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Short Communication

Comparative Availability of Two Oral Dosage Forms of Albendazole in Dogs

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Benzimidazole (BZD) anthelmintic compounds are widely used in antiparasite therapy in both veterinary and human medicine. The poor water solubility of BZD limits their development under alternative pharmaceutical formulations. Pharmaceutical formulations of BZD molecules, which enhance their bioavailability or extend their residence times in monogastrics, could improve their efficacy in these species. Gelucire lipid matrix was developed and studied for use in human medicine, particularly Gelucire 44/14 which is composed of a well-defined mixture of mono-, di- and triglycerides and mono- and difatty acid esters of polyethyleneglycol. They are characterized either by their melting temperature (44°C) or their hydrophilic-lipophilic balance (HLB) values (14 in this case) (Aungst *et al.*, 1997). Gelucire increases the solubility of poorly hydrosoluble drugs and produces stable slim dispersions on the gastrointestinal walls, giving enhanced drug absorption (Esquizabel *et al.*, 1996; Aïnaoui *et al.*, 1997; Aungst *et al.*, 1997). The present study was carried out with the purpose of investigating new therapeutic strategies to optimize the clinical efficacy of BZD compounds in dogs. The plasma pharmacokinetic profile of albendazole (ABZ) and its metabolites, formulated as standard tablets and hard gelatine capsules filled with Gelucire capsules was investigated after administration of a single dose to dogs.

In a previous in vitro study, lipidic matrices were prepared with an HLB between 02 and 14, using mixtures of Gelucires 44/14 and 37/02 in hard gelatine capsules. These were assessed by means of content uniformity and dissolution studies according to Savio *et al.* (1998). Six adult (5–7-year-old) male, parasite-free, mixed-breed dogs, weighing 26.6 kg ± 3.97, were used in this trial. The animals were allocated to individual cages 1 week prior to treatment and were fed 1 kg per day of a balanced commercial food. All dogs had free access to water. The present study was conducted in two phases. In phase I, three dogs received an oral treatment with ABZ (25 mg/kg) formulated as tablets for use in human medicine (Vastus, Labinca S.A., Argentina) and the other three dogs were treated with ABZ formulated as Gelucire 44/14 capsules (Gattefosse S.A., St Priest, France) at the same dose and administration route. After a 15-day wash-out period the groups were reversed and the treatment repeated as Phase II. In both experimental phases, heparinized blood samples were taken at 0 h (blank sample) and at: 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 24, 30, 36 and 48 h. Plasma was separated by centrifugation at 3000 ***g*** for 10 min.

Albendazole sulphoxide (ABZSO), albendazole sulphone ($ABZSO_2$) and oxibendazole (OXB) (used as internal standard) were extracted from plasma according to Lanusse and Prichard (1990).

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Table I
Plasma comparative disposition kinetic variables for albendazole sulphoxide (ABZSO) and albendazole sulphone ($ABZSO_2$) after the administration of albendazole (25 mg/kg) formulated as tablets or capsules filled with Gelucire as a lipid matrix to dogs

	Pharmaceutical formulation			
	Tablets		*Capsules (Gelucire)*	
Pharmacokinetic parameters	*ABZSO*	*$ABZSO_2$*	*ABZSO*	*$ABZSO_2$*
$T^1/_{2\ for}$ (h)	1.87 ± 0.10	3.26 ± 0.63	1.56 ± 0.50	2.73 ± 0.31
C_{max} (μg/mL)	1.42 ± 0.51	0.14 ± 0.05	0.86 ± 0.30*	0.14 ± 0.05
T_{max} (h)	7.20 ± 1.79	13.6 ± 2.61	6.00 ± 2.45	12.8 ± 1.10
AUC_{total} (μg.h/mL)	12.8 ± 4.06	2.04 ± 0.93	7.64 ± 2.20*[a]	1.68 ± 0.19
$AUMC_{total}$ (μg.h^2/mL)	111 ± 42.0	33.8 ± 19.8	63.1 ± 20.0*	22.5 ± 2.09
$T^1/_{2el}$ (h)	2.68 ± 0.56	6.66 ± 2.67	2.71 ± 0.48	4.18 ± 0.67
MRT (h)	8.48 ± 0.75	15.3 ± 4.00	7.07 ± 0.47	13.5 ± 1.36
PDP (h)	0.25 – 18	1 – 18	0.5 – 16	1.7 – 16
Ratio AUC SO/SO_2	7.62 ± 3.95	NA	4.71 ± 0.98	NA
$F_{(r)}$ (%)[b]	–	NA	59.6	NA

$T^1/_2$ for: metabolite formation half-life; C_{max}: peak plasma concentration; T_{max}: time at C_{max}; AUC: area under the concentration vs time curve extrapolated to infinity; AUMC: area under the first moment concentration vs time curve extrapolated to infinity; $T^1/_{2el}$: elimination half-life; MRT: mean residence time; PDP: plasma detection period; $F_{(r)}$: relative bioavailability. NA: not applicable.

Results given as Mean ± SD ($n = 6$).

*Values are statistically different from tablet group at $P < 0.05$.

[a]AUC normalized by the dose and AUC obtained for the tablet formulation.

[b]Relative bioavailability assuming 100% for the conventional tablet form.

The HPLC method utilized a linear gradient as reported by Sánchez *et al.* (1995). The method's precision (intra- and inter-assay) showed a coefficient of variation (CV) of 1.76 to 9%. The recovery percentages were 81%, 91% and 92% for ABZ, ABZSO and $ABZSO_2$, respectively. Calibration curves for each analyte were linear with correlation coefficients between 0.998 to 0.999. Quantification limits (QL) were 0.01 μg/mL (ABZ), 0.037 μg/mL (ABZSO) and 0.01 μg/mL ($ABZSO_2$). Pharmacokinetic analysis of plasma concentration versus time data for ABZSO and $ABZSO_2$ was performed using the software PK Solution 2.0 (Summit Research Services, Ashland, OH, USA). Relative bioavailability (F_r) was calculated by dividing the AUC of the tablet formulation (reference, *TabR*) by the AUC of the capsule formulation (Test, *CapT*). The AUC obtained for the capsule group was corrected for the administered dose rate. The mean plasma pharmacokinetic variables for ABZSO and $ABZSO_2$ (Table I) obtained for both groups were statistically compared by non-parametric analysis, using the Mann–Whitney Test (Bolton, 1984).

Gelucire's lipid matrix dissolution was more rapid as the hydrophilicity increased such that by 60 minutes after the start of the dissolution assay 0, 5, 20 and 70% of the ABZ content had dissolved from the 02, 08, 10 and 14 HLB, respectively (Fig. 1). The most hydrophilic-lipophilic Gelucire 44/14 (HLB = 14) matrix was chosen for the bioavailability study. After administration of either formulation, ABZ parent drug was detected in plasma but not at quantifiable concentrations due to an efficient first pass process. However, ABZSO (active metabolite) and $ABZSO_2$ (inactive) were detected in plasma between 0.25–18 h after the administration of the tablet formulation and between 0.5–16 h after the administration of Gelucire capsules (Fig. 2). In contrast with our findings, there are several in vivo/in vitro studies in humans (Dennis *et al.*, 1990; Sheen *et al.*, 1991) and in dogs (Aungst *et al.*, 1994; 1997) that have demonstrated that poorly water soluble drugs formulated as Gelucires capsules had better bioavailability compared with conventional dosage forms. Savio *et al.* (1998) demonstrated that the Gelucire 44/14

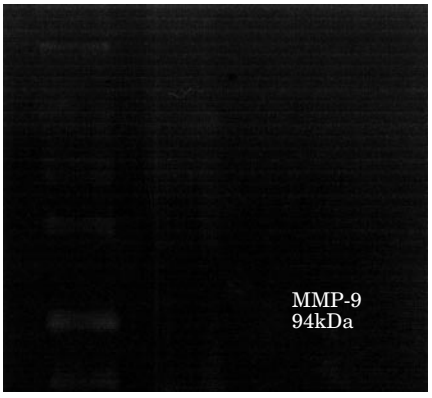

Fig. 1. 'In vitro' comparative dissolution profiles of albendazole (ABZ) at 35% in mixtures of Gelucires 37/02 and 44/14 with hydrophilic-lipophilic balance (HLB) 02, 08, 10 and 14, at 37°C and agitated at 120 r.p.m.

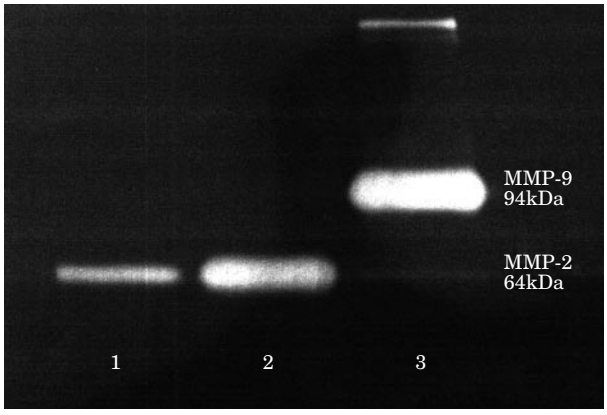

Fig. 2. Comparative pharmacokinetic profile ($n = 6$) of albendazole sulphoxide (ABZSO) obtained after the oral administration of albendazole (25 mg/kg) formulated as tablets and capsules containing Gelucires 44/14 in dogs.

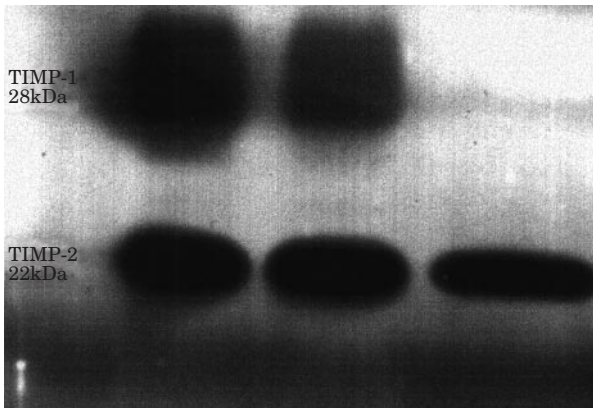

Fig. 3. Comparative absorption pattern of ABZ given as tablets and Gelucire capsules in dogs. The estimation is presented as the cumulative amount of ABZSO absorbed (formed) following the Wagner–Nelson method (Gibaldi & Perrier, 1982).

lipidic matrix formulation enhanced the ABZ dissolution (near 5-fold) compared with the commercial ABZ tablet formulation in vitro.

The low aqueous solubility of BZD may limit absorption during gastrointestinal transit (McKellar & Scott, 1990; McKellar *et al.*, 1990) and this may be compounded by the short gut transit time of the dog compared to other domestic species (McKellar *et al.*, 1993) and man (Ganong, 1995). The rate of dissolution in the stomach of BZD anthelmintics in different animal species is thought to be crucial in achieving adequate absorption and consequent availability and retrograde gastrointestinal secretion, and a high clinical efficacy. Albendazole formulated as tablets was absorbed to a greater extent than when administered as Gelucire capsules (Fig. 2, Table I). This could be explained by a faster dissolution rate of the tablet formulation. This is particularly likely in dogs owing to the short transit time in the gastrointestinal tract (García Sacristán *et al.*, 1995) compared to humans (Ganong, 1995). Hence, in dogs the Gelucires capsules may pass through the more absorptive portion of the small intestine before complete dissolution and drug release. The Wagner–Nelson method was used to analyse and compare the absorption processes in this trial. This analysis suggested large differences in the absorption of ABZ between the formulations assayed, which was measured indirectly using ABZSO plasma concentration (Fig. 3). The ABZSO absorption/formation displayed a similar profile during the first 4 h after administration for both dosage forms and this correlates with the short gastric emptying time of the dog (3–4 h). Maximum drug absorption was achieved earlier following Gelucires (1.8 μg/mL at 10 h post-treatment) than tablet treatment of dogs (3.2 μg/mL at 12 h post-treatment) (Fig. 3). These results suggest that, probably, the Gelucire capsule formulation may require a longer time at acidic pH (stomach) in dogs in order to increase the dissolution of the drug bound to the lipid matrix. Consequently, the erosion of and diffusion from the lipid matrix could be correlated with an incomplete absorption process for the drug in this dosage form. This could be reflected in a decreased plasma

availability with reduced antiparasite effect. These results should not be extrapolated to other species with slower gastric emptying time (including human beings) where the behaviour of gelucire matrix could be different.

The findings described in this article demonstrate that ABZ formulated in capsules as Gelucires 44/14 did not show a suitable pharmacokinetic profile compared with traditional tablets in dogs. Alternative pharmaceutical forms should be investigated for use in dogs in order to achieve improved bioavailability and clinical efficacy of BZD anthelmintics, thus providing practical drug administration and shorter dose regimens.

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