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Short Communications

Pharmacokinetics of a single oral administration of cefalexin in mares and foals

G. J. B. Ladaga, F. P. Lezica, A. M. Barboni, J. A. Picos, G. A. de Erausquin

CEFALEXIN is a first-generation broad-spectrum cephalosporin with well-documented efficacy in experimental and clinical studies in human (Clark and Turck 1968, Levison and others 1969, Thornhill and others 1969, Speight and others 1972) and veterinary (Ling and Ruby 1983, Crosse and Burt 1984a, Silley and Brewster 1988, Lees and others 1990) medicine. Its pharmacokinetics in horses has been studied after intravenous or intramuscular (Lees and others 1990, Villa and others 2002), but not oral administration. The comparative pharmacokinetics of adult horses and foals are not available. This study reports pharmacokinetic data following a single oral dose of cefalexin to mares and foals.

Four healthy, non-pregnant five-year-old thoroughbred mares, weighing 400 to 450 kg, and four unrelated three-month-old suckling female thoroughbred foals, weighing 140 to 160 kg, were included in the study. All the animals were grazed on pasture and had access to water ad libitum, and the foals had free access to their mothers.

A single oral dose of 30 mg/kg cefalexin monohydrate in the form of crushed tablets (Cefoxidin; Laboratorio Fundación) mixed with honey was administered.

Blood samples (10 ml) were collected from the jugular vein at 0, one, two, three, four, five, six, seven and eight hours following administration. Plasma was separated by centrifugation and stored at –20°C.

The concentration of cefalexin was measured using a standardised microbiological assay. Triplicate samples or cefalexin standards (200 µl) were placed in punched-out holes (6 mm width, 2 mm depth) in agar and inhibition halos were read using a micrometer after 24 hours at 37°C (Crosse and Burt 1984b). Data were fitted to a non-compartmental model using the trapezoidal rule.

Individual cefalexin concentration data for each animal are shown in Table 1. The concentration of cefalexin was highest at the first sampling time after administration (one hour). Elimination kinetics were estimated accurately by a non-compartmental model (Fig 1). Terminal elimination rate constants (λ_z) in foals were significantly smaller than in mares ($t=10.3557$, 6 df, $P<0.001$) (Fig 1b). The area under the curve (AUC) was increased twofold in foals ($t=2.4384$, 6 df, $P=0.05$) (Fig 1a) compared with mares. Times at which plasma concentrations exceeded 2 µg/ml or 4 µg/ml following cefalexin administration were extrapolated on a semilog time-concentration curve (Fig 1b). The mean (sd) time at which the plasma concentration exceeded 4 µg/ml was 3.6 (0.4) hours in mares and 4.9 (0.5) hours in foals, whereas the mean time at which the concentration exceeded 2 µg/ml was 4.4 (0.6) hours in mares and 5.9 (0.4) hours in foals. Therefore, an oral dose of 30 mg/kg cefalexin resulted in plasma concentrations above the minimum inhibitory concentration (MIC) for more than four hours in both mares and foals (Fig 1c).

TABLE 1: Serum concentration of cefalexin in four mares and four foals following administration of a single oral dose of 30 mg/kg cefalexin*

Time (hours)	Mare 1	Mare 2	Mare 3	Mare 4	Mean (sd)
0	0	0	0	0	
1	71.04	71.04	88.83	111.07	85.49 (19)
2	45.44	36.34	45.44	29.06	39.07 (7.93)
3	18.59	11.89	11.89	14.87	14.31 (3.18)
4	4.86	3.11	3.89	3.11	3.74 (0.83)
5	1.99	1.59	1.02	1.02	1.4 (0.47)
6	0.00	0.00	0.00	0.00	
7	0.00	0.00	0.00	0.00	
	Foal 1	Foal 2	Foal 3	Foal 4	Mean (sd)
0	0	0	0	0	
1	138.88	139.65	139.16	137.86	138.89 (0.65)
2	71.04	88.83	71.04	71.04	75.49 (8.89)
3	29.06	45.44	36.34	36.34	36.79 (6.71)
4	7.60	14.87	11.89	11.89	11.56 (2.99)
5	3.11	6.08	3.89	3.11	4.05 (1.40)
6	1.59	1.27	2.49	1.99	1.84 (0.52)
7	0.81	0.81	1.27	1.27	1.04 (0.26)

* Values represent the mean of three repeat samples; level of detection of cefalexin for this assay was 0.02 µg

The pharmacokinetics of two other cephalosporins have been studied in foals (Duffee and others 1989, 1997, Henry and others 1992), but no direct comparisons between foals and adult horses have been reported. The oral dose of cefalexin was chosen based on preliminary and published data (Speight and others 1972). The animals were fed a normal diet and occasional fatty samples, which could reduce bioavailability (data not shown), were observed. In human beings, food has been shown to decrease the absorption rate and maximum concentration (Cmax) of cefalexin, but AUC is reduced by less than 10 per cent (Levison and others 1969, Oclander 1971, Speight and others 1972); Cmax is reached within one hour of administration (Speight and others 1972). The volume of distribution has been reported to be 0.2 to 0.3 l/kg (Levison and others 1969, Speight and others 1972, Villa and others 2002). The present study did not compare different routes of administration, but a report in horses (Villa and others 2002) with doses significantly smaller than the ones reported here resulted in much lower Cmax values. In the present study, Cmax and half-life values were higher in foals than in mares, which is consistent with human data (Oclander 1971, Speight and others 1972). In human neonates, half-life is markedly prolonged and infants show intermediate values (Oclander 1971, Speight and others 1972). Lactants may have greater permeability in the gastrointestinal epithelium, or a lower gastric pH could facilitate cefalexin absorption (Welles and others 1968). Oral cefadroxil absorption decreases with age without increasing bioavailability (Duffee and others 1997), possibly due to its solubility in lipids and the increased body fat that results from ageing. Thus, oral cefadroxil is absorbed in foals but not in horses (Wilson and others 1985). Decreased glomerular filtration and tubular secretion in foals could explain the observed prolonga-

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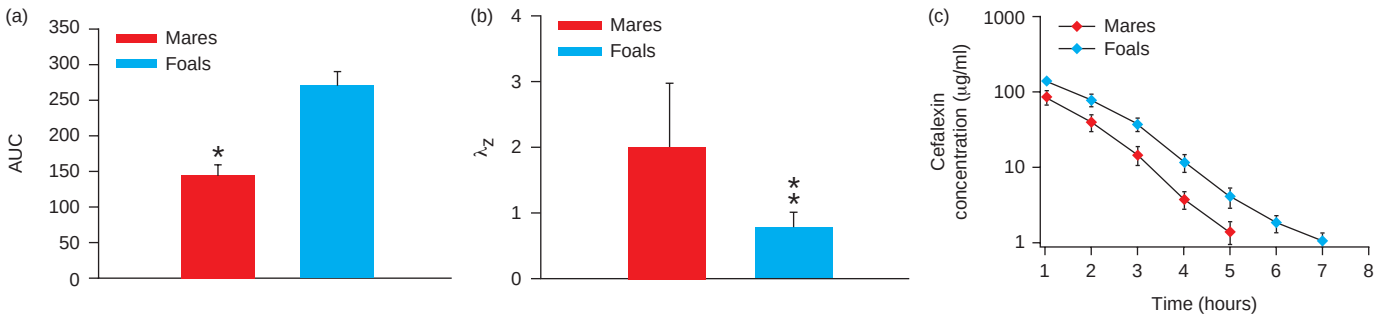

FIG 1: Non-compartmental modelling estimates of the pharmacokinetic parameters of cefalexin administered orally to four mares and four foals at a dose of 30 mg/kg in monohydrate form. (a) Area under the curve (AUC) extrapolated from 0 to infinity. * P=0.05. (b) λ_z=terminal elimination rate constant. ** P<0.001. (c) Plasma levels of cefalexin in mares and foals following a single oral administration of 30 mg/kg

tion in cefalexin half-life. Cmax values exceeded the MICs for most sensitive bacterial species fourfold in both mares and foals (Silley and Brewster 1988). Cefalexin concentrations remained above 2 µg/ml for 5.9 hours in foals and 4.4 hours in mares. Oral administration provides a Cmax and half-life comparable to that of intramuscular administration, with the additional advantage of a prolonged period during which the therapeutic concentration is exceeded.

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