Some Considerations Regarding Drug Therapy in Ruminant Animals

Lloyd E. Davis, *D.V.M., Ph.D.*
Professor of Clinical Pharmacology
Departments of Clinical Sciences and Physiology
College of Veterinary Medicine and Biomedical Sciences
Colorado State University
Fort Collins, Colorado 80523
and
William L. Jenkins, *B.V.Sc., Ph.D.*
Professor of Pharmacology
Faculty of Veterinary Medicine
University of Pretoria
Onderstepoort, Republic of South Africa

In order for a drug to exert its pharmacologic effects, it is necessary that it be present at the receptor site or locus of infection in adequate concentration for an interval of time. For this situation to prevail, the drug must traverse a series of biological membranes, be distributed within its unique distribution volume, and be retained in the body in its active chemical form for a sufficient length of time to induce a response.

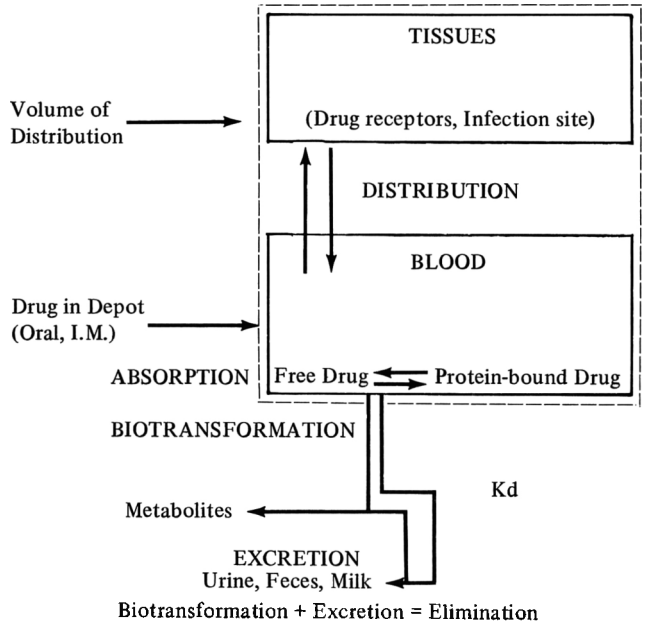
The presence of a complex, voluminous, hollow organ such as the reticulo-rumen as a component of the gastrointestinal tract might well be expected to influence the absorption, distribution, and excretion of any drug administered by practically any route. In addition, the matter of drug dosage in ruminant patients presents a problem, as the gastrointestinal tract and its contents comprise 20 per cent of the total body weight of ruminants as compared to a value of 4.6 per cent for dogs (10). The alimentary canal may or may not constitute a distribution compartment for a given drug. Hence, it would be possible for dosage (based on body weight) to be excessive or inadequate in the ruminant animal simply because it does or does not diffuse into the gastrointestinal contents.

Evidence has accumulated which indicates that many drugs are eliminated from ruminant animals much more rapidly than from other species such as the dog or human being. Since the matter of proper dosage regimens is so intimately associated with therapeutic efficacy, it is appropriate to consider briefly some of the differences observed in drug disposition between ruminants and a non-ruminant species, such as the dog.

Pharmacokinetics

Factors that determine the disposition of a drug in the body are shown in Figure 1. Following administration of its dosage form the drug must traverse a series of membranes to reach its site of action. Thus, following oral administration, the drug must cross the gastrointestinal epithelium into the blood, from which it diffuses across capillary endothelia into the interstitial fluid and subsequently into the intracellular space. Simultaneously, portions of the drug in the body will be bound to protein (nondiffusible and inactive), and portions will be eliminated, either by biotransformation or excretion. Since one generally cannot collect biologic specimens other than blood and

Figure 1. Factors determining disposition of a drug in the body.



urine from patients, the time-course of drug concentrations is described within the central compartment (plasma). For most drugs there is a fairly good correspondence between concentration in plasma and pharmacologic effect (7), e.g., the concept of minimum inhibitory concentration, MIC, in the case of antibacterial drugs.

The time-course of plasma concentrations of most drugs follow first-order kinetics. This means that the compound will be eliminated at a rate which is proportional to concentration present in the plasma, so drugs will be eliminated faster when plasma concentrations are high. If the logarithm of concentration is plotted as a function of time, a straight line results which has a constant slope (kd). This constant is the first-order disappearance rate constant and describes the rate at which the substance is eliminated. For example, if kd = 0.20 hr^{-1}, then during the first hour 20 percent of the amount originally present will have been excreted, at the end of the second hour 20 percent of the amount present at the end of the first hour will have been excreted, etc.

Another parameter describing the rate of elimination is the half-life (T 1/2). The half-life is the time necessary for the drug concentration in the plasma to be decreased to one-half its original value. It is related to kd as follows:

$$T\ 1/2 = \frac{0.693}{kd}$$

The rate of elimination of a drug determines the dosage regimen, i.e., how often to administer the dose to the patient.

The second parameter which is important is the apparent volume of distribution. The Vd is defined as that volume of fluid, in liters, into which the drug *appears* to distribute with a concentration equal to that in blood. It is determined as follows:

$$Vd = \frac{\text{Amount of drug in the body}}{\text{Concentration of drug in the blood}}$$

We frequently use the specific apparent volume of distribution V'd for comparative purposes because it expresses the volume per unit of body weight (liters/kilogram). **The apparent volume of distribution is important because it determines the dosage,** i.e., how much to administer to the patient.

The total does required to produce a given drug concentration in plasma is related to the specific apparent volume of distribution as follows:

Dose (mg) = V'd(l/kg) x body weight (kg) x desired concentration (mg/1).

The interval between doses (Δt) required to maintain a drug concentration in plasma above a certain minimal value (Pmin) is related to the initial concentration (Co) and kd by the following equation:

$$\Delta t = \frac{\ln[(1 + Co)/Pmin]}{kd}$$

Values for these kinetic parameters determined in healthy dogs and goats are tabulated in Table 1. It may be seen that there are sizeable differences existing between the ruminant and non-ruminant species. With the exception of phenylbutazone, values for T 1/2 are extremely short in goats as compared to dogs. This table illustrates why it is unwise to extrapolate drug information derived from studies in dogs to the ruminant patient. Furthermore, it explains why the ruminant is less susceptible to phenol intoxication (31), the absence of behavioral effects of amphetamine in goats (5), and the short duration of pentobarbital anesthesia in ruminants (13). The influence of rapid elimination on the efficacy of salicylates, quinidine, and chloramphicol in ruminant patients remains to be demonstrated. To illustrate the significance of these data, an I.V. dose of 45 mg/kg of salicylate would be given every 17 hours to a dog, but the same dose would have to be given every two hours to a ruminant. Likewise, it has been calculated that 34 mg/kg of chloramphicol would have to be given intravenously to a dog every six hours, whereas 25 mg/kg would have to be given every four hours to a ruminant animal in

Table 1
Comparison of Kinetic Parameters of Some Drugs in the Dog and Goat.

	Dog		Goat		
Drug	T ½ (hrs)	V'd (1/kg)	T ½ (hrs)	V'd (1/kg)	Reference
Salicylate	8.6	0.19	0.8	0.13	15
Phenol	2.6	1.59	0.5	1.09	31
Chloramphenicol	4.2	1.77	2.0	1.33	14
Quinidine	5.6	2.91	0.8	4.86	30
Amphetamine	4.5	2.67	0.6	3.08	4
Pentobarbital	3.7	0.58	0.9	0.80	13
Phenylbutazone	2.6		19.0	0.26	13
Oxyphenbutazone	1.7		0.7		13
Tetraethylammonium	0.8	1.04	0.8	4.12	11

order to maintain plasma concentrations of the drug in excess of the minimum inhibitory concentration.

The principal factor causing rapid elimination of most foreign chemicals from ruminants is their rapid biotransformation by microsomal enzymes. This point is illustrated in the case of tetraethylammonium, a drug which is not metabolized in the body. The drug was eliminated from dogs and goats at the same rate. Thus, we would not expect species differences in the rate of elimination of drugs which are not appreciably metabolized in the body (quaternary compounds, penicillin, tubocurarine, etc.). Another feature of acidic drugs is the alkaline reaction of ruminant urine. This would curtail tubular reabsorption and enhance the rate of excretion of acids.

Transfer of Drugs Across Ruminal Epithelium

Studies on the absorption and distribution patterns of drugs and other foreign chemicals across the stratified squamous epithelium have been limited until quite recently. Wester (40) suspected that chloral hydrate was absorbed from the bovine rumen, but the earliest contribution would appear to be that of Trautmann (37), who demonstrated the passage of atropine, pilocarpine, and an azo dye across the ruminal epithelium of sheep and goats. Rankin (33) showed that pilocarpine, strychnine, iodide, and cyanide could be rapidly absorbed from the bovine rumen.

More recently the ruminal epithelium has been shown to be bidirectionally permeable to the following substances: acetone and ethanol (38), sulfur (28), salicylate and para-toluidine (2), bicarbonate (1), thiabendazole (29), ephedrine (9), some sulfonamides (3), benzoate (35), and antipyrine (3). Compounds which do not seem to traverse the ruminal epithelium to any marked degree include: pectin (19), cobalt (32), choline (16), polyethyleneglycol (21), phenolsulfonphthalein (2), and Chromium ethylenediaminetetraacetate (18).

Several physiological peculiarities of the ruminant animal relevant to drug distribution have been reviewed by Dobson (17). Some of the more specific considerations concerning ruminant pharmacology and pharmacotherapy have been expounded by Jones (27), Austin (3), Stowe (35), and Jenkins (22).

Jenkins and Davis have developed methods for the rigorous study of drug transfer across ruminal epithelium *in vitro* (24) and *in vivo* (23). Employing these methods, they investigated the transfer of pentobarbital, salicylate, antipyrine, quinine, neostigmine, hexamethonium, and a homologous series of tetraalkylamines across isolated bovine ruminal epithelia (26). The factors investigated were concentration and pH dependance, influence of plasma protein binding on diffusion, effect of morphologic type of epithelium and aqueous diffusion by highly polar compounds. All compounds were shown to cross the epithelium by simple diffusion. The nonionized forms of pentobarbital, antipyrine, and quinine crossed by diffusion through lipoidal membranes. The quaternary ammonium compounds crossed by aqueous diffusion, and salicylate diffused by both routes. The binding of drugs by plasma proteins caused a greater rate of transfer, and there were no appeciable differences in permeability of the various morphologic types of epithelia. Aqueous pores associated with the cellular membranes of basal cells or of the basement membrane were found to have radii of about 6 Å.

The general principles derived from the *in vitro* investigations were confirmed by *in vivo* studies in goats (25). The rates of absorption from the rumen and rates of diffusion from the blood plasma (under conditions of constant drug concentration in plasma) into the ruminal contents were evaluated. The compounds studied underwent simple diffusion across the ruminal epithelium, and the rates of transfer were a function of intraruminal pH and the pKa of the drugs. Thus, acidic drugs such as salicylate, sulfonamides, barbiturates, phenol, and phenylbutazone would be more rapidly absorbed when the ruminal reaction is acidic, whereas basic drugs which include the alkaloids would be absorbed more readily from an alkaline medium. Because the ruminal reaction is normally acidic, basic drugs administered systemically will diffuse from the blood plasma into the ruminal contents and be sequestered there. This phenomenon has been shown for ephedrine (9), quinine (22), and amphetamine (5). This, together with efficient mechanisms for biotransformation and excretion, may explain the lack of behavioral effects of such bases as amphetamine, morphine, and pentazocine in ruminant animals.

Concentrations of many drugs in the plasma will be expected to be low following oral administration because of slow absorption from the rumen together with rapid elimination from the plasma. This has been shown to be true for salicylate (15) and oxyphenbutazone (13). Because of this feature it may be desirable to administer drugs following closure of the esophageal groove when systemic effects are desired. Closure of the groove can be effected in cattle (34) by administering ten percent sodium bicarbonate solution and in sheep (39) by a

five percent copper sulfate solution. The drug should then be given within one minute in order to bypass the rumen.

Destruction of Drugs by Ruminal Contents

The effects of antimicrobial drugs on the ruminal microflora are well known. A factor which will influence the disposition of orally-administered drugs is the effects of the ruminal contents on the drug itself. The ruminal environment is strongly reducing in character (6). There is also an abundance of hydrolytic enzymes present in the ruminal contents which will degrade certain groups of drugs.

Chloramphenicol is destroyed within the rumen (36) and blood levels of the drug were not detectable following oral administration (14). Parathione is reduced within the rumen (8); hence, the tolerance to toxicity is increased in the cow exposed to this insecticide. Cyanogenetic glycosides are readily hydrolysed in the rumen to release cyanide, which quickly results in intoxication. Cardiac glycosides are rapidly destroyed in the ruminal contents (41), necessitating parenteral administration of this group of drugs (12). Further studies are necessary to elucidate the general importance of drug destruction in the rumen.

Conclusions

The ruminant animal possesses several features which complicate pharmacotherapy and may bring into question matters of drug dosage and efficacy in such patients. Among these are extremely efficient mechanisms for elimination of drugs from the body, coupled with slow absorption from the reticulorumen and possible destruction by the ruminal contents. We propose that, in the absence of information concerning absorption and disposition of a particular drug in the ruminant animal, the drug should be given parenterally. There is a need to search for better dosage forms (repository) of drugs which are rapidly eliminated by ruminant animals. These should result in therapeutic concentrations which will be maintained for a realistic duration of time.

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establishments producing medical preparations, and investigation into the misuse of drugs. At the present time there are eight veterinarians assigned to the district offices who assist the directors with veterinary activities and affairs.

In summary, our total effort is for the single purpose of safeguarding the health of our animal population and the wholesomeness of foods of animal origin. We have available the combined talents of industry, the veterinary medical profession, and government. Each must do his share, and each must be alert to the responsibilities and the legitimate interests of the other. As servants of the people, we in FDA have a public trust which must be met at all costs. As practitioners, you can accept no lesser responsibility in serving the public.

Please note: The Food and Drug Administration has no control over veterinary biologics. These are regulated by the U.S. Department of Agriculture.

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