THE DISPOSITION OF METRONIDAZOLE IN GOATS AND ITS RELEVANCE TO THE TREATMENT OF ANAEROBIC INFECTIONS

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ABSTRACT

The recent commercial developments in goat farming in New Zealand, have led to an increase in the value of individual goats and to a growing interest in caprine diseases.

The importance of anaerobic bacteria other than the clostridia, as potential pathogens in humans and animals, has also only recently been recognised, even though anaerobic bacteria have been identified since 1861. Various members of this bacterial group are known to be involved in different conditions of goats, particularly in wound and foot infections.

Metronidazole (Flagyl[1]) is a bactericidal agent which has a specific action against anaerobic micro-organisms. This drug is already widely used in the treatment of selected diseases in dogs, cats and humans, but there was little information available on its use in goats.

The study which forms the basis of this thesis, was to investigate the disposition of metronidazole in eight goats. Both IV and IM routes of administration were studied in the form of a cross-over experiment. Silicone tubing "cages" were implanted subcutaneously, so that the metronidazole concentration versus time profile could be determined, both in serum and in interstitial fluid.

The analysis of serum and tissue cage fluid samples was undertaken using a high pressure liquid chromatography unit, which proved to be reliable over the range of concentrations tested. The system consisted of a Waters Model 6000 A solvent delivery system, a U6K injector, a Z-module radial compression separation system and a Waters programmable automator, Model 710. The mobile phase used was a 75:25 mixture of aqueous potassium hydrogen phosphate and methyl alcohol; this was adjusted to a running speed of 1.5 mls per min. A 450 variable wavelength detector was set at either 0.01 or 0.04 absorbance units, and a constant wavelength of 312 nm.

Given these concentration profiles, a full pharmacokinetic analysis was carried out using standard statistical procedures. The following values were determined:

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[1]. 'Flagyl', May & Baker (NZ) Ltd.

maximum serum and tissue cage fluid concentrations ($C_{max}IV$, $C_{max}IM$, $C_{max}IV_{tc}$), time to maximum serum and tissue cage concentration ($T_{max}IV$, $T_{max}IM$, $C_{max}IM_{tc}$, $T_{max}IM_{tc}$), serum concentration (extrapolated) at zero time (B, B'), half-life ($t_{\frac{1}{2}}$), elimination rate constant (β,β'), volume of distribution ($V_{d(area)}$), area under the concentration curve (AUC), total body clearance (Cl_B), absorption rate constant (k_{ab}), percentage penetration of metronidazole into tissue cage fluid, percentage of drug absorbed into the systemic circulation following IM administration (F), and the total amount of drug which was absorbed into the systemic circulation (in mg/kg).

Following IV administration of a 0.5% w/v solution of metronidazole at a dose rate of 20 mg/kg BWgt, the $t_{\frac{1}{2}}$ at 0.94 ± 0.08 per hour (n=8) was rapid and consistent with a high figure for the elimination rate constant at 0.79 ± 0.09 per hour (n=8). The total body clearance, a more sensitive indicator of the biotransformation and excretion processes than $t_{\frac{1}{2}}$, was also rapid (0.32 ± 0.06 L/kg/hr) which is in keeping with the efficient drug metabolism of the goat. This may account for the low $V_{d(area)}$ which was unexpected for a basic drug of this nature in the ruminant.

Critical parameters for drug concentrations and durations of effect are summarized in Table I.

Metronidazole was rapidly detected in both sera and interstitial fluid (within 0.25 hrs) following the intramuscular administration of a 40% suspension of metronidazole at a dose rate of 20 mg/kg BWgt. The uptake of metronidazole from the injection sites differed markedly between individual goats, resulting in a mean absorption percentage of 42.4% ± 8.8% (n = 8), equivalent to 8.4 mg/kg BWgt. Maximum serum levels were achieved within approximately one hour of IM administration, but the peak was more than ten-fold lower than the corresponding concentration found in serum following IV administration. Peak tissue cage drug concentrations were not achieved until four hours after IM administration.

The maximum drug concentration in tissue cage fluid was greater than the MIC upper threshold for a variety of anaerobic bacteria (12.5 mcg/ml), and this was maintained for 5.5 hrs. The lower limit of the MIC of 3.0 mcg/ml was exceeded for a correspondingly longer period.

TABLE I **Serum and tissue cage fluid drug concentrations and durations of effect, following aministration of metronidazole solutions**

Metronidazole (dose rate : 20 mg/kg BWgt)		C_{max} mcg/ml	T_{max} (hr)	Period that nominated serum conc. was exceeded (hr) 50 mcg/ml	12.5 mcg/ml	3.0 mcg/ml
0.5% w/v solution IV	serum	63.9 ± 12.2 (n=5)	<0.25 (n=5)	0.3 ± 0.05 (n=5)	1.4 ± 0.2 (n=8)	3.1 ± 0.2 (n=8)
	t.c.f	23.67 ± 4.46 (n=8)	1.41 ± 0.58 (n=8)	0	1.5 ± 0.6 (n=6)	7.9 ± 1.0 (n=8)
40% w/v suspension IM	serum	5.5 ± 0.8 (n=8)	1.06 ± 0.6 (n=8)	0	0	4.1 ± 0.7 (n=8)
	t.c.f	13.2 ± 3.9 (n=8)	4.1 ± 0.7 (n=8)	0	5.0 ± 1.5 (n=5)	8.6 ± 1.6 (n=7)

t.c.f Tissue cage fluid

Further pharmacokinetic analysis of the experimental data made it possible to calculate specific medication schedules for the goat. These were established on the basis that serum metronidazole concentrations should be maintained at a level which was bactericidal for the majority of anaerobic bacteria, which included Bacteroides spp., Fusibacterium spp., and Clostridia spp. The recommendation given was that 0.5% w/v metronidazole solution should be administered at a dose rate of 20 mg/kg BWgt and repeated every 4-6 hrs. Using the 40% w/v metronidazole suspension, the dose rate should be 45 mg/kg BWgt and the medication should be repeated every 10-12 hrs. In each case the loading dose was only fractionally greater at 20.3 mg/kg BWgt and 48.5 mg/kg BWgt respectively.

The drug concentration in interstitial fluid (tissue cage fluid), gave some indication of the antimicrobial activity in extravascular tissues, a feature which can not be extrapolated from a profile of serum concentrations.

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