Interspecies Scaling of Cimetidine–Theophylline Pharmacokinetic Interaction: Interspecies Scaling in Pharmacokinetic Interactions

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The aim of the present study was the use of an interspecies scaling approach to predict drug interactions during preclinical drug disposition studies. Theophylline and cimetidine were selected because of their documented interaction. The literature was searched for pharmacokinetic data of intravenously administered theophylline alone and in the presence of cimetidine in humans, dogs and rats. Further, we determined the theophylline-cimetidine drug interaction in rabbits. Application of allometric equations to the pharmacokinetic parameters and the conversion of chronological time into pharmacokinetic time allowed us to obtain the complex Dedrick plot for theophylline when administered alone or in combination with cimetidine. A superimposable kinetic profile was obtained for the plasma levels of theophylline in all species studied, both with and without cimetidine. From the terminal phase of the curves it is possible to calculate the elimination half-life: 2.69 apolisychrons for theophylline when it is administered alone and 3.86 apolisychrons when it is administered in combination with cimetidine. This 43% increase in $t_{1/2}$ is similar to the increase in the elimination half-life of theophylline in humans when it is administered after pretreatment with cimetidine. These results show that an interspecies scaling approach may be useful to predict the effect of interactions in humans from the results obtained in preclinical research with new drugs.

KEY WORDS: interspecies scaling; drug interactions; theophylline; cimetidine.

INTRODUCTION

The intensity and duration of the pharmacologic effect of a systematically acting drug are functions not only of the intrinsic activity of the drug, but also of its disposition characteristics. Knowledge of the pharmacologically efficacious systemic concentration in animal models can be utilized to guide studies in humans. The actual form of drug disposition, however, may differ among species because of the qualitative and quantitative differences in the metabolism of a drug among those species. When interspecies variation in pharmacokinetic parameters prevents extrapolation of animal disposition data to man, human pharmacokinetic characteristics can be estimated by interspecies scaling (1).

Interspecies scaling is a method of interpolation and extrapolation based on the underlying anatomical, physiological and biochemical similarities in mammals (2). It allows one to extrapolate animal data to human beings under many experimental conditions. When interspecies scaling concepts are incorporated into the experimental design and the data analysis of preclinical studies, we can expect to 1) produce more clinically meaningful data from animal experiments; 2) predict the activity, efficacy and toxicity of pharmaceutical compounds in human beings with greater accuracy; 3) decrease the number of animals required for experimentation and 4) accelerate the drug testing and approval process.

The effect of a drug may be modified as a consequence of drug interactions when administered in multiple therapy which can lead to a variation of the efficacy and/or toxicity of the drug therapy. In clinical trials preceding the introduction of a new drug, little information is available about possible drug interactions. Most drug interactions are discovered after the drug has been marketed and administered to a large number of people. Therefore, it might be valuable to incorporate an interspecies scaling approach to the prediction of clinically relevant drug interactions.

Changes in the pharmacokinetic behavior of theophylline caused by cimetidine have been studied in several animals species (3,4). Thus, the main goal of the present paper is to apply an interspecies scaling methodology to those cases where a metabolic inhibition phenomenon occurs. Our aim was to demonstrate the validity of an interspecies scaling method in the prediction of clinically relevant metabolic interactions.

MATERIAL AND METHODS

Data Acquisition

Data acquisition consisted of searching the literature for papers describing the pharmacokinetics of intravenously administered theophylline along (to avoid pharmacokinetic modifications due to absorption processes) and coadministered with cimetidine, at the lowest possible dose (to avoid problems due to nonlinear kinetics). The dose of the theophylline inhibitor (cimetidine) must be equivalent in all species. We found data from rats (5), dogs (6) and humans (7). In order to increase our prediction capabilities, the effect of cimetidine on pharmacokinetics of theophylline was also carried out in rabbits.

Pharmacokinetic Studies on Rabbits

Chemicals

Theophylline, β-hydroxyethyltheophylline and cimetidine were purchased as pure powder from SIGMA (Madrid, Spain). Aminophylline (EUFILINE®) was obtained from ELMU Laboratories S.A. (Madrid, Spain). $ZnSO_4$, sodium acetate and acetic acid were analytical grade and were purchased from MERCK (Barcelona, Spain). HPLC grade methanol was supplied by CARLO ERBA (Barcelona, Spain).

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Assay Procedure

Five New Zealand male rabbits obtained from the University of Salamanca Animal Unit, weighing 2.67 ± 1.30 (SD) Kg were used for this study. Animal rooms had controlled temperature (20°C), humidity (60%) and light cycle (12/12h). Animals were fed "ad libitum" until the night before each experiment, when they were deprived of food but not water. The animals received two different treatments in random order with a minimum of 7 days elapsed between treatments: 1) theophylline alone (as Aminophylline, 12 mg/Kg); 2) theophylline (as Aminophylline, 12 mg/Kg) following pretreatment with cimetidine (50 mg/Kg, twice daily for 3 days) by oral route.Theophylline was administered through one of the marginal ear veins. Blood samples were collected from a vein on the non-injected ear in heparinized tubes at various times (0.08, 0.16, 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 4.00, 6.00, 9.00 and 12.00 hours). After centrifugation, plasma was immediately frozen and kept at −20°C until analysis. Theophylline concentrations in plasma were determined by a technique of reversed-phase high performance liquid chromatography developed in our laboratory (8).

Pharmacokinetic Analysis of Theophylline

Complete pharmacokinetic evaluation of the plasma concentration-time data was done by compartment model independent analysis and the pharmacokinetic parameters were calculated from conventional equations (9) using the PKCALC (10) program. The theophylline elimination rate constant (Ke) was determined as the absolute value of the least squares estimate of the slope of a log-linear plot of plasma concentrations versus time using all data points in the elimination phase. The mean disposition residence time (MRT) and the volume of distribution at steady-state (Vd) were calculated according to Yamaoka (11) and Benet and Galeazzi (12), respectively. Significant differences between the log-transformed values of the pharmacokinetic parameters of theophylline when administered alone and in combination with cimetidine were determined by using a one-way analysis of variance (13). $p<0.05$ was considered significant.

Since the main route of theophylline elimination in humans and animals is by hepatic metabolism, we assume, like Gaspari and Bonati (14) that the body clearance (Cl) is almost equivalent to the metabolic clearance and to hepatic clearance (Cl_h). Therefore, utilizing the well-stirred hepatic disposition model for theophylline (15), and taking into account that the blood/plasma ratio is close to unity (16) the following equation was used to calculate the total intrinsic clearance (Clu_{int}) (17):

$$Clu_{int} = Q \times Cl_h/[fu \times (Q - Cl_h)] \quad \text{(eq 1)}$$

where fu is the fraction of unbound drug which was assumed for all species to be similar to the value reported for man (14), and Q is the liver blood flow calculated from the allometric relationship proposed by Boxenbaum (18):

$$Q = 0.0554 \times B^{0.894} \quad \text{(eq 2)}$$

where B is the body weight.

The maximum potential lifespan (MPL), parameter that allows to relate brain weight and the biotransformation rate of drugs, was calculated by means of the following allometric equation (19):

$$MPL = 10.389 \times (\text{brain weight})^{0.636} \times B^{-0.225} \quad \text{(eq 3)}$$

Allometric Adjustment

Allometric adjustment and interspecies scaling have been performed according to the procedure previously reported by Boxenbaum (20) and Mordenti (2). Interspecies relationship between pharmacokinetic parameters and body weight were analysed plotting data on a log-log scale and the best fits were obtained by the least squares method. The pharmacokinetic parameters analysed were: volume of distribution, half-life, hepatic clearance, intrinsic clearance and intrinsic clearance corrected in terms of the maximum potential lifespan. The overlapping of the evolution of the theophylline plasma levels, when administered alone or in the presence of cimetidine in the different species studied, was carried out by using the complex Dedrick plot (21).

RESULTS AND DISCUSSION

Pharmacokinetic Interaction of Theophylline and Cimetidine in Rabbits.

A drug-drug interaction by inhibition of the metabolism

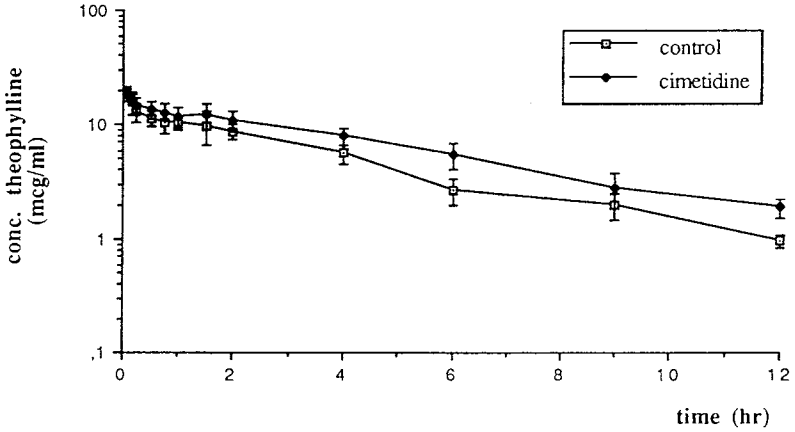

Figure 1. Plasma concentration-time profile (mean±SD) for theophylline following an intravenous dose (12 mg/Kg) when given alone (control) or in combination with oral cimetidine (100 mg/Kg/day four days) in rabbits.

Table I. Effect of cimetidine pretreatment on pharmacokinetic parameters of theophylline in rabbits (mean ± SD).

	THEOPHYLLINE	THEOPHYLLINE + CIMETIDINE
Ke (h^{-1})	0.23 ± 0.02	0.17 ± 0.02*
t1/2 (h)	3.04 ± 0.25	5.54 ± 1.52*
AUC (mgh/L)	58 ± 12	87 ± 18.*
Cl (L/h/Kg)	0.21 ± 0.04	0.14 ± 0.03*
Vd (L/Kg)	0.90 ± 0.15	0.80 ± 0.15
MRT (h)	4.25 ± 0.55	5.67 ± 0.68*
	N = 5	N = 5

* significantly different ($p < 0.05$)

can be investigated by comparing the pharmacokinetics of the inhibited drug before and after the administration of the inhibitor drug. If there is an inhibition process, plasma levels of the drug after parenteral administration will increase and the clearance of the drug after oral and intravenous administration will decrease (22).

The mean (±SD) theophylline plasma concentration time plots, when theophylline is administered alone (control) and in combination with cimetidine in rabbits, are presented in figure 1. Plasma concentration of theophylline declined according to a first-order process in the control and in cimetidine pretreated animals. A significant increase in plasma concentration of theophylline can be noted after treatment with cimetidine. Table I shows the mean pharmacokinetic parameters (mean±SD) of theophylline in both situations. In the group of animals that received a previous treatment with cimetidine, a significant decrease ($p<0.05$) in the value of the plasma clearance was observed in relation to the control group. At the same time, a significant increase ($p<0.05$) in the half-life value could be observed with the corresponding decrease in the elimination rate constant. These modifications in the clearance, plasma half-life and elimination rate constant without any significant modification in the volume of distribution ($p>0.05$) show that there exists an interaction between the two drugs regarding elimination processes. Grygiel et al. (4) have observed that cimetidine is able to inhibit demethylation in positions 1 and 3 of the theophylline molecule without affecting oxidation processes that take place in position 8.

Interspecies Scaling of Cimetidine-Theophylline Drug Interaction

Pharmacokinetic scaling is an important tool in the development of new drugs. This approach normally requires at least three to four animal species for a valid prediction. Table II shows the average values for physiological and experimental theophylline pharmacokinetic parameters in the four species used in our study. Figure 2 shows the relationship between the volume of distribution of theophylline and the body weight for all species studied when the drug is administered alone or in combination with cimetidine. The H_2-receptor antagonist does not modify this parameter, and the correlation is the same in both situations. When theophylline half-life is plotted versus the species' body weight, the graph in figure 3 is obtained. There is a good correlation between the half-life and the body weight when theophylline is administered alone. When theophylline is administered after a

Table II. Average values for physiological and experimental theophylline pharmacokinetic parameters in the species studied.

	MAN	DOG	RABBIT	RAT
PHYSIOLOGICAL PARAMETERS				
B (Kg)[a]	63	10	2.7	0.26
MPL (years)[b]	76	23	9	4
Brain weight (g)[c]	1,510	90	14	2
Q (ml/min)[d]	2262	457	133	16.6
fu[c]	0.58	0.58	0.58	0.40
PHARMACOKINETIC PARAMETERS				
Theophylline				
Vd (L)	33.8	6.8	2.4	0.1
t1/2 (min)	439.2	279.6	182.4	120
Cl_h (ml/min)	54.5	17.3	9.3	0.7
Clu_{int} (ml/min)	96.3	31.0	17.3	1.8
Clu_{int} (L/MPL) × 10^{-5}	38.6	3.7	0.8	0.03
Theophylline-cimetidine				
Vd (L)	31.4	6.9	2.1	0.1
t1/2 (min)	634	365	240	168
Cl_h (ml/min)	34.8	13.3	6.2	0.5
Clu_{int} (ml/min)	61	24	11	1.2
Clu_{int} (L/MPL) × 10^{-5}	24.5	2.8	0.5	0.02

B: body weight, MPL: maximum potential lifespan, Q: liver blood flow, fu: fraction of unbound drug, Vd: volume of distribution, Cl_h: hepatic clearance, Clu_{int}: intrinsic clearance.

[a]: body weight of the animals and humans included in the study. [b]: calculated from the equation n° 3 included in the text (ref. 19) [c]: from ref. 14, [d]: calculated from the equation n° 2 included in the text (ref. 18).

Control $Vd = 0.54 \times B^{1.05}$ (L) R = 0.99
Cimetidine $Vd = 0.52 \times B^{1.04}$ (L) R = 0.99

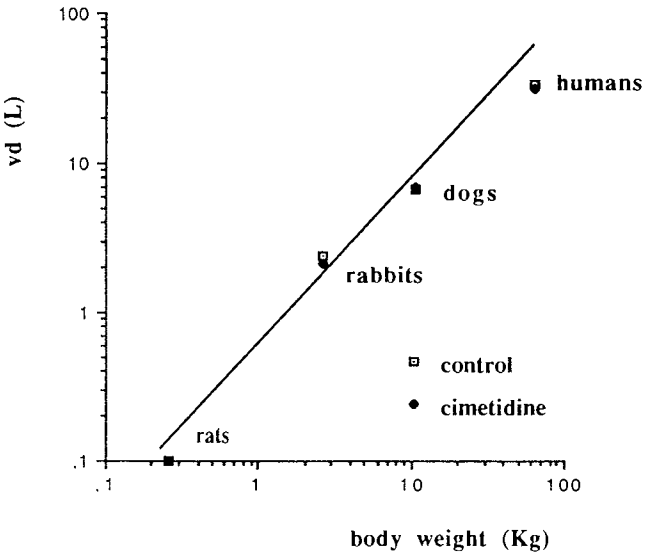

Figure 2. Allometric relationship between theophylline volume of distribution and species' body weight.

treatment with cimetidine, the value of this parameter increases in all species in the same proportion.

Figure 4 shows the relationship between theophylline clearance and body weight in both situations: theophylline alone and after treatment with cimetidine. The correlation is good for rats, rabbits and dogs, and there is a small deviation for humans. If we consider the intrinsic clearance (parameter

Control $t_{1/2} = 157 \times B^{0.33}$ (min) R = 0.99
Cimetidine $t_{1/2} = 214 \times B^{0.24}$ (min) R = 0.98

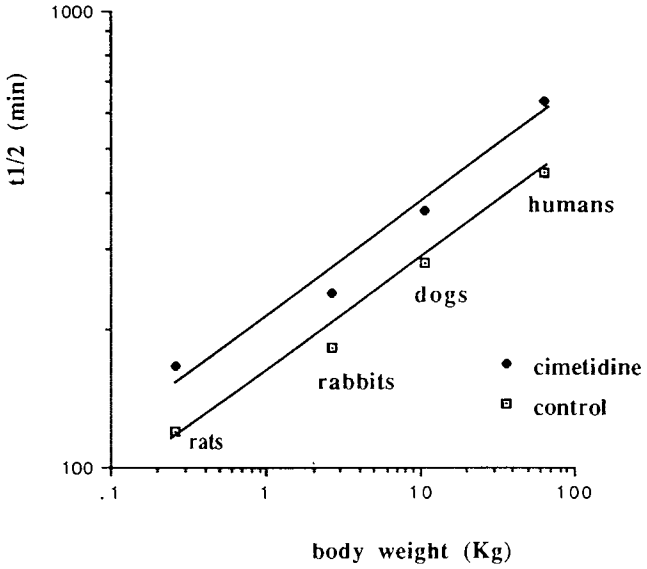

Figure 3. Allometric relationship between theophylline half-life and the species' weight.

Control $Cl_h = 2.63 \times B^{0.90}$ (ml/min) R = 0.98 (without humans)
Cimetidine $Cl_h = 1.81 \times B^{0.93}$ (ml/min) R = 0.99 (without humans)

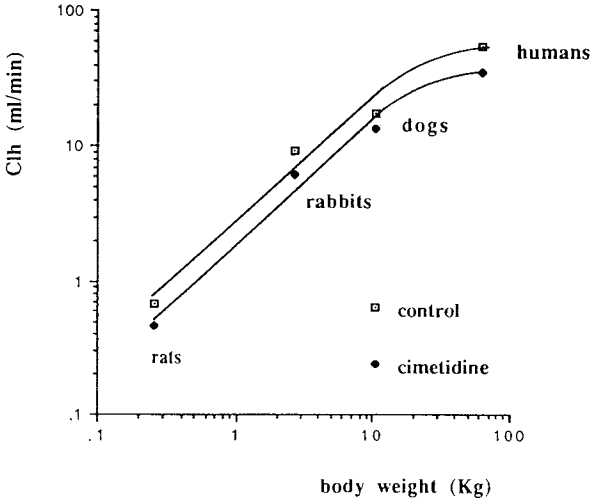

Figure 4. Allometric relationship between theophylline clearance and the species' body weight.

where the influence of some other parameters such as hepatic blood flow, protein binding is eliminated) we obtain the graph plotted in figure 5. The correlation between this parameter and body weight is maintained for rats, rabbits and dogs, and the value of the theophylline intrinsic clearance for humans in both situations (with and without cimetidine) is smaller than the correlation for the other species. Similar results were obtained by Gaspari et al. (14) in a previous report about the interspecies scaling of theophylline and by others for antipyrine (18).

These results are mainly due to the fact that humans biotransform drugs at a lower rate, approximately 1/7 of what would be expected on the basis of body weight. The

Control $Clu_{int} = 5.80 \times B^{0.79}$ (ml/min) R = 0.98 (without humans)
Cimetidine $Clu_{int} = 3.91 \times B^{0.82}$ R = 0.99 (without humans)

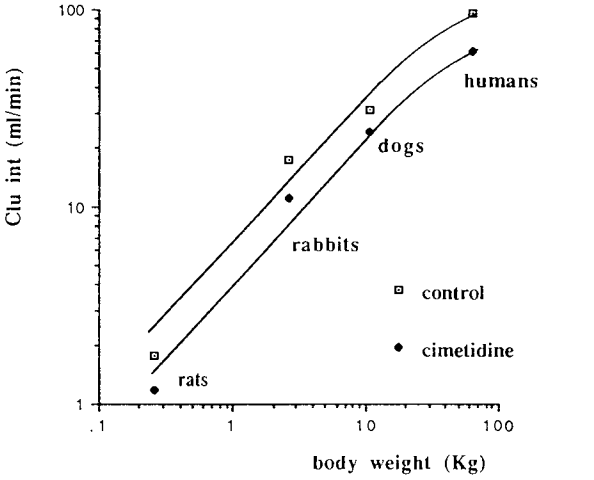

Figure 5. Allometric relationship between theophylline intrinsic clearance and the species' body weight.

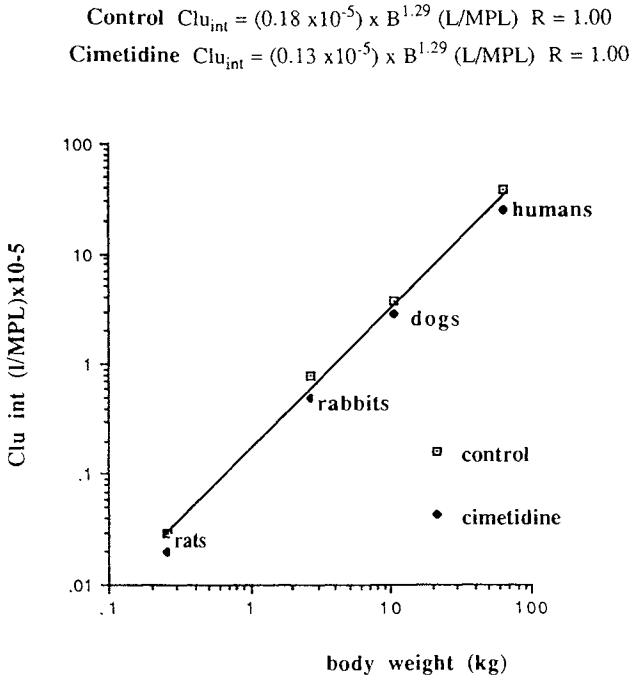

Figure 6. Allometric relationship between (theophylline Clu_{int} × MPL) and species' body weight.

reason for this decrease appears to be related to the neoteny phenomenon (23). Neoteny is one of the main determinants in the evolution of the human species, and it is responsible for numerous characteristics such as a longer life, slower maturity, a longer pregnancy and a heavier brain. However, and regardless of this phenomenon, the changes produced in

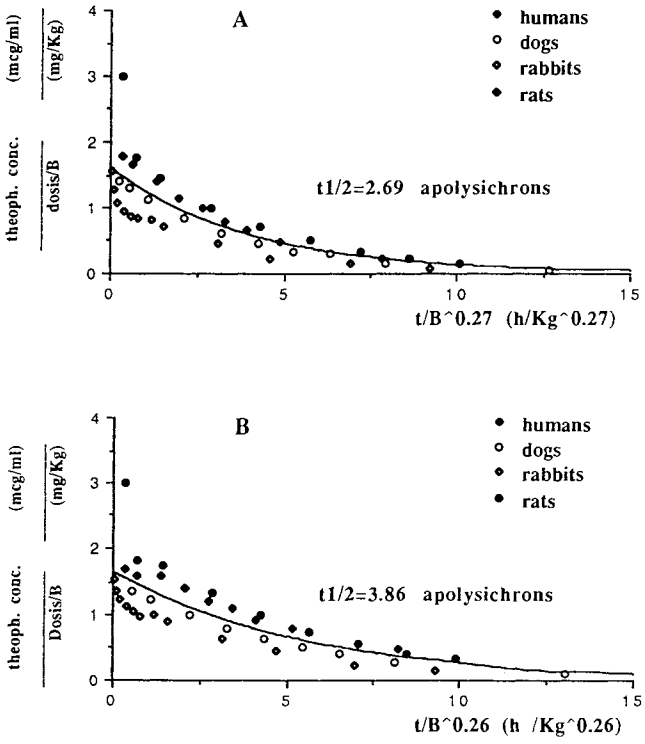

Figure 7. Complex Dedrick plot of theophylline for the four species before (A) and after (B) cimetidine pretreatment.

the intrinsic clearance of theophylline as a consequence of cimetidine are proportional in all the species studied, which could be used to predict these changes in human beings.

Because brain weight and the biotransformation rate of xenobiotics are affected by the neoteny, one might expect both variables to be related. Boxenbaum (18) has shown that the antipyrine clearance, frequently used as a biotransformation capacity index, might be predicted from body and brain weight. The correlation between these two parameters is the reason why the intrinsic clearance of the drugs can be corrected in terms of the maximum potential lifespan.

A relationship was obtained for theophylline when the species' intrinsic clearance was multiplied by the maximum potential lifespan (MPL, as the maximum documented longevity for a species). Figure 6 illustrates this plot. The excellent correlation between Clu_{int} × MPL and all the species' body weight (including humans) can be observed. Further, there is no difference between the group receiving theophylline alone and the group receiving theophylline after pretreatment with cimetidine. This can be explained because cimetidine increases theophylline clearance in a rather short time interval with relation to the maximum potential lifespan.

As a good correlation has been established between pharmacokinetic parameters of theophylline and the species' body weight, by using a complex Dedrick plot, a superimposable kinetic profile can be obtained for theophylline for the species investigated when it is administered alone or after treatment with cimetidine. Figure 7 illustrates the complex Dedrick plot for theophylline in both situations (with and without cimetidine) where the new unit of time is the apolysichron (21). In one apolysichron, the species have eliminated the same fraction of drug from their bodies and have cleared the same volume of plasma per kilogram$^{\alpha_1}$ of body weight, being α_1 the allometric exponent of the volume of distribution. Cimetidine treatment produces a 43% increase in the half-life of theophylline (2.69 vs 3.86 apolysichrons), a value that is similar to the percentage of increase in the half-life of theophylline when it is administered in humans after treatment with cimetidine (7).

Our results suggest that an interspecies scaling methodology may predict pharmacokinetic interactions with clinical relevance of a new drug.

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