats, dogs and chickens), 'moderate' (cats and sheep), and 'poor' (guinea pigs, rabbits and rhesus monkeys) biliary excretors (Williams, 1971).

Skin type

Preparations applied topically for either local or systemic availability will have to be developed with a knowledge of the skin type to which the preparation is to be applied. For example, levamisole, 'spot-on' topical formulation was only of limited value in pigs, whereas in other species it has been most effective. Pigs have an extensive layer of keratin which must be considered when designing dermatologic preparations (Wohrl, 1977). Horses appear to have a particular sensitivity to drugs formulated in an oily vehicle in that they show an urticarial reaction in the region of the injection site. Other aspects of skin type and selection of the delivery vehicle have been reviewed by Pope and Baggot (in press), Pope (in press) and Pitman (1981).

Endocrinology

Species variation in endocrine function can be illustrated by the wide variation in pattern of estrus cycles and duration of estrus periods. Estrus in the cow lasts 14–18 h; in sheep, 24–35 h; in pig, 2–3 days; and in the mare, 5–10 days (Huber and Reddy, 1978). A knowledge of endocrine function is important in formulation, especially if we wish to prevent estrus or to control estrus for synchronization of breeding and parturition, to increase rate and gain of feed efficiency, to prevent hypocalcemia and to increase twinning in cattle and sheep.

Animal behavior

Cats are constant groomers, hence drug substances applied topically are likely to be ingested by the animals. Even disinfectants and other chemicals applied to cages and floors are picked up on the cats' paws and ingested. Hence, a disinfectant considered safe for use in a canine kennel may be detrimental when used in a cattery (Spinelli and Enos, 1978).

Flea collars, their composition and mode of action reviewed by Pope (1978; in press), may cause local severe irritation problems with one breed of animal yet not exhibit problems with another. Because flea collars often cause severe local reactions when wetted, Spinelli and Enos have stated that, breeds which are water-loving may show the problem more so than other breeds. In addition, since flea collars are impregnated with organophosphorus compounds and are worn constantly by the animal, the administration of a usual therapeutic dose of a drug (such as succinylcholine) that is inactivated by cholinesterase enzymes, can cause prolonged or even toxic effects.

Drug distribution

Very lean animals, for example, greyhounds, respond differently than other animals to drugs which are lipophilic. For example, in the normal animal, redistribution of the lipophilic drug, thiopental, into tissues less well perfused than the central nervous system (CNS) is responsible for this drug's CNS short anesthetic effect. In the greyhound, because of the lesser proportion of fatty tissue, the anesthetic effect of the drug is extended. It is usual to use methohexital following premedication with promazine for induction of anesthesia in greyhounds.

Age

The age of an animal affects a number of parameters. For example, Baggot (1977) and Pope and Baggot (in press) have reviewed a number of studies which have shown that drugs may be more widely distributed and are eliminated more slowly in

neonatal (usually taken to mean from birth to 4 weeks) animals than in mature animals of the same species.

In addition, the structure of the gastrointestinal tract may be different in the neonate as compared to the adult. At birth, in ruminants, the capacity of the rumen and reticulum is smaller in relation to the abomasum than in the adult. Development of these organs is highly dependent upon diet. The onset of rumination is considerably slower in animals subsisting on milk alone than in free ranging calves. Free ranging calves begin to consume grass within 10–14 days of birth and are eating considerable quantities by the time they are 4 weeks old. Thus calves, depending upon their diet, may, at the same age, have different anatomical systems for digestion. Therefore, in testing the release characteristics and bioavailability of a drug administered to calves, consideration of whether the calf is or is not ruminating is of considerable importance. It is interesting that both glomerular filtration rate and renal plasma flow are comparable in the neonatal calf and human adult.

Disease states

Drug distribution and elimination is likely to be affected in disease states, such as scours, impaired renal function, congestive heart failure and fever, as well as in physiological conditions such as pregnancy and dehydration. For example, the body clearance of digoxin was decreased in azotemic dogs (Gierke et al., 1978). The decrease in clearance was not associated with a proportional increase in the half-life of the drug but rather with a reduction in the volume of distribution. It has been postulated that the change may be a result of a decrease in the tissue binding of the drug.

Residues

Residue tissue levels of drugs in food-producing animals is of considerable importance. For example, if penicillins are used in a formulation for intramammary treatment of mastitis, contamination of milk for human use is likely if a sufficient withdrawal period is not allowed. This is of extreme importance as anaphylatic shock, on intracutaneous or parenteral administration into humans, has been observed with less than 0.1 unit of penicillin (Hellberg, 1971). There are reports of allergic reactions down to 0.00003 units. The risks seem to be less on oral administration with different reports citing 0.4, 5 or 40 units to be dangerous (Booth, 1972; Spark, 1971; Willis and Phair, 1970; Batson, 1960).

Thus, in formulating for treatment for mastitis in the lactating cow, one has to consider both efficacy and tissue residue. If emphasis is placed on efficacy and efficiency in maintaining an MIC for an extended period, veterinary surgeons and dairymen may be loathe to use the formulation because of the long milk-withholding period. If the formulation is so designed to allow minimal tissue residues, then the therapeutic benefit of the product may be minimal. Thus, formulations to be used in

the lactating cow tend to be a compromise between efficacy and minimal tissue residues.

One approach to the problems of the dairymen accidently not withholding milk sufficiently long, is to include a marker dye such as Brilliant Blue in the antibiotic formulation. The excretion rate of the dye must be either slower than or the same as but not faster than the excretion rate of the antibiotic for it to be an efficient marker.

The parenteral administration of an aminoglycoside antibiotic, even as an aqueous solution, necessitates a long (> 28 days) preslaughter withdrawal time due to high affinity-reversible binding of the drug to renal tissue. In this case, the disposition characterization of the drug, rather than the formulation of its parenteral preparation, influence the rate of its elimination from the body. Consequently, when developing a drug product for use in food-producing animals, both the disposition features of the drug itself and the formulation of the preparation have to be considered.

Single or herd dosing

For the single animal dosing situation, most dosage forms are acceptable. For herd dosing, however, consideration should be given to the entire drug delivery system. Use of a powder drench gun, or balling guns for tablet or bolus administration would prove very time consuming. The formulation should be designed as a solution or a suspension for oral drenching, for multi-automatic injection, or for application to the back of the animal as a pour-on. To facilitate dosing, new dosing equipment may need to be developed; for example, a flexible needle to alleviate the problems of breakage when vaccinating or injecting livestock (Wulff, 1975). Formulations and other methods of delivery have been extensively reviewed by Pope (in press).

Wild of tame

Again a difference in the administration technique and hence the type of formulation should be considered. Delivery of the active drug to wild animals usually requires specialized systems to enable the administrator to be able to work at an extended distance from the animal because of: (a) danger to himself, and/or (b) difficulty in capturing and restraining the species. Pole-mounted syringes, projectile syringes, and ballistic implants may be considered, each should be formulated giving due regard to the proposed method of delivery. When a projectile system is used as the technique of administration, it is important that the drug has a wide margin of safety and that a chemical antidote be available. The latter should perhaps be a requirement for registration of chemical restraining preparations.

Stability

With the variety of conditions and temperatures to which a veterinary product may be subjected, it is wise to formulate that for the convenience of the veterinarian and to overcome misuse which is expected, the product should be formulated to withstand the widest possible storage conditions. For example, feed blocks have to withstand weathering, dips have to remain stable for a suitable period when mixed with typical dip water.

Even though a pharmaceutical company cannot hold itself responsible for storage and use in conditions outside the recommended, in order to ensure a continuing market of an 'effective' product, the adverse storage conditions should be considered and the product so formulated.

Conclusion

From this limited review, it will be seen that correct formulation of an active drug entity for veterinary use will provide an interesting and exciting challenge. Not only must the physicochemical aspects of a drug formulation be considered, but also the formulator must consider the species difference question, the route and method of delivery, and the product stability storage requirements. With an understanding of these requirements, new innovative drug delivery systems offering idealized drug delivery and targeting will surely ensue. Veterinary drug delivery design has an extremely bright and challenging future.

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