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 apolysychrons for theophylline when it is administered alone and 3.86 apolysychrons when it is administered in combination with cimetidine. This 43% increase in t1/2 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.

KEYWORDS: 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 animal 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). ZnSO4, 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).
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 (Ch). 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 (Clint) (17):

$$\text{Cl}_{\text{int}} = \frac{Q \times Cl_{b}}{f_{u} \times (Q - Cl_{b})}$$

(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):

$$Q = 0.0554 \times B^{0.894}$$

(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):

$$\text{MPL} = 10.389 \times \text{brain weight}^{0.636} \times B^{-0.225}$$

(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.