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SHORT COMMUNICATION

PHARMACOKINETICS OF METRONIDAZOLE IN CALVES

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Metronidazole [1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole] has received wide acceptance in the treatment of amoebiasis, giardiasis and trichomoniasis (McDougald & Roberson, 1988). Recently, metronidazole has been indicated against infections caused by obligate anaerobic bacteria such as *Bacteroides* spp. and *Clostridium* spp. (Hirsh *et al.*, 1985; Dow & Papich, 1991). Despite its therapeutic use in the treatment of protozoal and obligate anaerobic bacterial infections of cattle, the important details concerning kinetics of absorption, distribution and elimination of metronidazole are not available in this species. The present study was designed to determine the pharmacokinetics, bioavailability and dosage regimens of metronidazole in calves.

Eight clinically healthy male crossbred calves, aged 6 to 12 months and weighing between 47 and 110 kg were used. Metronidazole, 20 mg kg^{-1} body wt [Metronidazole Injection (Vet), May and Baker] was injected into the left jugular vein. Blood samples were collected from the right jugular vein into heparinized test tubes immediately before metronidazole administration and at various times from 2 min to 24 h after injection. Blood samples were centrifuged immediately after collection and plasma was harvested. Four animals from the intravenous (i.v.) study were used in a cross-over design for determining pharmacokinetics and bioavailability of metronidazole after oral administration. An interval of at least 21 days elapsed between i.v. and oral studies in any individual calf. Metronidazole tablets (Flagyl, May and Baker) were crushed and suspended in 100 ml distilled water before being administered by drench to animals at a dosage of 50 mg kg^{-1} body wt. Blood samples were collected into heparinized test tubes immediately before metronidazole administration and at various times from 5 min to 24 h after dosing. Plasma was obtained as described above. Metronidazole concentration in plasma was estimated spectrophotometrically according to the method of Urtasun *et al.* (1975). The minimum quantifiable concentration of metronidazole in calf plasma was 0.5 μg ml^{-1}.

The plasma metronidazole concentrations were plotted against time on a semi-

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logarithmic scale and the two-compartment open model was applied. The area under plasma metronidazole concentration time curve ($AUC_{0-\infty}$) was measured by the trapezoidal rule. Other pharmacokinetic parameters and optimal i.v. dosage regimens of metronidazole were calculated according to the equations previously described (Baggot, 1977; Gibaldi & Perrier, 1982).

Plasma concentrations of metronidazole at various time intervals after i.v. and oral administration of metronidazole are presented in Fig. 1. The drug concentrations in plasma after i.v. injection indicated that the data could be fitted to a two-compartment open model and were adequately described by a biexponential equation,

$$C_p = Ae^{-\alpha t} + Be^{-\beta t}$$

where C_p was the concentration of metronidazole in the plasma at time t, A and B were the zero-time plasma metronidazole concentration intercepts of the biphasic disposition curve, and α and β were the first-order rate constants related to the distribution and elimination phases, respectively, and e was the base of natural logarithm. The elimination half-life, apparent volume of distribution and total body clearance of metronidazole were 1.92±0.05 h, 0.79±0.03 l kg^{-1} and 283.5± 6.16 ml h^{-1} kg^{-1}, respectively (Table I).

Evaluation of the results on observed plasma concentrations of metronidazole following oral administration indicated that the data could be fitted to a two-compartment open model with first-order absorption and were adequately described by the equation,

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} + A'e^{-K_a t}$$

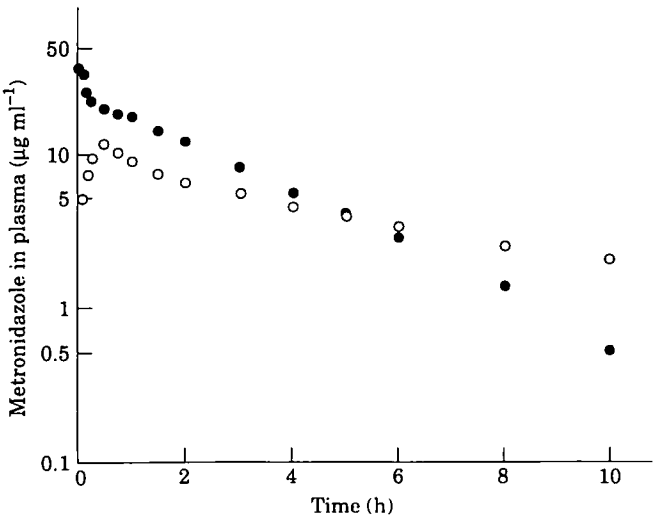

Fig. 1. Mean plasma metronidazole concentration *vs.* time curve in six calves given a single intravenous dose of 20 mg kg^{-1} (●) or oral dose of 50 mg kg^{-1} (○).

Table I
Pharmacokinetic parameters of metronidazole in calves after single intravenous administration (20 mg kg^{-1} body wt)

Pharmacokinetic parameter	*Unit*	*Mean±SE (n=6)*
C_pO	$\mu g\ ml^{-1}$	47.59±4.12
A	$\mu g\ ml^{-1}$	22.69±4.55
α	h^{-1}	12.08±2.10
B	$\mu g\ ml^{-1}$	24.89±0.91
β	h^{-1}	0.36±0.01
$t_{1/2\beta}$	h	1.92±0.05
K_{12}	h^{-1}	5.39±1.36
K_{21}	h^{-1}	6.43±0.96
K_{el}	h^{-1}	0.62±0.07
$AUC_{(0-\infty)}$	$\mu g\ h\ ml^{-1}$	70.70±1.55
$V_{d(area)}$	$l\ kg^{-1}$	0.79±0.03
Cl_β	$ml\ h^{-1}\ kg^{-1}$	283.54±6.16
FC		0.81±0.19
T/P	Ratio	0.67±0.22

Pharmacokinetic parameters are described by Baggot (1977) and Gibaldi and Perrier (1982).

where C_p was the concentration of metronidazole in plasma at time t. A, B and A were the zero-time plasma metronidazole concentration intercepts for the three components and α, β and K_a were the first-order rate constants related to the distribution, elimination and absorption phases, respectively and e was the base of natural logarithm. The absorption, distribution and elimination half-lives of metronidazole were 0.10±0.02, 0.45±0.04 and 4.38±0.23 h, respectively. The total body clearance and bioavailability were 259.8±10.48 ml h^{-1} kg^{-1} and 33.7±1.86%, respectively (Table II).

The concentrations of the drug in plasma $\geq 2\ \mu g\ ml^{-1}$ persisted from 2 min to 6 h and 5 min to 10 h after i.v. (20 mg kg^{-1}) and oral (50 mg kg^{-1}) administration of metronidazole, respectively. The presence of appreciable concentration of metronidazole in plasma (5.23±0.23 $\mu g\ ml^{-1}$) within 5 min of dosing and short absorption half-life (0.10±0.02 h) suggested that the drug is absorbed rapidly from the gastrointestinal tract of calves.

The elimination half-life after i.v. injection (1.92±0.05 h) was shorter than that reported in buffalo calves (Mandal *et al.*, 1986) and horses (Specht *et al.*, 1992). However, the low sensitivity of the assay may have led to an underestimation of elimination half-life. The elimination half-life of metronidazole in cow calves following oral administration was longer than that determined after i.v. injection. The calculated value of volume of distribution (0.79±0.03 l kg^{-1}) suggested wide distribution of metronidazole in body fluids and tissues of cow calves. The total body clearance of metronidazole (283.5±6.16 ml h^{-1} kg^{-1}) established in cow calves is relatively slower than that reported in goats (Mandal *et al.*, 1987).

The systemic availability of metronidazole in cow calves following oral administration was low (33.7±1.86%). Higher bioavailability values have been reported in horses (97±5.7%) and dogs (59–100%) (Neff-Davis *et al.*, 1981; Specht *et al.*,

Table II
Pharmacokinetic parameters of metronidazole in calves after single oral administration (50 mg kg^{-1} body wt)

Pharmacokinetic parameter	*Unit*	*Mean±SE (n=6)*
A	$\mu g\ ml^{-1}$	6.45±1.52
K_a	h^{-1}	7.68±1.18
$t_{1/2\,Ka}$	h	0.10±0.02
A	$\mu g\ ml^{-1}$	7.64±0.71
α	h^{-1}	1.56±0.13
$t_{1/2\alpha}$	h	0.45±0.04
B	$\mu g\ ml^{-1}$	9.16±0.49
β	h^{-1}	0.16±0.01
$t_{1/2\beta}$	h	4.38±0.23
$AUC_{(0-\infty)}$	$\mu g\ h\ ml^{-1}$	56.88±2.99
Cl_B	$ml\ h^{-1}\ kg^{-1}$	259.8±10.48*
$C_{max(obs)}$	$\mu g\ ml^{-1}$	11.68±0.30
$T_{max(obs)}$	min	30
F	%	33.70±1.86*

Pharmacokinetic parameters are described by Baggot (1977) and Gibaldi and Perrier (1982).

*Mean±SE (n=4).

Table III
Calculated intravenous dosage regimens of metronidazole for calves

Desired plasma concentration ($\mu g\ ml^{-1}$)	*Dosing interval (h)*	*Priming dose ($mg\ kg^{-1}$)*	*Maintenance dose ($mg\ kg^{-1}$)*
2	6	13.7	12.1
	8	28.2	26.6
3	6	20.6	18.2
	8	42.2	39.8
4	6	27.4	24.2
	8	56.3	53.1
5	6	34.2	30.3
	8	70.4	66.4
6	6	41.1	36.4
	8	84.4	79.7

1992). Low estimates of bioavailability in cow calves tend to suggest that the oral route would be less appropriate for administration of metronidazole in this species.

Based on the pharmacokinetic values as established in the present study, i.v. dosage regimens of metronidazole were computed (Table III). The dosage regimens so determined can only serve as guidelines since the final proof of effective plasma concentration of an antibacterial agent resides in clinical effectiveness. The minimum inhibitory concentration of metronidazole for the majority of

anaerobic bacteria is in the range of 2–4 μg ml^{-1} (Prescott & Baggot, 1988). A satisfactory i.v. dosage regimen of metronidazole for maintaining plasma drug concentration of 2 μg ml^{-1} would be 28 mg kg^{-1} body wt as priming dose and 26 mg kg^{-1} body wt as maintenance dose which should be repeated at 8 h intervals.

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