THE PHARMACOKINETICS OF A SLOW-RELEASE THEOPHYLLINE PREPARATION IN HORSES AFTER INTRAVENOUS AND ORAL ADMINISTRATION

J.O. ERRECALDE AND M.F. LANDONI

Cátedra de Farmacología, Facultad de Ciencias Veterinarias, Universidad Nacional de La Plata, Calle 60 y 118, cc 296, 1900 La Plata, Argentina

ABSTRACT

Errecalde, J.O. and Landoni, M.F., 1992. The pharmacokinetics of a slow-release theophylline preparation in horses after intravenous and oral administration. *Veterinary Research Communications*, 16 (2), 131–138

The pharmacokinetics of a slow-release theophylline formulation was investigated following intravenous and oral administration at 10 mg/kg in horses. A tricompartmental model was selected to describe the intravenous plasma profile. The elimination half-life ($t_{1/2\beta}$) was 16.91 ± 0.93 h, the apparent volume of distribution (Vd) was 1.35 ± 0.18 L/kg and the body clearance (Cl_B) was 0.061 ± 0.009 L kg^{-1} h. After oral administration the half-life of absorption was 1.24 ± 0.30 h, and the calculated bioavailability was above 100%. The $t_{1/2\beta}$ after oral administration was 18.51 ± 1.75 h, only a little longer than that after intravenous administration. The slow release formulation did not exhibit any advantage in prolonging the $t_{1/2\beta}$ of theophylline in the horse.

Keywords: horses, pharmacokinetics, slow release formulation, theophylline

INTRODUCTION

Theophylline has repeatedly been shown to be a useful drug for treating bronchial obstruction in humans (Jenne *et al.*, 1972; Mitenko and Ogilvie, 1973; Jacobs *et al.*, 1976; Pollock *et al.*, 1977; Hendeles and Weinberger, 1982). It has also been indicated as a treatment for respiratory conditions in domestic animals (Davis, 1980; McKiernan *et al.*, 1981; Koritz *et al.*, 1986). This drug is a methylxanthine derivative, a phosphodiesterase inhibitor (Ziment, 1978), and has been used in horses suffering from chronic obstructive pulmonary disease (COPD) (Beech, 1979; Thomson and McPherson, 1983).

There are previous reports concerning the pharmacokinetic behaviour of theophylline after intravenous and/or oral administration (Errecalde *et al.*, 1984; Kowalczyk *et al.*, 1984; Ayres *et al.*, 1985; Ingvast Larson *et al.*, 1985; Short *et al.*, 1986). However, there are no reports of the pharmacokinetics of the sustained release form of this drug in horses. Oral theophylline has been used in the treatment of lung diseases (Hendeles and Weinberger, 1982; Derksen, 1983). In order to achieve maximum therapeutic benefit with relatively low risk of severe side-effects, the plasma concentration should be maintained within the narrow range of 5–20 µg/ml (Hendeles and Weinberger, 1982), assuming that theophylline has the same range of therapeutic plasma concentrations in the horse as it has in man and small animals. Indeed, it has been demonstrated by McKiernan and Koritz (1990) that below 10.63 µg/ml there was no consistent bronchodilator effect and that above 15.13 µg/ml some collateral effects were present.

A long biological half-life of theophylline in horses after oral administration has been reported (Errecalde *et al.*, 1984; Ingvast Larson *et al.*, 1985). The aims of this study were to determine the pharmacokinetic characteristics of a slow-release formulation of theophylline (TheoDur, Pfizer, Argentina) in horses and to ascertain whether it offers pharmacological advantages in the horse as it does in humans.

MATERIALS AND METHODS

Six female adult horses of mixed breeding, with an average estimated age of 10 years, were used. At least 1 week was allowed to elapse between each administration of the drug.

In the intravenous trial, theophylline was given in the form of aminophylline (Sigma Co). Because theophylline makes up about 78% of aminophylline by weight (Wade, 1977), a conversion factor was used to convert the weight of theophylline to the weight of aminophylline. A single infusion of 10 mg/kg theophylline was given into the right jugular vein over a 3-min period. Blood samples were drawn into heparinized tubes from a permanent catheter in the left jugular vein immediately before and at 2.5, 5, 7.5, 10, 15, 20, 30 and 40 min, and 1, 1.5, 2. 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36 and 48 h after administration of the theophylline.

In the intragastric trials, a slow-release dosage form of theophylline (Theodur 300 mg) was used. This pharmaceutical is presented as tablets grooved to be cut into halves. Because the minimal unit of formulation is a half a 300-mg tablet (i.e. 150 mg), the total dose was the sum of the whole tablets with the addition, if necessary, of a final half tablet. This was the only way of avoiding physical disruption of the dose formulation, which could have altered dissolution and subsequent theophylline absorption. The drug was given by intragastric tube and the tube was rinsed with 1 litre of water to ensure full delivery of the dose. Blood samples were collected in the same way as for intravenous administration, immediately before and at 5, 10, 15, 20, 30 and 40 min, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36, 48, 60, 72, 84 and 96 h after administration of the theophylline.

Plasma samples for theophylline assay by liquid chromatography were extracted as follows: 1 ml of the thawed plasma was deproteinized by adding 1 ml 20% trichloroacetic acid. After agitation and centrifugation, 20 μl of the supernatant fluid was injected onto a reverse-phase column (5ODS-1 Kontron Instruments). The chromatographic system comprised a pumping unit (LC 414 Kontron Instruments) a fixed-wavelength detector (Uvikon 740 Kontron Instruments) and a strip chart recorder (Kipp and Zonen BD 40). The mobile phase was a 905 : 95 mixture of buffer PO4H2K 20 mmol/L, pH 3.6 (adjusted with phosphoric acid), and acetonitrile (Sintorgan S.A., Argentina). A flow rate of 1 ml/min was used to elute theophylline. Theophylline was detected at 280 nm, with retention time of about 18 min. Theobromine was used as an internal standard.

The MAICE test (Yamaoka *et al.*, 1978; Akaike, 1976) was applied to the curve of plasma concentration against time to determine the best fitting model to describe the pharmacokinetic behaviour of theophylline after intravenous administration. A tricompartmental model was indicated as defined by the expression

$$C_p = A\exp(-\alpha t) + P\exp(-\pi t) + B\exp(-\beta t)$$

where C_p is the plasma concentration; A, P and B are intercept terms; α, π and β are the slopes of the fast and slow distribution and the elimination phases; and t is time.

The disposition curve was analysed following a tricompartmental model using the non-linear iterative computer program ADAPT (D'Argenio and Schumitzky, 1979), which uses the SIMPLEX algorithm (Nelder and Mead, 1965).

The plasma disposition curve of theophylline after oral administration was analysed following a single-compartment model with first-order absorption, using a non-linear iterative computer program (D'Argenio and Schumitzky, 1979). The following equation defined the curve:

$$C_p = B\exp(-\beta t) - D\exp(-K_a t)$$

where C_p is the plasma concentration; B and D are interception terms; K_a and β are the slopes of the absorption and elimination phases; and t is time.

The absorption phase was analysed by the method of Wagner (1983).

RESULTS

The MAICE test indicated that a tricompartmental model best represented the intravenous concentration versus time data.

The individual and mean pharmacokinetic values from the intravenous study are presented in Table I and the plasma theophylline versus time profile for the intravenous study, as defined by the three-compartment model, is shown in Figure 1. In the intravenous curve, three phases can be seen, the first with the highest slope corresponding to rapid distribution, the second with an intermediate slope corresponding to slow distribution and the final one, with the lowest slope, corresponding to elimination.

In the case of the oral administration, the MAICE test indicated that a one-compartment open model with first-order absorption was the best description of the concentration versus time data.

The individual and mean pharmacokinetic values from the oral theophylline administration are presented in Table II, while the concentration versus time curve is also presented in Figure 1.

DISCUSSION

The use of a tricompartmental model to define the pharmacokinetic behaviour of theophylline was described by Ayres et al. (1985). However, the majority of authors use bicompartmental models (Errecalde et al., 1984; Ingvast Larson et al., 1985).

Considerable variation was observed between the animals, especially as regards the distribution (Table I). Such variation has been reported in previous studies (Ingvast Larson et al., 1985). The first distribution phase (α) was rapid, being faster than that in some previous reports (Errecalde et al., 1984; Ingvast Larson et al., 1985) but agreeing with that reported by Ayres et al. (1985). This difference may have been caused by the different models used in the analysis.

TABLE I

Individual and mean pharmacokinetic parameters obtained after intravenous injection of 10 mg/kg aminophylline in six horses

Parameter	1	2	3	4	5	6	Mean ± SE
A (μg ml^{-1})	6.95	4.01	14.47	64.59	20.50	18.11	21.44 ± 9.01
α (L h^{-1})	10.36	1.94	12.63	40.65	13.06	6.31	14.16 ± 5.57
$t_{1/2}\alpha$ (min)	4.01	21.43	3.29	1.02	3.18	6.59	6.58 ± 3.06
P (μg ml^{-1})	2.02	3.99	2.91	6.53	4.93	9.79	5.03 ± 1.15
π (L h^{-1})	0.54	0.38	1.40	0.60	0.51	0.18	0.60 ± 0.17
$t_{1/2}\pi$ (h)	1.28	1.82	0.49	1.15	1.36	3.85	1.66 ± 0.47
B (μg ml^{-1})	6.05	4.25	4.48	10.28	6.21	6.82	6.35 ± 0.88
β (L h^{-1})	0.036	0.052	0.036	0.045	0.041	0.040	0.042 ± 0.002
$t_{1/2}\beta$ (h)	19.25	13.33	19.25	15.40	16.90	17.32	16.91 ± 0.93
V_c (L)	0.66	0.82	0.37	0.12	0.44	0.28	0.45 ± 0.10
K_{12} (L h^{-1})	4.57	0.46	6.55	31.49	8.36	3.35	9.13 ± 4.60
K_{21} (L h^{-1})	5.64	1.37	4.72	8.14	4.57	3.55	4.66 ± 0.91
K_{13} (L h^{-1})	0.22	0.18	1.84	0.92	0.59	0.16	0.65 ± 0.26
K_{31} (L h^{-1})	0.41	0.21	0.78	0.41	0.39	0.23	0.40 ± 0.08
K_{10} (L h^{-1})	0.088	0.13	0.17	0.33	0.15	0.16	0.17 ± 0.03
V_d (L kg^{-1})	1.56	1.79	1.77	0.87	1.36	0.74	1.35 ± 0.18
Cl_B (L kg^{-1} h^{-1})	0.059	0.106	0.063	0.040	0.057	0.045	0.061 ± 0.009
AUC (μg.h ml^{-1})	139.3	80.7	103.8	213.2	149.3	201.0	147.9 ± 21.30
MRT (h)	16.60	10.89	17.47	15.79	13.97	13.31	14.67 ± 0.98

A, P, and B are y-axis intercepts of the best-fit regression for the distribution and elimination data, respectively; α, π and β are the distributive (fast and slow) and the eliminative rate constants; $t_{1/2}\alpha$, $t_{1/2}\pi$ and $t_{1/2}\beta$ are their respective half-lives; AUC is the area under the plasma concentration-time curve; V_c is the apparent volume of the central compartment; V_d is the apparent volume of distribution calculated by the steady-state method; Cl_B is the body clearance; K_{12}, K_{21}, K_{13}, K_{31} and K_{10} are microconstants associated with the three-compartment pharmacokinetic model; MRT is the mean residence time

The second distributive phase (π) was longer, again agreeing with that reported by Ayres et al. (1985).

The mean elimination half-life ($t_{1/2}\beta$) of 16.91 h indicates that the horse eliminates theophylline more slowly than other species (see Table III). This value agrees with some previous reports (Errecalde et al., 1984; Ingvast Larson et al., 1985), although a faster elimination rate was reported by Short et al. (1986).

The large mean volume of the central compartment (V_c) of 446 ml agrees with that of 455 ml reported by Errecalde et al. (1984). However, values smaller than ours (mean 298 ml) were found by Short et al. (1986).
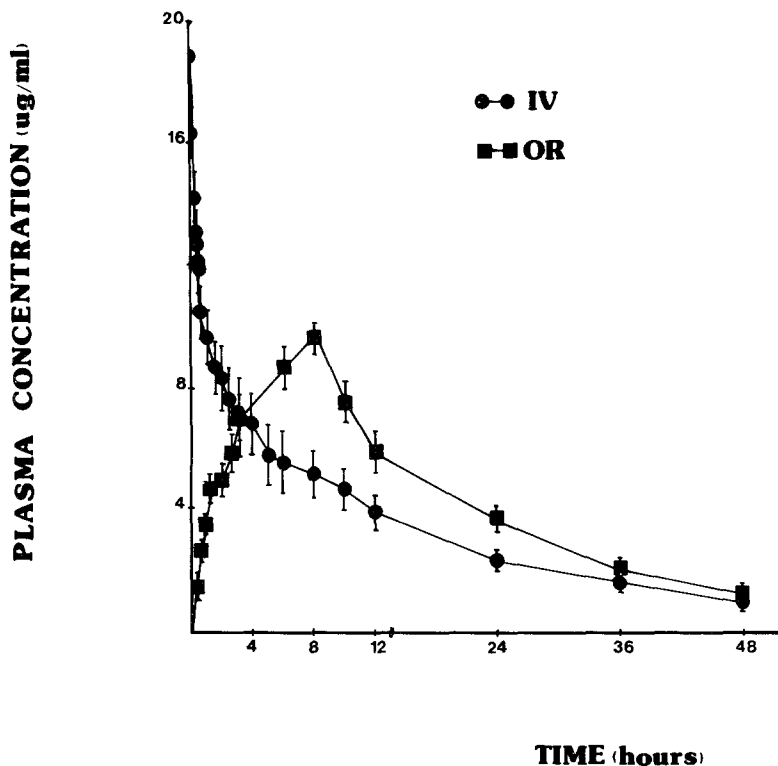
Figure 1. Averaged plasma theophylline concentrations for six mares after intravenous (IV) and oral (OR) administration of theophylline 10 mg/kg

The mean apparent volume of distribution (V_d) of 1.35 L/kg indicates extensive distribution to the extravascular tissues. This result is larger than those given by Ingvast-Larson *et al.* (1985) (1.02 L/kg) and by Ayres *et al.* (1985) (1.02 L/kg). Even smaller volumes were reported by Errecalde *et al.* (1984) (0.85 L/kg) and Short *et al.* (1986) (0.703 L/kg), although in all these studies the V_d values can be considered as relatively high.

Although there are no reports concerning the pharmacokinetics of slow-release formulations after oral administration in horses, there is a report of a study in dogs, in which the absorption time was 4.9 h for the same pharmaceutical preparation as that used in the present work (Koritz *et al.*, 1986). The elimination half-life obtained in the dogs was 12.10 h. Although the absorption time is longer than in horses, it is still short for a slow-release formulation.

The calculated bioavailability was over 100%; such results have been reported previously (Hendeles and Weinberger, 1982; Errecalde *et al.*, 1984; Ingvast Larson *et al.*, 1985) for animals and human beings.

TABLE II

Individual and mean pharmacokinetic parameters obtained after oral administration of 10 mg/kg theophylline in slow-release pharmaceutical form in horses

Parameter	1	2	3	4	5	6	Mean ± SE
K_a (h^{-1})	0.62	0.75	1.06	0.31	0.25	0.33	0.55 ± 0.12
$t_{1/2}$abs (h)	1.12	0.92	0.65	2.23	0.44	2.10	1.24 ± 0.30
β (h^{-1})	0.040	0.048	0.030	0.033	0.054	0.031	0.039 ± 0.004
$t_{1/2}\beta$ (h)	17.32	14.44	23.10	21.00	12.83	22.35	18.51 ± 1.75
AUC (μg.h ml^{-1})	160.2	119.3	197.7	194.2	238.1	169.5	179.8 ± 16.40
MRT (h)	15.89	12.77	17.22	15.73	15.63	19.98	16.20 ± 0.96
F (%)	115.0	148.0	190.0	91.0	64.0	84.0	115.3 ± 19.02
C_{max} (μg ml^{-1})	8.56	9.06	11.03	8.71	11.65	8.69	9.62 ± 0.55
T_{max} (h)	8.00	9.00	8.00	8.00	8.00	8.00	8.17 ± 0.16
Lag time (h)	0.50	0.50	0.33	0.66	0.50	4.00	1.08 ± 0.58

K_a is the absorption rate constant and $t_{1/2}$abs its half-life; Lag time is the interval between drug administration and its detection in plasma; C_{max} is the maximum observed plasma concentration and T_{max} is the time at which the maximum concentration occurred; F is bioavailability. Other symbols are explained at the foot of Table I

TABLE III

Elimination half-life $(t_{1/2}\beta)$ values of theophylline after intravenous administration to various species

Species	$t_{1/2}\beta$ (h)	Reference
Horse	17.00	Errecalde et al., 1984; Ingvast Larson et al., 1985
Dog	5.77	McKiernan et al., 1981
Cat	7.79	McKiernan et al., 1983
Human	9.00	Rall, 1980
Goat	6.93	Davis et al., 1987
Swine	11.00	Koritz et al., 1981

A longer half-life is one of the goals in designing a slow-release formulation. This has not been accomplished in this case. The formulation studied did not appreciably improve the pharmacokinetic behaviour of a simple aminophylline suspension ($t_{1/2}\beta$ IV = 16.91 h vs $t_{1/2}\beta$ oral = 18.51 h). It is important to consider here that theophylline has a longer half-life after intravenous administration in horses than in other species. The biological half-life for conventional theophylline after oral

administration is about 17 h (Errecalde *et al.*, 1984; Ingvast Larson *et al.*, 1985) (see Table III). For that reason, a half-life of 18.51 h is not particularly long. The biological half-life for conventional theophylline after oral administration is about 17 h (Errecalde *et al.*, 1984; Ingvast Larson *et al.*, 1985).

REFERENCES

Akaike, H., 1976. An information criterion (AIC). *Mathematical Science*, **14**, 5–9

Ayres, J., Pearson, E., Riebold, T. and Chang, S., 1985. Theophylline and diphylline pharmacokinetics in the horse. *American Journal of Veterinary Research*, **46**, 2500–2506

Beech, H., 1979. Principles of therapy. *Veterinary Clinics of North America. Large Animals Practice*, **1**, 73–88

D'Argenio, D. and Schumitzky, A., 1979. A program package for simulation and parameter estimation in pharmacokinetic systems. *Computer Programs in Biomedicine*, **9**, 115–134

Davis, L.E., 1980. Applied pharmacodynamics of digitalis, theophylline, diuretics and selected antiarrythmics drugs. In: R.W. Kirk (ed), *Current Veterinary Therapy VII. Small Animal Practice*, (W.B. Saunders, Philadelphia), 352–359

Davis, L.E., Neff Davis, C., Koritz, G.D., Bevill, R.F., Sharma, G.C., Langston, V.C. and Munsiff, I.J., 1987. Effect of organic vehicles in pharmacokinetics of aminophylline administered intravenously to goats. *Journal of Veterinary Pharmacology and Therapeutics*, **10**, 144–149

Derksen, F.J., 1983. Chronic airway disease. In: E. Robinson (ed), *Current Therapy in Equine Medicine*, (W.B. Saunders, Philadelphia), 509

Errecalde, J.O., Button, C., Baggot, J.D. and Mulders, M.S.G., 1984. Pharmacokinetics and bioavailability of theophylline in horses. *Journal of Veterinary Pharmacology and Therapeutics*, **7**, 255–264

Hendeles, L. and Weinberger, M., 1982. Improved efficacy and safety of theophylline in the control of airways hyperactivity. *Annals of Allergy*, **49**, 247–256

Ingvast-Larson, C., Paalzow, L., Ottosson, T. and Appelgreen, L.E., 1985. Pharmacokinetic studies of theophylline in horses. *Journal of Veterinary Pharmacology and Therapeutics*, **8**, 76–81

Jacobs, M.H., Senior, R.M. and Kessler, G., 1976. Clinical experience with theophylline: relationship between dosage, serum concentration and toxicity. *Journal of the American Medical Association*, **235**, 1983–1986

Jenne, J.W., Wyze, E., Rood, F.S. and McDonald, F.M., 1972. Pharmacokinetics of theophylline: application to adjustment of the clinical dose of theophylline. *Clinical Pharmacology and Therapeutics*, **13**, 349–360

Koritz, G., Borne, D., Hunt, J. and Prasad, V., 1981. Pharmacokinetics of theophylline in swine: a potential model for human drug bioavailability studies. *Journal of Veterinary Pharmacology and Therapeutics*, **4**, 233–239

Koritz, G., McKiernan, B. and Neff Davies, C., 1986. Bioavailability of four slow release formulations in the Beagle dog. *Journal of Veterinary Pharmacology and Therapeutics*, **9**, 293–302

Kowalczyk, D.F., Beech, J. and Littlejohn, D., 1984. Pharmacokinetic disposition of theophylline in horses after intravenous administration. *American Journal of Veterinary Research*, **45**, 2272–2275

McKiernan, B.C. and Koritz, G.D., 1990. Plasma theophylline concentration and lung function in ponies with recurrent obstructive lung disease. *Equine Veterinary Journal*, **22**, 194–197

McKiernan, B.C., Neff Davis, C., Koritz, G.D. and Pheris, D., 1981. Pharmacokinetic studies of theophylline in dogs. *Journal of Veterinary Pharmacology and Therapeutics*, **4**, 103–110

McKiernan, B.C., Koritz, G.D., Davis, E. and Munsiff, I., 1983. Pharmacokinetic studies of theophylline in cats. *Journal of Veterinary Pharmacology and Therapeutics*, **6**, 99–104

Mitenko, P. and Ogilvie, R., 1973. Rational intravenous doses of theophylline. *New England Journal of Medicine*, **289**, 600–603

Nelder, J. and Mead, R., 1965. A simplex method for function minimization. *Computers Journal*, **4**, 300–313

Pollock, J., Kiechel, F., Cooper, D. and Weinberger, M., 1977. Relationship of serum theophylline concentration to inhibition of exercise induced bronchospasm and comparison with chromolyn. *Pediatrics Springfield*, **60**, 840–844

Rall, T.W., 1980. The xanthines. In: A.G. Gilman, L.S. Goodman and A. Gilman (eds), *The Pharmacological Basis of Therapeutics*, 6th edn, (McMillan, New York), 592–607

Short, C.R., Horner, M.W., Blay, P.K., Moss, M.S., Edington, N. and Clarke, C.R., 1986. The lack of effect of inoculation with equine influenza vaccine on theophylline pharmacokinetics in the horse. *Journal of Veterinary Pharmacology and Therapeutics*, **9**, 426–432

Thomson, J.R. and McPherson, E.A., 1983. Chronic obstructive pulmonary disease in the horse 2: Therapy. *Equine Veterinary Journal*, **15**, 207–210

138

Wade, A., 1977. In *Martindale, The Extra Pharmacopoeia*, 27th edn, (Pharmaceutical Press, London)

Wagner, J.G., 1983. *Farmacocinética Clínica*, (Reverté, Barcelona, Spain), 175–232

Yamaoka, K., Nakagawa, T. and Uno, T., 1978. Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetic equations. *Journal of Pharmacokinetics and Biopharmaceutics*, **6**, 165–175

Ziment, I., 1978. Phosphodiesterase inhibitors. *Respiratory Pharmacology and Therapeutics*, (W.B. Saunders, Philadelphia), 190–207