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Etophylline and theophylline pharmacokinetics when administered concomitantly in rabbits

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Summary

Etophylline and theophylline (aminophylline) were administered intravenously alone and concomitantly to rabbits. Both model-dependent and model-independent approaches were used for pharmacokinetic analysis of the data. Analysis of variance and the Kruskal-Wallis test showed that differences among pharmacokinetic parameters in different treatments were not statistically significant at $\alpha = 0.05$ for etophylline or theophylline. No apparent toxicities were observed for concomitant plasma concentrations of 50–100 μg/ml theophylline plus 100–300 μg/ml etophylline even when maintained for up to 2 h by zero-order infusion.

Introduction

Etophylline is an N-7-substituted theophylline derivative (β-hydroxyethyltheophylline) which is an effective bronchospasmolytic agent (Ufkes et al., 1981). It does not release theophylline in vitro or in vivo and has its own pharmacokinetic and pharmacodynamic properties. Etophylline has a shorter half-life and is eliminated more rapidly than theophylline, is metabolized with only 20% eliminated unchanged by the kidneys in humans, and has been widely used in many countries (especially F.R.G.) in the treatment of asthma as a bronchodilator (Merkus and Zuidema, 1980; Zuidema et al., 1981). It is available in many trade preparations alone and in combinations (Jauch and Zimmer, 1978; Sharma and Sharma, 1979), including a theophylline and etophylline complex (Sharma and Sharma, 1979). Etophylline is reported to be 0.14 times as potent as theophylline in producing bronchorelaxation in rat tracheas (Mitenko and Ogilvie, 1973) and is believed to have lower toxicity (McColl et al., 1956).

Aminophylline should not be given concurrently with other xanthine preparations (Physicians Desk reference, 1984), presumably because of expected potentially synergistic toxicities due to their similar structures and mechanisms of action. Although etophylline is formulated with low doses of theophylline (Sharma and Sharma, 1979), a literature search failed to reveal any reports of concomitant toxicities or pharmacokinetics. Etophylline has been administered in combination with fominoben in their usual normal doses with

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no pharmacokinetic drug interaction (Jauch and Zimmer, 1978). There is, however, no similarity in the fominoben and etophylline structures as there is between etophylline and theophylline.

In emergency cases in countries where etophylline is used, it may be desirable to rapidly administer etophylline to patients who are currently receiving theophylline or theophylline salts. Etophylline might even replace aminophylline for intravenous administration if it is safe and effective when given as an intravenous bolus to patients who have been taking theophylline. These patients already have a partial "theophylline load" and should only receive adjusted doses of aminophylline infused over 20 min (Zuidema and Merkus, 1981a). This study was undertaken to investigate the pharmacokinetic behavior and gross toxicity of theophylline and etophylline when given alone and concomitantly in rabbits.

Materials and Methods

Six female New Zealand white rabbits weighing 1.9–3.1 kg received each treatment, without complete cross-over. Any rabbits which received both treatments had an elapsed time of at least two weeks between treatments. Rabbits were restrained with a cloth body cloak with safety pins. The hair on both ears was shaved and the ears cleaned with warm water and then with alcohol [1]. The rabbit was placed on a heating pad and lidocaine [2] was injected subcutaneously close to an ear vein or artery for local anesthesia prior to catheterization. A catheter [3] (26-gauge) was inserted into the outer marginal ear vein of one ear for drug infusion. In the other ear, a catheter (22-gauge) was inserted into the mid-ear artery for collection of blood samples. Catheters were closed with infusion plugs [4].

Etophylline [5] was dissolved in D-5-W [6] (dextrose 5% in water) and filtered [7] (2 μm) and diluted with D-5-W when used. Aminophylline [8] was diluted with D-5-W to a desired concentration. Drugs were injected into the ear vein through the infusion plug using a laboratory infusion pump [9] or hospital IV pump [10].

Arterial blood samples were collected through the infusion plug using a needle (21-gauge 1.5 inch) [11] which had been connected to 12 inches of heparin-washed intramedic polyethylene tubing PE 90 [12]. Blood was allowed to flow freely after the needle penetrated the infusion plug of the arterial catheter. About 300 μl of the first blood collected was discarded and then about 300 μl was collected in a 500 μl heparinized microcentrifuge tube [13]. 200 μl of 20 units/ml of heparin [14] in D-5-W was injected into the infusion plug prior to and after each blood sample collection. Samples were collected at 10, 20, 30, 45 and 60 min, 2, 3, 4, 5, 6, 8, 10 and 12 h.

Drug administration treatments

Treatment 1. Aminophylline (40 mg/kg, equivalent to 31.58 mg/kg of theophylline on a molecular weight basis) was diluted with D-5-W to 6.3 ml and was administered by intravenous infusion at the rate of 0.21 ml/min over 30 min.

Treatment 2. 150 mg/kg of etophylline (50 mg/ml) was administered by intravenous infusion at the rate of 1.02 ml/min over 3–5 min.

[1] Sterile Alcohol Prep. Professional Disposables, Mt. Vernon, NY 10500-1890, Mississauga, Ontario L4T 1GE, Canada.

[2] Lidocaine Hydrochloride injection USP 2% (2 mg/ml), Rugby Laboratories, Rockville Center, L.I., NY.

[3] Quik-Cath Travenol Laboratories, Deerfield, IL.

[4] Intermittant infusion plug, Argyle, St. Louis, MO.

[5] β-Hydroxyethyltheophylline, Sigma Chemical Co., St. Louis, MO.

[6] Dextrose 5% in water, Abbott Laboratories, North Chicago, IL.

[7] Acrodisc, Disposable Filter Assembly, Gelman.

[8] Aminophylline injection USP 250 mg (25 mg/ml), Abbott Laboratories, North Chicago, IL.

[9] Infusion/Withdrawal Pump, model 902, Harvard Apparatus Co., Millis, MA.

[10] Life Care IV Pump, Abbott Laboratories, North Chicago, IL.

[11] Hypodermic needle sterile, Becton Dickinson and Co., Rutherford, NJ.

[12] Intramedic Polyethylene tubing PE90.

[13] Microcentrifuge tube, Centaur Sciences, Standford, CT.

[14] Panheprin, Heparin sodium injection USP, Abbott Laboratories, North Chicago, IL.

Treatment 3. 40 mg/kg in 6.3 ml of aminophylline was administered by intravenous infusion at the rate of 0.21 ml/min over 30 min. Then 30 min after stopping aminophylline, 150 mg/kg of etophylline (50 mg/ml) was administered by intravenous infusion at the rate of 1.02 ml/min over 3–5 min, followed by a maintenance dose of 30 mg/kg/h in 27.6 ml at the rate of 0.23 ml/min over 2 h.

Treatment 4. 150 mg/kg of etophylline (50 mg/ml) was administered by intravenous infusion at the rate of 1.02 ml/min over 3–5 min. Then 30 min after stopping etophylline, 40 mg/kg of aminophylline in 6.3 ml D-5-W was administered by intravenous infusion at the rate of 0.21 ml/min over 30 min.

Blood samples were collected and centrifuged at 2000 rpm at 4°C for 30 min [15]. Plasma was separated and frozen until assayed.

Assay

25 μl of plasma was mixed with 25 μl of internal standard (120 μg/ml of β-hydroxypropyltheophylline [16] in acetonitrile [17]) and centrifuged at 2000 rpm at 4°C for 30 min. The supernatant solution was separated from the deposited plasma protein and 10 μl injected into the HPLC system.

Standard solutions were prepared in the same way as unknown samples, but using standard stock solutions to add to plasma to obtain 5, 10, 20, 30, 40, 50, 75, 90 and 100 μg/ml of etophylline or theophylline as well as a mixture of both.

HPLC [18] analyses were performed on a reverse phase μ-Bondapak C_{18} column and a pre-column (10 cm long packed with C_{18} packing powder). An acetonitrile–water (7% v/v) mixture adjusted to pH 6.0 with sufficient acetic acid [19] was used as mobile phase at a flow rate of 2.0 ml/min. Absorbance was monitored at 280 nm. Peak height ratios were used for drug quantification.

Both model-dependent and model-independent approaches were used for pharmacokinetic analysis of the data. For model-dependent analysis data were weighted 1/C and fitted by AUTOAN2 [20] and NONLIN [21]. The best-fitted models by AUTOAN2 were chosen, except for etophylline when administering etophylline in the presence of aminophylline (Treatment 3). For this treatment, the terminal slopes of post-infusion data of etophylline were obtained from linear regression of natural log of concentration vs time. Estimates obtained from AUTOAN2 and NONLIN were used to calculate pharmacokinetic parameters [22]. Model-independent analysis was non-compartmental analysis based on statistical moment theory. Parameters such as Mean Residence Time (MRT_b), volume of distribution at steady state (Vd_{ss}) and clearance (Cl) were obtained from area under the concentration time curve (AUC_∞) calculated by the log trapezoidal equation (Riegelman and Collier, 1980; Gibaldi and Perrier, 1981). All parameters were corrected for infusion time (Perrier and Mayersohn, 1982). Parameters for etophylline when administering etophylline in the presence of aminophylline (Treatment 3) were determined as suggested by Perrier and Mayersohn for two consecutive infusions. All ± values in the tables are standard deviations (S.D.).

Results and Discussion

Model-dependent pharmacokinetic analysis

Plasma theophylline concentration–time curves for 6 rabbits each after administration of aminophylline alone, aminophylline followed by etophylline, or etophylline followed by aminophylline are shown in Figs. 1, 2 and 3, respectively. Data are essentially superimposable for all three

[15] Model TJ-6 Centrifuge, Model TJ-R Refrigeration Unit, Beckman Instruments, Palo Alto, CA.

[16] β-Hydroxypropyltheophylline, Sigma Chemical Co., St. Louis, MO.

[17] Acetonitrile, HPLC, J.T. Baker Chemical Co., Phillipsburg, NJ.

[18] Waters Associates, Milford, MA.

[19] Acetic acid, J.T. Baker Chemical Co., Phillipsburg, NJ.

[20] A.J. Sedman and J.B. Wagner, "AUTOAN is a Decision Making Pharmacokinetic Digital Computer Program", Publication Distribution Service, Ann Arbor, MI, 1976.

[21] C.M. Metzler, G.L. Elfring and A.J. McEwen, "A Users Manual for NONLIN and Associated Programs," The Upjohn Co., Kalamazo, MI, 1974.

[22] M. Gibaldi and D. Perrier, "Pharmacokinetics," Dekker, New York, NY, 1975.

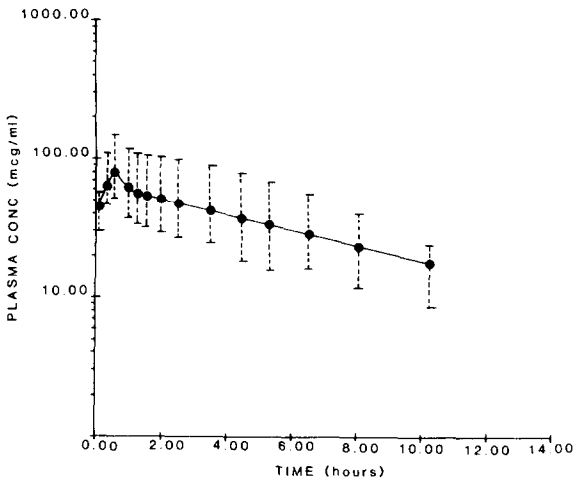

Fig. 1. Mean of plasma concentration–time curves for theophylline after administration of aminophylline (40 mg/kg i.v. infusion over 30 min) in 6 rabbits. (Error bars represent the range and not S.D.)

figures. Each curve for theophylline is quite log-linear post-infusion and distribution. All plasma theophylline concentration–time curves were well described mathematically by assuming a two-compartment open pharmacokinetic model with a rapid α distribution phase. Pharmacokinetic

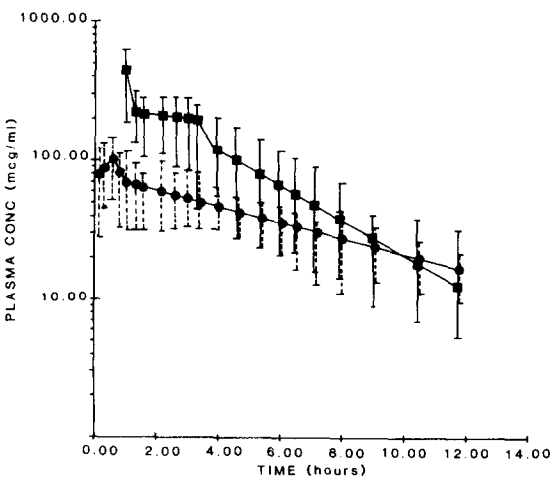

Fig. 2. Means of plasma concentration–time curves for theophylline (●) and etophylline (■) after administration of aminophylline (40 mg/kg i.v. infusion over 30 min) followed by etophylline loading dose (150 mg/kg i.v. infusion over 5 min) and etophylline maintenance dose (30 mg/kg/h i.v. infusion over 2 h) in 6 rabbits. (Error bars represent the range and not S.D.)

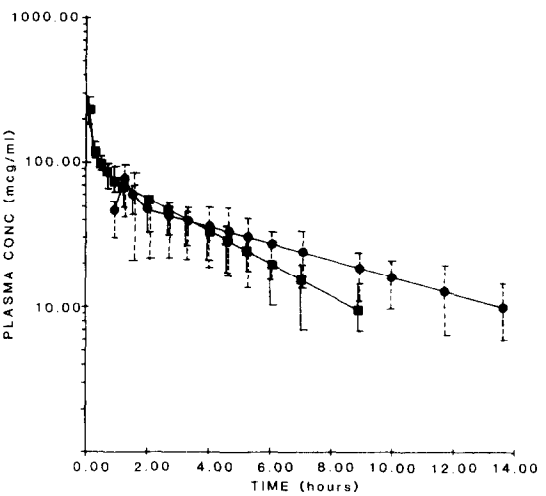

Fig. 3. Means of plasma concentration–time curves for etophylline (■) and theophylline (●) after administration of etophylline (150 mg/kg i.v. infusion over 5 min) followed by aminophylline (40 mg/kg i.v. infusion over 30 min) in 6 rabbits. (Error bars represent the range and not S.D.)

parameters for theophylline are shown in Tables 1, 2A and 3B. All calculated pharmacokinetic parameters have been corrected for the infusion time (Loo and Riegelman, 1970).

Aminophylline alone (Table 1, Fig. 1) had a mean elimination half-life of 5.2 h and mean V_{d_β} of 0.71 l/kg. These are consistent with data reported earlier for rabbits (El-Yazigi and Sawchuk, 1981) with mean elimination half-lives of 4.4 h and V_{d_β} of 0.708 l/kg. Ng and Locock (1979) also reported a mean elimination half-life of 5.5 h and V_{d_β} 0.545 l/kg.

As expected for theophylline, the β elimination phase was quite variable in all three treatments (see standard deviations in Tables 1, 2A and 3B). Analysis of variance and the Kruskal-Wallis test showed that differences in β elimination rate constants, V_{d_β} (volume of distribution) and area under the curve (AUC_∞), among the treatments are not significant ($P < 0.05$).

Plasma etophylline concentration time curves for 6 rabbits each after administration of etophylline alone (Fig. 4), etophylline followed by aminophylline (Fig. 3), or aminophylline followed by etophylline (Fig. 2), are superimposable. Data for etophylline administered alone (Fig. 4) were well described by a two-compartment open model

TABLE 1

PHARMACOKINETIC PARAMETERS FOR THEOPHYLLINE AFTER ADMINISTERING AMINOPHYLLINE (40 mg/kg INTRAVENOUSLY OVER 30 min) IN RABBITS

Compartmental		non-compartmental	
Two-compartment open model (n = 6)			
β (h^{-1})	0.13 ± 0.03	$1/MRT_b$ (h^{-1})	0.15 ± 0.02
α (h^{-1})	3.37 ± 3.87		
V_{d_β} (l/kg)	0.71 ± 0.27	$V_{d_{ss}}$ (l/kg)	0.57 ± 0.20
Cl (l/kg/h)	0.09 ± 0.03	Cl (l/kg/h)	0.08 ± 0.02
$t_{1/2}$ (h)	5.2	MRT_b (h)	6.74 ± 1.29

for 3 rabbits and a three-compartment open model for the other 3 rabbits, as determined by AUTOAN2. Pharmacokinetic parameters are shown in Table 4. Differences in β, $t_{1/2}$ and V_{d_β} are not statistically significant for the groups of rabbits best described by the two- vs three-compartment open models. Overall average $t_{1/2}$ was 1.7 h.

Pharmacokinetic parameters for bolus etophylline when followed by aminophylline infusion were also obtained from either a two-compartment open model or a three-compartment open model as determined by AUTOAN2, depending on the subject as shown in Table 3A. There is also no statistically significant difference in β or V_{d_β} between these groups of subjects best described by the two- vs three-compartment models.

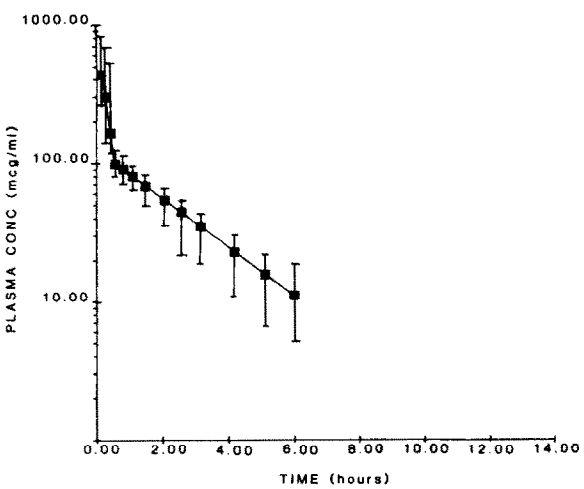

Fig. 4. Mean of plasma concentration–time curves for etophylline after administration of etophylline (150 mg/kg i.v. infusion over 5 min) in 6 rabbits. (Error bars represent the range and not S.D.)

Etophylline β and $t_{1/2}$ when administering aminophylline followed by both a loading dose and maintenance dose of etophylline are shown in Table 2B (Fig. 2). The β elimination values for etophylline were determined by regression of post-infusion data which are shown in Fig. 2. Only 2 of 6 rabbits reached steady-state when all received the same loading dose (150 mg/kg) and maintenance dose (30 mg/kg/h for 2 h). This indicates a high variation in elimination rate which was also reported in humans (Zuidema et al., 1981b). Overall, analysis of variance and Kruskal-Wallis test showed that differences in $t_{1/2}$ among treatments are not significant.

Non-compartmental method of pharmacokinetic analysis

Data were also analyzed by non-compartment analysis using Statistical Moment Theory. Area under the concentration–time curve (AUC_∞) and area under the moment curve ($AUMC_\infty$) were estimated by linear trapezoid for the portion up to the peak and log trapezoidal equation for all fall-off curve portions (Riegelman and Collier, 1980). All parameters were corrected for infusion time and multiple modes of administration for etophylline in Treatment 3 (Chan and Gibaldi, 1982; Gibaldi and Perrier, 1981; Perrier and Mayersohn, 1982).

Analysis of variance and the Kruskal-Wallis test showed no statistically significant difference ($P \leq 0.05$) in MRT_b, $V_{d_{ss}}$ and Cl. In one case where one subject received two treatments with theophylline, β was essentially the same when the rabbit received aminophylline followed by etophylline (0.136 h^{-1}), compared to when aminophylline was given alone (0.143 h^{-1}). Thus, the elimination half-life differed by only about 5.5% (5.1 h vs 4.8 h) and MRT differed by about 9% (6.48 h vs 5.90 h). However, in this one rabbit the total volume of distribution, V_{d_β} was increased about 2.5 times (0.78 l/kg vs 0.32 l/kg) and $V_{d_{ss}}$ increased about 3 times (1.79 l/kg vs 0.60 l/kg) more than for theophylline given alone.

For two individual rabbits that received two

TABLE 2A:

PHARMACOKINETIC PARAMETERS FOR THEOPHYLLINE AFTER ADMINISTERING AMINOPHYLLINE (40 mg/kg INTRAVENOUSLY OVER 30 min) FOLLOWED BY ETOPHYLLINE (150 mg/kg INTRAVENOUSLY OVER 5 min AND 30 mg/kg/h MAINTENANCE DOSE BY INTRAVENOUS INFUSION OVER 2 h) IN RABBITS

Compartmental		Non-compartmental	
Two-compartment open model (n = 6)		*(n = 6)*	
β (h^{-1})	0.14 ± 0.06	$1/MRT_b$ (h^{-1})	0.16 ± 0.09
α (h^{-1})	0.35 ± 0.12		
V_{d_β} (l/kg)	0.56 ± 0.19	$V_{d_{ss}}$ (l/kg)	0.46 ± 0.15
Cl (l/kg/h)	0.08 ± 0.03	Cl (l/kg/h)	0.07 ± 0.03
$t_{1/2}$ (h)	4.8	MRT_b (h)	8.83 ± 6.99

TABLE 2B:

PHARMACOKINETIC PARAMETERS FOR ETOPHYLLINE AFTER ADMINISTERING AMINOPHYLLINE (40 mg/kg INTRAVENOUSLY OVER 30 min) FOLLOWED BY ETOPHYLLINE (150 mg/kg LOADING DOSE INTRAVENOUSLY OVER 5 min AND 30 mg/kg/h MAINTENANCE DOSE BY INTRAVENOUS INFUSION OVER 2 h) IN RABBITS

Compartmental		Non-compartmental	
The post-infusion data fitted by one-compartment open model (n = 6)		*(n = 6)*	
β (h^{-1})	0.32 ± 0.12	$1/MRT_b$ (h^{-1})	0.35 ± 0.09
		$V_{d_{ss}}$ (l/kg)	0.94 ± 0.47
		Cl (l/kg/h)	0.43 ± 0.21
$t_{1/2}$ (h)	2.2	MRT_b (h)	2.47 ± 0.99

treatments with etophylline, the half-life and MRT were slightly longer when etophylline followed by aminophylline was administered vs etophylline administered alone. This effect occurred for both subjects, one which was described by a triexponential equation ($t_{1/2}$ of 2.6 h vs 2.2 h and MRT of 2.78 h vs 2.50 h) and another subject described by a biexponential equation ($t_{1/2}$ of 2.2 vs 1.4 h and MRT of 2.33 h vs 0.99 h). Etophylline clearance was reduced by 21% (0.34 vs 0.43 l/kg/h) and 12.8% (0.34 vs 0.39 l/kg/h) respectively when etophylline followed by aminophylline was administered as compared to that of etophylline when administered alone.

This effect may be caused by competition for the same enzyme in a metabolic pathway since both drugs are extensively biotransformed (Zuidema et al., 1981b). Overall grouped animal data show no differences in β, $t_{1/2}$, V_{d_β}, $V_{d_{ss}}$, MRT_b or Cl. Therefore, on the average, theophylline had no effect on etophylline pharmacokinetic behavior when administered concomitantly with etophylline. For the two individuals which received cross-over treatments, theophylline appeared to increase etophyllines' $t_{1/2}$ by 18–50% which may be a real effect, but may also be only a result of intrasubject variation.

TABLE 3A:

PHARMACOKINETIC PARAMETERS FOR ETOPHYLLINE AFTER ADMINISTERING ETOPHYLLINE (150 mg/kg INTRAVENOUSLY OVER 5 min) FOLLOWED BY AMINOPHYLLINE (40 mg/kg INTRAVENOUS INFUSION OVER 30 min) IN RABBITS

Compartmental				Non-compartmental	
Two-compartment open model (n = 4)		*Three-compartment open model (n = 2)*		*(n = 6)*	
β (h^{-1})	0.35 ± 0.03	β (h^{-1})	0.21 ± 0.09	$1/MRT_b$ (h^{-1})	0.35 ± 0.09
α (h^{-1})	8.27 ± 2.68	α (h^{-1})	0.97 ± 0.49		
		γ (h^{-1})	14.89 ± 0.99		
V_{d_β} (l/kg)	1.33 ± 0.20	V_{d_β} (l/kg)	1.34 ± 0.19	$V_{d_{ss}}$ (l/kg)	1.03 ± 0.19
Cl (l/kg/h)	0.64 ± 0.47	Cl (l/kg/h)	0.27 ± 0.08	Cl (l/kg/h)	0.36 ± 0.12
$t_{1/2}$ (h)	1.96	$t_{1/2}$ (h)	3.65	MRT_b (h)	3.08 ± 1.10

TABLE 3B:

PHARMACOKINETIC PARAMETERS FOR THEOPHYLLINE AFTER ADMINISTERING ETOPHYLLINE (150 mg/kg INTRAVENOUSLY OVER 5 min) FOLLOWED BY AMINOPHYLLINE (40 mg/kg INTRAVENOUS INFUSION OVER 30 min) IN RABBITS

Compartmental		Non-compartmental	
Two-compartment open model (n = 6)		*(n = 6)*	
β (h^{-1})	0.12 ± 0.04	$1/MRT_b$ (h^{-1})	0.12 ± 0.04
α (h^{-1})	3.28 ± 2.30		
V_{d_β} (l/kg)	0.70 ± 0.06	$V_{d_{ss}}$ (l/kg)	0.62 ± 0.13
Cl (l/kg/h)	0.08 ± 0.03	Cl (l/kg/h)	0.08 ± 0.02
$t_{1/2}$ (h)	5.8	MRT_b (h)	8.65 ± 2.24

Clearance values obtained were essentially the same (Tables 1–4) for the two pharmacokinetic methods employed in this study and overall grouped data showed no differences in any pharmacokinetic parameters. It should be noted that Chanter has reported that an absolute error of up to 100% may occur in calculating MRT_b for data obtained for two-compartment open pharmacokinetic models (Chanter, 1985). Further research is needed in this area and relative MRT_b values are useful for comparison.

Rabbits became 'jumpy' and exhibited some minor muscular fasciculations at plasma theophylline concentrations of about 100 μg/ml. Death preceded by a generalized convulsion occurs at about 250–400 μg/ml of theophylline in plasma for rabbits as observed in our laboratory. No side-effects were observed for etophylline even at plasma concentrations as high as 700 μg/ml. It is remarkable that no drug toxicities were observed with concomitant aminophylline (theophylline plasma concentrations of 50–100 μg/ml) and etophylline bolus injection plus infusion (Fig. 2b) plasma concentrations maintained for 2 h at 100–300 μg/ml. Total plasma methyl xanthine concentrations were up to 400 μg/ml without apparent synergistic toxicities.

References

Angel, J.E., Physician's Desk Reference, Medical Economics, Oradell NJ, 1984, p. 1822.

Chan, K.K.H. and Gibaldi, M., Estimation of statistical moments and steady state volume of distribution for a drug given by intravenous infusion. J. Pharmakin. Biopharm., 10 (1982) 551–558.

Chanter, D.O., The determination of mean residence time using statistical moments: is it correct? J. Pharmakin. Biopharm., 13 (1985) 93–100.

El-Yazigi, A. and Sawchuk, R.J., Theophylline absorption and disposition in rabbits: oral, intravenous and concentration-dependent kinetic studies. J. Pharm. Sci., 70 (1981) 452–455.

Gibaldi, M. and Perrier, D., Pharmacokinetics, 2nd Edn., Mercel Dekker, New York, 1982, pp. 409–417.

Jauch, R. and Zimmer, A., Human Pharmacokinetic von

TABLE 4

PHARMACOKINETIC PARAMETERS FOR ETOPHYLLINE AFTER ADMINISTERING ETOPHYLLINE (150 mg/kg) INTRAVENOUSLY OVER 5 min) IN RABBITS

Compartmental				Non-compartmental	
Two-compartment open model (n = 3)		*Three-compartment open model (n = 3)*		*(n = 6)*	
β (h^{-1})	0.41 ± 0.09	β (h^{-1})	0.39 ± 0.13	$1/MRT_b$ (h^{-1})	0.59 ± 0.24
α (h^{-1})	4.72 ± 1.57	α (h^{-1})	1.68 ± 0.87		
		γ (h^{-1})	19.99 ± 6.78		
V_{d_β} (l/kg)	1.14 ± 0.31	V_{d_β} (l/kg)	1.03 ± 0.34	$V_{d_{ss}}$ (l/kg)	0.71 ± 0.30
Cl (l/kg/h)	0.37 ± 0.12	Cl (l/kg/h)	0.39 ± 0.08	Cl (l/kg/h)	0.37 ± 0.08
$t_{1/2}$ (h)	1.7	$t_{1/2}$ (h)	1.8	MRT_b (h)	1.94 ± 0.70

Oxyethyltheophyllin und Fominoben-HCl. Arzneim. Forsch., 28 (1978) 693–697.

Loo, J.C.K. and Riegelman, S., Assessment of pharmacokinetic constants for postinfusion blood curves obtainded after i.v. infusion. J. Pharm. Sci., 59 (1970) 53–55.

Merkus, F.W.H.M. and Zuidema, J., Theophylline and hydroxethyltheophylline are different drugs. Int. J. Clin. Pharmacol. 18 (1980) 97.

McColl, J.D. Parker, J.M. and Ferguson, J.K.W., A comparison of a series of methylated xanthine derivatives. N. Engl. J. Med., 116 (1955) 343–350.

Mitenko, P.A. and Ogilvie, R.I., Bioavailability and efficiency of a sustained-release the theophylline tablet. Clin. Pharmacol. Ther., 16 (1974) 720–726.

Mitenko, P.A. and Ogilvie, R.I., Rational intravenous doses of theophylline. N. Engl. J. Med., 289 (1973) 600–603.

Ng, P.K. and Locock, R.A., Comparative pharmacokinetics of theophylline and dyphylline following intravenous injection in rabbits. Res. Commun., 26 (1979) 509–524.

Perrier, D. and Mayersohn, M., Noncompartmental determination of the steady-state volume of distribution for any mode of administration. J. Pharm. Sci., 71 (1982) 372–373.

Reynolds, E.F. and Martindale, The Extra Pharmacopoeia, N.W. Blacow (Ed.), 27th edn., The Pharmaceutical Press, London, U.K., 1982, p. 342.

Riegelman S. and Collier, P., The application of statistical moment theory to the evaluation of in vivo dissolution time and absorption time. J. Pharmacokin. Biopharm., 8 (1980) 509–534.

Sharma, P.L. and Sharma, R.M., Comparative bioavailability of sustained-release and conventional tablets of hydroxyethyltheophylline in man. Int. J. Clin. Pharmacol., 17 (1979) 394–396.

Ufkes, J.G.R., Leeuwin, R.S., Ottenhof, M., Zeegers, A. and Zuidema, A., Efficacy of theophylline and its N-7-substituted derivatives in experimentally induced bronchial asthma in the guinea-pig. Arch. Int. Pharmacodyn., 253 (1981) 301–314.

Zuidema, J. and Merkus, F.W.H.M., Clinical and biopharmaceutical aspects of theophylline and its derivatives. Curr. Med. Res. Opin., 6, Suppl. (1979) 14.

Zuidema, J. and Merkus, F.W.H.M., Pharmacokinetics and Pharmacodynamics of Diprophylline. Pharm. Weekbl., Sci. Ed., 3 (1981) 1320–1325.

Zuidema, J., Verhoeven, J. and Merkus, F.W.H.M., Pharmacokinetics of etophylline after intravenous and oral administration to humans. Int. J. Clin. Pharmacol., 19 (1981) 310–313.