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Short Communication

SOME PHARMACOKINETIC PARAMETERS OF OXFENDAZOLE IN SHEEP

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ABSTRACT

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Abbreviations: AUC, area under the concentration–time curve; i.v., intravenous(ly); K_{10}, fractional rate constant central compartment → out; K_{12}, fractional rate constant central → peripheral compartment; K_{21}, fractional rate consant peripheral → central compartment; OFZ, oxfendazole; SO_2OFZ, oxfendazole sulphone; $t_{\frac{1}{2}\alpha}$, distribution half-life; $t_{\frac{1}{2}\beta}$, elimination half-life; $t_{\frac{1}{2}abs}$, absorption half-life; V_d, apparent volume of distribution

INTRODUCTION

Oxfendazole (OFZ), a benzimidazole (BDZ) anthelmintic, has a broad spectrum of activity against nematodes and tapeworms (Marriner and Bogan, 1981). Knowledge of the pharmacokinetics of the BDZ drugs is of importance because anthelmintic efficacy is a consequence of the concentration achieved and the time during which the concentration is maintained (Marriner and Bogan, 1981). The purpose of the present report is to describe further the pharmacokinetics and bioavailability of OFZ in the plasma of sheep.

MATERIALS AND METHODS

Six healthy adult Lincoln ewes (weighing 40 ± 8 kg) were used. Each was given OFZ at 10 mg/kg both i.v. and by drench, using a cross-over design in which each sheep received OFZ either i.v. or orally. Ten weeks separated the two trials. For i.v. administration, the OFZ was dissolved in DMSO at 40 mg/ml and injected into the

right jugular vein ($\sim$10 ml). A commercial formulation was administered orally at 10 mg/kg (2.265% Synanthic, Cooper, New Zealand).

Blood samples were drawn through a heparinized polyethylene catheter placed in the left jugular vein at 0, 5, 20, 15, 20, 30 and 40 min and at 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72 and 96 h after i.v. administration, and at 2, 4, 8, 12, 24, 48, 72, 96, 120, 144 and 168 h after oral administration.

The samples, of 8 ml each, were centrifuged and the plasma was separated and stored at –20°C until assayed.

OFZ and its metabolites were extracted using disposable Bakerbond spe columns (vacuum manifold column processor). (J.T. Baker, Phillipsburg, NJ, USA). The column was prepared by washing with 4 ml of methanol followed by 4 ml 0.017 mol/L $NH_4H_2PO_4$, pH 5.5. Plasma (1 ml) was passed through a C18 column and was rinsed with 2 ml distilled water and methanol (50% in distilled water). The OFZ was eluted with 2 ml methanol (100%). After elution, the OFZ was concentrated under nitrogen, dissolved in 200 µl methanol, and analysed by high-performance liquid chromatography (Kontron Instruments, Messgerate, Germany) Lichrosorb RP18 column (10 µm), with a Uvikon 740 (Kontron) variable-wavelength absorbance detector set at 292 nm (Hennessy *et al.*, 1985). The limit of detection for OFZ and its metabolites was 0.01 µg/ml.

The pharmacokinetic model that best fits the OFZ profile was determined by means of the MAICE (Minimum Akaike Information Criterion) test (Yamaoka *et al.*, 1978).

The first pharmacokinetic estimates were obtained by linear regression. Definitive pharmacokinetic parameters were estimated for each ewe by means of a nonlinear regression program known as ADAPT (D'Argenio and Schumitzky, 1979), which uses the simplex algorithm. The systemic availability of OFZ after oral administration was determined by the method of corresponding areas. The area under the curve was calculated by the trapezoidal rule (Baggot, 1978).

RESULTS

The mean plasma OFZ and SO_2OFZ concentration–time profiles after i.v. and oral administration of OFZ 10 mg/kg are shown in Figures 1 and 2, respectively.

Individual and mean pharmacokinetic parameters corresponding to the i.v. and oral routes are given in Table I.

DISCUSSION

Following i.v. administration, the disappearance of OFZ from the blood was clearly a bi-phasic phenomenon, which was confirmed by the MAICE test.

The large volumes of distribution obtained for OFZ could be related to the basic nature of the benzimidazoles. This property may be associated with their anthelmintic efficacy against parasites which are localized in relatively inaccessible body tissues and fluids, such as the lungs and the gastrointestinal walls and contents. Galtier and

Figure 1. Arithmetic plot of the mean plasma concentrations of OFZ and its sulphone in sheep ($n = 6$) after i.v. dosage of 10 mg/kg body weight of OFZ

Figure 2. Arithmetic plot of the mean plasma concentrations of OFZ and its sulphone in sheep ($n = 6$) after oral dosage of 10 mg/kg body weight of OFZ

TABLE I
Pharmacokinetic parameters of OFZ after i.v. and oral administration of OFZ at a dose of 10 mg/kg body weight to sheep ($n = 6$)

	Administration route			
	Intravenous		Oral	
Parameter	$\bar{x}$	SEM	$\bar{x}$	SEM
$t_{\frac{1}{2}\alpha}$ (h)	0.79	0.11		
$t_{\frac{1}{2}abs}$ (min)			15.76	2.62
$t_{\frac{1}{2}\beta}$ (h)	6.08	0.82	22.00	1.10
B (μg/ml)			25.60	7.82
AUC (μg.h/ml)	105.54	43.00	64.29	9.20
F%			61.94	2.77
C_{max} (μg/ml)			0.97	0.15
T_{max} (h)			26.00	4.82
Lag time (h)			3.00	0.45
K_{12} (h^{-1})	0.31	0.04		
K_{21} (h^{-1})	0.56	0.08		
K_{10} (h^{-1})	0.20	0.02		
V_c (L/kg)	0.51	0.02		
V_d (area) (L/kg)	0.91	0.07		
MRT (h)	8.76	1.84	50.34	2.24
Cl_b (L/h/kg)	0.10	0.01		

B, coefficient for the sum of exponentials; AUC, area under the curve; F%, bioavailability; C_{max}, the peak concentration in the plasma; T_{max}, the time at which the peak concentration in the plasma was reached; lag time, time prior to detection; V_c, volume of the central compartment; MRT, mean residence time; Cl_b, clearance

colleagues (1991), working with albendazole in sheep, also found a high V_d (1.7 L/kg), correlating with the drug's efficacy.

The K_{12}/K_{21} ratio suggested that OFZ was slowly distributed extravascularly in sheep; this finding correlates well with a $t_{\frac{1}{2}\alpha}$ of 0.79 h.

The elimination half-life was intermediate between the mean time reported for goats $t_{\frac{1}{2}\beta} = 5.25$ h) and sheep ($t_{\frac{1}{2}\beta} = 7.5$ h) (Bogan *et al.*, 1987).

The application of the MAICE test showed that a monocompartmental model, with first-order absorption, best fitted the oral data sets.

OFZ achieved its peak mean plasma concentrations 24 h after oral administration, and was detectable for up to 7 days after administration. The interval between drug administration and its detection in the plasma was similar to that obtained by Marriner and Bogan (1981). In three sheep, fenbendazole (FBZ) was also measurable. The concentrations of FBZ were 0–16% of those for OFZ.

OFZ was absorbed slowly ($t_{\frac{1}{2}abs}$ = 15.76 h), which could be related to its low solubility (Marriner and Bogan, 1981). The rumen may act as a reservoir of undissolved OFZ (Hennessy, 1991; MacKellar and Scott, 1990), thus prolonging the duration of drug absorption and/or outflow down the gastrointestinal tract (Marriner and Bogan, 1981).

OFZ bioavailability after oral administration was significantly higher than that reported by Hennessy *et al.* (1985) (F = 18%). This difference may be attributed to the use of different commercial formulations or diets. Formulating OFZ as an oily suspension significantly increased the systemic availability of OFZ. Moreover, the production of an amorphous form of OFZ by treatment with acids resulted in a significant change in its water solubility from approximately 4 μg/ml for the crystalline form to 11.3 μg/ml for the amorphous form at pH 7.6 (Lanusse and Prichard, 1993).

The half-life of elimination ($t_{\frac{1}{2}\beta}$) after oral administration was similar to that (21.9 h) reported by Hennessy and colleagues (1991). The long oral residence time (50.34 h) as against the shorter i.v. residence time (8.76 h) shows that the rumen, by slowing down the passage of digesta, significantly modified the pharmacokinetic behaviour of oxfendazole and its metabolites.

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