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Brief Communication

DIMINAZENE/BERENIL: BIOAVAILABILITY AND DISPOSITION IN DAIRY GOATS

Information about the disposition kinetics of the trypanocide diminazene is important for the establishment of safe and effective dosage regimen. In a preliminary cross-over study, single doses of diminazene diaceturate (2 mg diminazene base/kg, i.v.) and Berenil (3.5 mg diminazene base/kg, i.m.) were administered to 3 clinically healthy dairy goats on 2 separate occasions 6 weeks apart. Concentrations of intact diminazene in plasma, urine and milk were determined by HPLC (*Aliu & Ødegaard* 1983) and its plasma-proteinbinding by dialysis.

The kinetic data are presented in Table 1. Disappearance of diminazene from plasma after i.v. bolus injection showed three exponential phases (Fig. 1). The volume of the central compart-

Table 1. Pharmacokinetic parameters which describe the disposition of diminazene after intravenous and intramuscular administration to 3 dairy goats.

Kinetic Parameter	Diminazene diaceturate, 2 mg/kg, i.v.		Berenil®, 3.5 mg/kg, i.m.	
	Mean	s	Mean	s
Coefficients, μg/ ml				
P	24.34	11.42	4.46	0.89
A	8.41	4.13	2.49	0.84
B	2.16	0.41	1.45	1.04
Exponents, h^{-1}				
π	6.12	0.63	1.89	0.10
α	0.54	0.21	0.318	0.023
β	0.068	0.008	0.0355	0.013
K_a, min^{-1}	—	—	1.88	0.47
$t_{1/2}$, h	10.3	1.1	21.4	7.8
AUC_∞, μg/h/ml	51.3	6.2	47.2	8.3
$AUMC_\infty$, $\mu g/h^2/ml$	517	139	1099	111
F, %	—	—	50.6	11.4
t-peak, min	—	—	48.3	40.1
$t_{1/2}$ K_a, „	—	—	15.9	12.7
V_c, l/kg	0.062	0.023	0.198	0.040
V_{ss}, „	0.393	0.068	0.900	0.266
f_u, %	—	—	19.75	8.77
CL, ml/kg/min	0.656	0.080	0.624	0.063
CL_R, „	0.072	0.007	—	—
f_e — 24 h, %	11.2	3.0	—	—

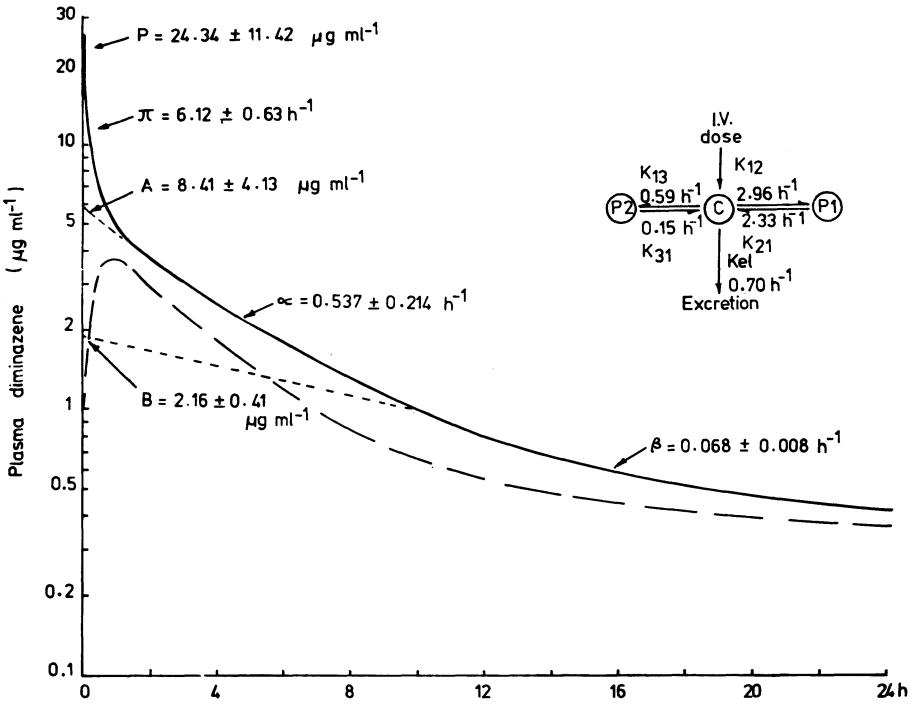

Figure 1. Plasma diminazene concentration versus time in one goat given a single intravenous dose (2 mg/kg) of diminazene dieaceturate (————) and an intramuscular dose (3.5 mg/kg) of Berenil (— — — — — — —). The i.v. disposition curve, described by tri- exponential expression:

$$c_p = Pe^{-\pi t} + Ae^{-\alpha t} + Be^{-\beta t}$$

is based on non-linear regression analysis of the data, indicating a three-compartment, open system model depicted in the insert.

ment (V_c) averaged 0.062 ± 0.023 l/kg which is slightly larger than goat plasma volume of about 0.053—0.055 l/kg. Since 60—90 % diminazene was found to be bound to plasma proteins, the actual extent of distribution of the unbound fraction (f_u) is considerably greater. The volume of distribution (V_{ss}) was 0.393 ± 0.068 l/kg. Total body clearance (Cl) was 0.656 ± 0.08 ml/min/kg. Renal clearance (Cl_R), 0.072 ± 0.007 ml/min/kg, accounted for only 11 % of total body clearance. Peak concentration of diminazene in milk was 1.68 μg/ml and occurred at 4 h after i.v. dosing. A milk to plasma ratio of about 0.45 was maintained at equilibrium. Approximately 0.14 % of the i.v. dose was eliminated unchanged in milk in 24 h. Trace amounts (0.05 μg/ml) were

present up to 72 h. After i.m. administration of Berenil, peak plasma concentrations occurred at an average of 48 min and ranged from 4.5 to 3.9 μg/ml.

The systemic availability of Berenil i.m. ranged from 43.5 to 63.8 %. After attainment of peak plasma levels, the fall-off was tri-exponential (Table 1). Berenil half-time ($t_{1/2}$), values of 14—30 h were shorter than in cattle, 40—138 h (*Klatt & Hajdu* 1976, *Fouda* 1978), but longer than in sheep, 10—13 h. (*Aliu & Ødegaard*, in press).

Doses between 0.5 and 3 mg/kg in babesiosis and between 1 and 3.5 mg/kg in trypanosomiasis are considered curative (*Kuttler* 1981, *Hawking* 1963). An in vitro concentration of 0.5 μg/ml is trypanocidal (*Hawking* 1963). Toxic symptoms are reported at doses between 3.5 and 17.5 mg/kg (*Fairclough* 1963, *Homeida et al.* 1981). In order to maintain a minimum plasma diminazene concentration of 0.5 μg/ml (C_{∞}^{min}), the initial i.m. dose of Berenil should be 2.5 mg/kg, calculated according to *Baggot* 1978. This dose will maintain a mean plasma concentration ($\bar{C}_{\infty}$) of 1.36 ± 0.46 μg/ml for 25 h. A second dose, 2 mg/kg, which should be given 24 h later to maintain these steady-state plasma levels was calculated according to *Wagner* 1975.

A pre-slaughter withdrawal time of 7 days was estimated according to modified *Nouws & Ziv* (1978) formula:

$$t = (\ln R.C_o - \ln C_{lim}) \cdot t_{1/2}/\ln 2)$$

where C_o (8.4 μg/ml) is extrapolated zero-time plasma concentration; C_{lim} (0.05 μg/ml) is the detection limit of the assay method; and R, an accumulation factor of 1.8543 ± 0.4453 which was calculated according to *Gibaldi & Perrier* (1975).

Pre-slaughter withdrawal times estimated from studies on normal animals should be multiplied by a safety factor of 4—5 (*Nouws & Ziv* 1978). For Berenil, therefore, a pre-slaughter withdrawal period of 28—35 days may be recommended.

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REFERENCES

Aliu, Y. O. & S. Ødegaard: Paired-ion extraction and highperformance liquid chromatographic determination of diminazene in plasma. J. chromatogr. 1983, *276*, 218—223.

Baggot, J. D.: Some aspects of clinical pharmacokinetics in veterinary medicine II. J. vet. Pharmacol. Therap. 1978, *1*, 111—118.

Fairclough, R.: Observations on the use of berenil against trypanosomasis of cattle in Kenya. Vet. Rec. 1963, *75*, 1107—1112.

Fouda, H. G.: Chromatography chemical ionization mass spectrometric analysis of diminazene in plasma. Biomed. Mass Spectrom. 1978, *5*, 72—75.

Gibaldi, M. & D. Perrier: Pharmacokinetics. Marcel Dekker, New York 1975, 329 pp.

Hawking, F.: Chemotherapy of trypanosomiasis. In Experimental Chemotherapy, Eds. Schnitzer, R. J. and F. Hawking. Academic Press, New York 1963, pp. 129—256.

Homeida, A. M., E. A. El-Amin, S. E. I. Adam & M. M. Mahmoud: Toxicity of diminazene aceturate (Berenil) to camels. J. comp. Path. 1981, *91*, 355—360.

Klatt, P. & P. Hajdu: Pharmacokinetic investigations on diminazene and rolitetracycline in comparison to a combination of both. Vet. Rec. 1976, *99*, 372—374.

Kuttler, K. L.: Chemotherapy of babesiosis: A review. In Babesiosis, Eds. Ristic, M. and J. P. Kreier, Academic Press, New York 1981, , pp. 65—85.

Nouws, J. F. & G. Ziv: Pre-slaughter withdrawal times for drugs in dairy cows. J. vet. Pharmacol. Therapeutics 1978, *1*, 47—56.

Wagner, J. G.: Do you need a pharmacokinetic model, if so, which one? J. Pharmacokinet. Biopharm. 1975, *3*, 457—478.

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