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Proxyphylline and theophylline pharmacokinetics when administered concomitantly in rabbits

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Summary

Proxyphylline and theophylline (aminophylline) were administered intravenously alone and concomitantly to rabbits. Both model-dependent and model-independent pharmacokinetic analyses were conducted. Analysis of variance and the Kruskal–Wallis test showed that differences among slopes for the terminal elimination phase (β or γ as appropriate) and Vd_{area} for proxyphylline or for theophylline in the different treatments were not statistically significant at $\alpha = 0.05$. No apparent toxicities were observed even for concomitant plasma concentrations of total xanthines of about 1000 μg/ml.

Introduction

Proxyphylline is an *N*-7-substituted theophylline derivative (β-hydroxypropyltheophylline) which was introduced in 1956 (Zuidema and Merkus, 1979). It is an effective bronchospasmolytic agent (Ufkes et al., 1981) which has been used outside the United States in the treatment of asthma and obstructive lung disease (Selvig and Bjerve, 1977).

Proxyphylline products are available in many different pharmaceutical preparations such as injectable solutions, tablets, slow-release tablets and suppositories. Commercial preparations also contain proxyphylline in combination with other xanthines such as dyphylline or dyphylline and theophylline (Unlisted Drugs, 1976; Unlisted Drugs 1979). The potency of proxyphylline was reported to be 0.2 and 0.6 that of theophylline in relaxing guinea pig trachea (Ufkes et al., 1981; Boardman, 1980). In humans, proxyphylline was reported to be 5 and 7 times less potent than theophylline (Svedmyr et al., 1977; Zuidema and Merkus, 1979) although it produces clinically noticeable reversion of airway obstruction at concentrations of about 18 μg/ml (Tivenius, 1971).

Proxyphylline is excreted 21–29% unchanged in the urine and the rest is metabolized but theophylline was not one of its metabolites (Selvig and Bjerve, 1980). Proxyphylline pharmacokinetics in man were studied and half-lives were reported to be 4.3 (Ritschel and Banarer, 1973), 6.5 (Graffner et al., 1973), 7.3 (Selvig, 1982) and 8.8 h (Selvig, 1981). The volume of distribution was reported to

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be 0.57 and 0.6 liter/kg (Graffner et al., 1973; Selvig, 1982).

Because of known toxic properties of theophylline, proxyphylline may be more useful than theophylline and theophylline salts in emergency cases in countries where proxyphylline is used. Proxyphylline could replace aminophylline for intravenous administration if it is safe and effective when given as an intravenous bolus to outpatients who may have been taking theophylline preparations. This study was undertaken to investigate the pharmacokinetic behavior and gross toxicity of theophylline and proxyphylline when given alone and concomitantly in rabbits.

Materials and Methods

Female New Zealand white rabbits weighing 1.9–3.5 kg were used in this study. Six rabbits were used in each treatment except for Treatment 2, where 7 rabbits were used. Proxyphylline [1] was dissolved in D-5-W [2] (dextrose 5% in water) and filtered [3] (2 μm) and diluted with D-5-W when used. Aminophylline [4] was also diluted to the desired concentration with D-5-W. Materials and methods for preparation of rabbits, blood sample collection, sample storage, and analytical methods were the same as previously described (Tavipatana and Ayres, 1986).

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 i.v. infusion at the rate of 0.21 ml/min over 30 min.

Treatment 2: 135 mg/kg of proxyphylline (100 mg/ml) was administered by i.v. infusion at the rate of 1.02 ml/min over 3–5 min.

Treatment 3: 40 mg/kg of aminophylline in 6.3 ml of solution was administered by i.v. infusion at the rate of 0.21 ml/min over 30 min, then 30 min after stopping aminophylline, 135 mg/kg of proxyphylline (100 mg/ml) was administered by i.v. infusion at the rate of 1.02 ml/min over 3–5 min, followed by a maintenance dose of 15 mg/kg/h of proxyphylline which was administered at the rate of 0.23 ml/min over 2 h.

Treatment 4: 135 mg/kg of proxyphylline (100 mg/ml) was administered by i.v. infusion at the rate of 1.02 ml/min over 3–5 min, then 30 min after stopping proxyphylline, 40 mg/kg of aminophylline in 6.3 ml solution was administered by i.v. infusion at the rate of 0.21 ml/min over 30 min.

Pharmacokinetic analysis

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 (Sedman and Wagner, 1976) and NONLIN (Metzler et al., 1974). The best-fitted models by AUTOAN2 were chosen, except for proxyphylline when administering proxyphylline in the presence of aminophylline (Treatment 3). For this treatment, the terminal slopes of postinfusion data of proxyphylline were obtained from linear regression of natural log of concentration vs time. Estimates obtained from AUTOAN2 and NONLIN were used to calculate pharmacokinetic parameters [Vd_{area} = clearance/slope of terminal elimination phase; *clearance* = (volume of central compartment) × (elimination rate constant for central compartment) as obtained from computer fits to data]. 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_∞) and area under the moment curve ($AUMC_\infty$) calculated by the linear trapezoidal equation for data up to the peak and log trapezoidal equation for all log linear decay por-

[1] Proxyphylline, β-hydroxypropyltheophylline. Sigma Chemicals Company, St. Louis, MO, U.S.A.

[2] Dextrose 5% in water, Abbott Laboratories, North Chicago, IL, U.S.A.

[3] Acrodisc, Disposable Filter Assembly, Gelman, Ann Arbor, MI, U.S.A.

[4] Aminophylline injection USP 250 mg (25 mg/ml), Abbott Laboratories, North Chicago, IL, U.S.A.

[5] β-hydroxyethyltheophylline, Sigma Chemicals Company, St. Louis, MO, U.S.A.

tions (Riegelman and Collier, 1980; Gibaldi and Perrier, 1981). All parameters were corrected for infusion time (Perrier and Mayersohn, 1982). Parameters for proxyphylline when administering proxyphylline 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.). Relationships used were: MRT_b corrected for infusion = $(AUMC_\infty/AUC_\infty) - T/2$; MRT_b corrected for multiple dosing is = $AUMC_\infty/AUC_\infty - \Sigma\int_0^x x\ dT/\Sigma dose$; $Cl = dose/AUC_\infty$; $Vd_{ss} = (MRT_b) \times (Cl)$. Mean values presented are the means of values for individuals and not calculated from means for the groups. That is, Vd_{ss} in the tables is the mean of individual Vd_{ss} which readily allows calculation of a S.D. Note that the product of means for small samples is usually not the mean of products so the Vd_{ss} in the tables cannot be obtained by multiplying the tabled MRT_b by Cl.

Results and Discussion

Model-dependent pharmacokinetic analysis

Average plasma concentrations of theophylline and proxyphylline vs. time curves for 6 rabbits after administration of aminophylline followed by proxyphylline (Treatment 3) or proxyphylline followed by aminophylline (Treatment 4) are shown in Figs. 1 and 2, respectively. Theophylline pharmacokinetic parameters after these treatments are shown in Tables 1 and 2. Theophylline data in 5 of 6 rabbits for Treatment 3 were best described (Table 1) by a two-compartment open model with a mean $t_{1/2}$ of 5.46 h and mean Vd_{area} of 0.82 liter/kg. Theophylline in the other rabbit was best described by a one-compartment open model (Table 1) as determined by AUTOAN2 (Sedman and Wagner, 1976), and had a half-life of 3.89 h and a Vd_{area} of 0.62 liter/kg.

Theophylline pharmacokinetic parameters after administration of proxyphylline followed by aminophylline (Treatment 4, Fig. 2) are shown in Table 2. Data were best described in 3 rabbits each by a one-compartment open model or a two-compartment open model, with mean half-

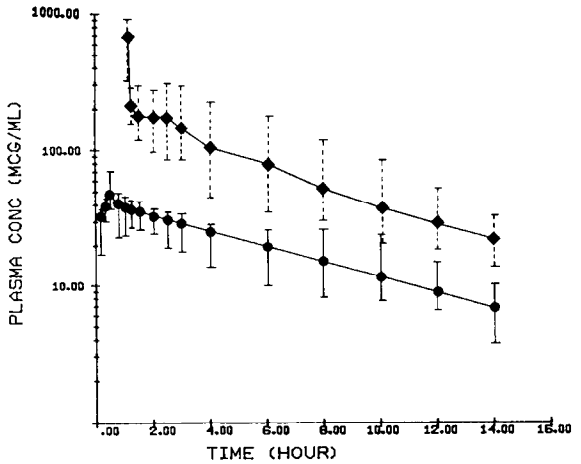

Fig. 1. Plasma concentration–time curves for theophylline (●) and proxyphylline (◆) after administration of aminophylline (40 mg/kg i.v. infusion over 30 min) followed by proxyphylline loading dose (135 mg/kg i.v. infusion over 5 min) and proxyphylline maintenance dose (15 mg/kg/h i.v. infusion over 2 h) in 6 rabbits. (Error bars represent the range and not S.D.).

lives of 4.47 and 4.42 h and Vd_{area} of 0.39 and 0.70 liter/kg, respectively.

Theophylline pharmacokinetic parameters after administration of aminophylline alone have been previously reported (Ng and Locock, 1979; Tavipatana and Ayres, 1986). Plasma drug data were

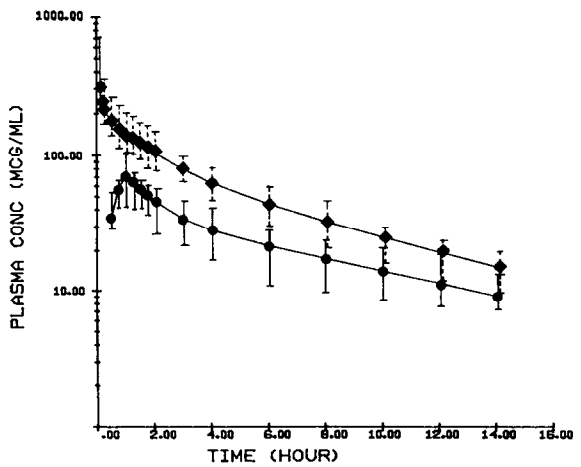

Fig. 2. Plasma concentration–time curves for proxyphylline (◆) and theophylline (●) after administration of proxyphylline (135 mg/kg i.v. infusion over 5 min) followed by aminophylline (40 mg/kg i.v. infusion over 30 min) in 6 rabbits. (Error bars represent the range and not S.D.).

TABLE 1

Pharmacokinetic parameters for theophylline after administering aminophylline (40 mg/kg i.v. over 30 min) followed by proxyphylline (135 mg/kg loading dose i.v. over 5 min and 15 mg/kg/h maintenance dose by i.v. infusion over 2 h) in rabbits

Compartmental				Non-compartmental ($n = 6$)	
One-compartment open model ($n = 1$)		Two-compartment open model ($n = 5$)			
kel (h^{-1})	0.18	β (h^{-1})	0.13 ± 0.02	$1/MRT_b$ (n^{-1})	0.15 ± 0.04
		α (h^{-1})	9.53 ± 9.02		
Vd_{area} (liter/kg)	0.62	Vd_{area} (liter/kg)	0.82 ± 0.19	Vd_{ss} (liter/kg)	0.74 ± 0.22
Cl (liter/kg/h)	0.11	*Cl* (liter/kg/h)	0.10 ± 0.04	*Cl* (liter/kg/h)	0.11 ± 0.03
$t_{1/2}$ (h)	3.89	$t_{1/2}$ (h)	5.46	MRT_b (h)	7.28 ± 2.19

well described by a two-compartment open model with a mean half-life of 5.5 or 5.2 h and Vd_{area} of 0.55 or 0.71 liter/kg, respectively. Thus, proxyphylline administration prior to aminophylline (Treatment 4) did not significantly affect average Vd_{area} or $t_{1/2}$. Prior presence of proxyphylline in the tissues may have changed theophylline distribution characteristics somewhat to induce more one compartment behavior in some rabbits (Table 2). However, analysis of variance and Kruskall–Wallis test showed that differences in Vd_{area}, terminal slopes, and clearance among the treatments are not statistically significant. Data for Treatment 3 (Fig. 1), Treatment 4 (Fig. 2), and Treatment 1 (Tavipatana and Ayres, 1986) are essentially superimposable. Therefore, one must conclude that proxyphylline had no significant effect on theophylline pharmacokinetic behavior when administering proxyphylline concomitantly with aminophylline under the conditions studied herein.

Proxyphylline plasma concentration time curves for 7 rabbits after administration of proxyphylline alone are shown in Fig. 3. Data were well described by a two-compartment open model for 3 rabbits and a three-compartment open model for 4 rabbits as determined by AUTOAN2, depending on the subjects as shown in Table 4, with mean half-lives of 2.85 and 4.61 h and mean Vd_{area} of 0.98 and 1.49 liter/kg respectively. Proxyphylline pharmacokinetic parameters when followed by aminophylline (Treatment 4, Table 3, Fig. 2) were also described by either a two-compartment open model or a three-compartment open model with mean half-lives of 3.86 and 5.63 h and mean Vd_{area} of 1.15 and 1.66 liter/kg.

The terminal elimination slope for proxyphylline and $T_{1/2}$ values when administering aminophylline followed by a loading dose and maintenance dose of proxyphylline (Treatment 3, Fig. 1) are shown in Table 5. The elimination slope values for proxyphylline were determined by

TABLE 2

Pharmacokinetic parameters for theophylline after administering proxyphylline (135 mg/kg i.v. over 5 min) followed by aminophylline (40 mg/kg i.v. infusion over 30 min) in 6 rabbits

For units see Table 1.

Compartmental				Non-compartmental ($n = 6$)	
One-compartment open model ($n = 3$)		Two-compartment open model ($n = 3$)			
kel	0.15 ± 0.03	β	0.16 ± 0.05	$1/MRT_b$	0.19 ± 0.06
		α	6.73 ± 8.14		
Vd_{area}	0.39 ± 0.14	Vd_{area}	0.70 ± 0.40	Vd_{ss}	0.49 ± 0.06
Cl	0.06 ± 0.03	*Cl*	0.10 ± 0.02	*Cl*	0.10 ± 0.03
$t_{1/2}$	4.47	$t_{1/2}$	4.42	MRt_b	5.59 ± 1.61

TABLE 3

Pharmacokinetic parameters for proxyphylline after administering proxyphylline (135 mg/kg i.v. over 5 min) followed by aminophylline (40 mg/kg loading dose i.v. infusion over 30 min) in 6 rabbits

For units see Table 1; γ is in h^{-1}

Compartmental				Non-compartmental ($n = 6$)	
Two-compartment open model ($n = 3$)		Three-compartment open model ($n = 3$)			
β	0.18 ± 0.05	γ	0.12 ± 0.05	$1/MRT_b$	0.17 ± 0.05
α	4.92 ± 4.02	β	0.57 ± 0.12		
		α	13.25 ± 3.98		
Vd_{area}	1.15 ± 0.11	Vd_{area}	1.66 ± 0.57	Vd_{ss}	1.06 ± 0.58
Cl	0.20 ± 0.04	Cl	0.19 ± 0.05	Cl	0.20 ± 0.04
$t_{1/2}$	3.86	$t_{1/2}$	5.63	MRt_b	6.30 ± 2.13

TABLE 4

Pharmacokinetic parameters for proxyphylline after administering proxyphylline (135 mg/kg i.v. over 5 min) in 7 rabbits

For units see Table 1; γ in h^{-1}.

Compartmental				Non-compartmental ($n = 7$)	
Two-compartment open model ($n = 3$)		Three-compartment open model ($n = 4$)			
β	0.24 ± 0.05	γ	0.15 ± 0.06	$1/MRT$	0.22 ± 0.07
α	9.54 ± 5.77	β	0.68 ± 0.41		
		α	16.25 ± 1.59		
Vd_{area}	0.98 ± 0.13	Vd_{area}	1.49 ± 0.51	Vd_{ss}	1.05 ± 0.20
Cl	0.24 ± 0.04	Cl	0.21 ± 0.06	Cl	0.23 ± 0.06
$t_{1/2}$	2.85	$t_{1/2}$	4.61	MRT_b	4.91 ± 1.59

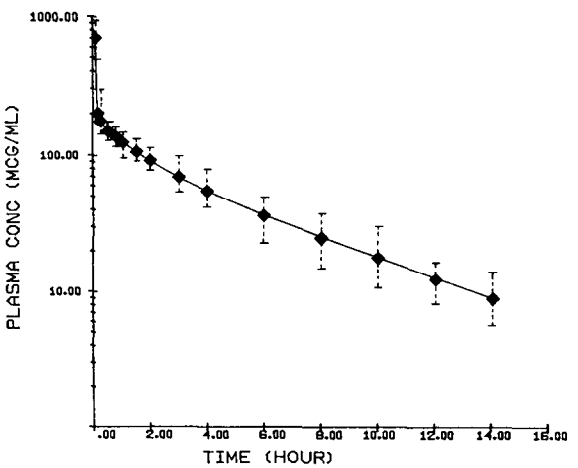

Fig. 3. Plasma concentration–time curves for proxyphylline after administration of proxyphylline (135 mg/kg i.v. infusion over 5 min) in 7 rabbits. (Error bars represent the range and not S.D.).

regression of log concentration of infusion data on time. Proxyphylline plasma concentration time data in Figs. 1–3 are superimposable and very similar to post-infusion data, Table 5.

Non-compartmental method of pharmacokinetic analysis

Analysis of variance and the Kruskal–Wallis test showed no statistically significant difference ($P \leq 0.05$) in average MRT_b, Vd_{ss} and Cl. For two individual rabbits (Treatments 1 and 3) that received cross-over treatments, there were some differences. Theophylline MRT_b increased by 7% (6.9 h vs. 7.3 h) and Vd_{ss} increased by 53% (0.76 liter/kg vs. 1.16 liter/kg) in one rabbit and theophylline MRT_b increased by 77% (6.4 h vs. 11.3 h) and Vd_{ss} increased by 31% (0.5 liter/kg vs. 0.7 liter/kg) in the other rabbit when they received

TABLE 5

Pharmacokinetic parameters for proxyphylline after administering aminophylline (40 mg/kg i.v. over 30 min) followed by proxyphylline (135 mg/kg loading dose i.v. over 5 min and 15 mg/kg/h maintenance dose by i.v. infusion over 2 h) in rabbits

For units, see Table 1; terminal elimination slope (Slope) of log concentration vs time data is in h^{-1}.

Compartmental; post-infusion data fitted by linear regression ($n = 6$)		Non-compartmental ($n = 6$)	
Slope	0.20 ± 0.02	$1/MRT_b$	0.21 ± 0.02
		Vd_{ss}	0.89 ± 0.49
		Cl	0.18 ± 0.11
$t_{1/2}$	3.41	MRT_b	4.93 ± 0.60

aminophylline alone vs aminophylline followed by proxyphylline. For two other individual rabbits that received treatments 2 and 4 (proxyphylline alone and proxyphylline followed by theophylline), the proxyphylline MRT_b and Vd_{ss} increased by 32% and 25%, respectively (4.7 h vs. 6.2 h; 1.2 liter/kg vs 1.5 liter/kg) for one rabbit and increased 135% (3.4 h vs 8 h) and 18% (1.1 liter/kg vs 1.3 liter/kg) respectively, for the other rabbit. From these observations one may suggest that administration of a second methylxanthine seems to increase the volume of distribution and residence time of the methylxanthine already in the body for proxyphylline and theophylline. However, the study was not conducted as a cross-over design and overall there were no statistically significant differences. The lack of statistical sensitivity in this non-cross-over study may result from high intersubject variation. One must conclude that concomitant theophylline did not significantly influence the pharmacokinetics of proxyphylline, just as concomitant proxyphylline did not have statistically significant effects on theophylline pharmacokinetics in this study.

Total xanthine plasma concentrations of theophylline plus proxyphylline reached about 1000 μg/ml (Figs. 1 and 2) but no toxicities were observed. Thus, bolus intravenous proxyphylline can be administered even if a full therapeutic "load" of theophylline is present without expected additive toxicity in rabbits. Further work is needed with greater populations and a complete cross-over design in humans to know if similar administration of proxyphylline would be safe for people.

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