Unbound Total (Plasma) Clearance Approach in Interspecies Pharmacokinetics Correlation: Theophylline-Cimetidine Interaction

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INTRODUCTION

In a recent study (1) on the interspecies scaling of cimetidine-theophylline pharmacokinetics interactions, it was reported that the volume of distribution and half-life of theophylline in rats, rabbits, dogs and humans with or without coadministration of cimetidine are well correlated (correlation coefficients being 0.98 or 0.99) with their body weights. For theophylline hepatic clearance and unbound intrinsic clearance (CLu_{int}), it was reported (1) that either in the presence or absence of cimetidine, the values for humans were smaller than expected from the extrapolation of three animal species. These results were attributed to that humans metabolize drugs at a lower rate, approximately 1/7 of what would be expected on the basis of body weight (1). The lower rate of metabolism in humans was also reported to be related to the neoteny phenomenon since excellent correlation was obtained ($r = 0.999$; it was reported as 1.00) when all four species were analyzed after also considering maximum potential lifespan (MPL); correlation was made with $CLu_{int} \times MPL$.

Unbound total (plasma) clearance (CLu) is probably the most accurate kinetic parameter to directly measure the eliminating (excretion and biotransformation) capacity of a subject for a given compounds. It is probably also the most useful kinetic parameter since it is directly (for simplicity only linear kinetics is assumed throughout this study) related to unbound plasma concentration or its area under the curve that is in turn more directly related to the efficacy and/or toxicity of compounds (2). The unbound total (plasma) clearance approach has been employed (3,4) to successfully correlate the eliminating capacity for six β-lactam antibiotics (such as cefazolin and cefmetazole) in six species (mouse, rat, rabbit, dog, monkey and human). It has also been used to correlate the elimination of 15 extensively metabolized drugs (2), hydrochlorothiazide (5) and verapamil (6) between humans and rats. The rationale behind the interspecies correlation using unbound total clearance has been postulated (2). It was discussed (2) that mean CLu values for all "natural" substances involved in the basal metabolism in different species can be scaled allometrically. Therefore, drugs may also resemble these "natural" substances in their clearance from the body according to the allometric relationship. The purpose of this communication is to report that such a simple approach can also be used to successfully correlate the eliminating capacity of theophylline in the absence or presence of cimetidine in the four species studied earlier (1).

METHODS

Mean total clearances (CL) of theophylline with or without co-administration of cimetidine in rats, rabbits, dogs, and humans were obtained from the same sources as reported earlier (1). The CLu was calculated by (2)

$$CLu = CL/fu \quad (1)$$

where fu is the fraction of drug unbound in plasma, being 0.58 for rabbits, dogs, and humans and 0.40 for rats (1).

Allometric analysis and statistical analysis of CLu data from the four species were similarly made as described before (1).

RESULTS AND DISCUSSION

Mean CLu and body weight (BW) of the four species employed in this study are summarized in Table I. The results of allometric analysis are shown in Fig. 1. It is of interest to note that the r is 0.989 for both correlations that is practically identical to those reported earlier (1) for correlation with the volume of distribution, half-life and $CLu_{int} \times$ MPL indicating that humans are no different from the other three animal species in their ability to eliminate (in this case mainly biotransformation) theophylline. The observed CLu for humans is lower than that predicted based on the three animal species. However, the difference is not statistically significant. The present and previous (1) results, however, do not necessarily indicate that drug interactions in general are scalable.

The unbound total clearance approach seems especially useful when there is a marked interspecies difference in plasma protein biding (2–6). Under such conditions half-life and plasma clearance may not be good parameters for correlation; this may often lead one to falsely (see examples in ref. 2) conclude that there is no general trend or predictability in eliminating capacity among different species. Thus, it appears useful first to conduct plasma protein binding study in humans and laboratory animals before performing any interspecies scaling in kinetics or dosing regimens.

Table I. Summary of Relevant Kinetic Parameters of Theophylline

Species	BW (kg)	CLu[a] (ml/min)	CLu[b] (ml/min)
Human	63	93.8	60.0
Dog	10.6	29.8	22.9
Rabbit	2.7	16.0	10.7
Rat	0.26	1.75	1.25

[a] In the absence of cimetidine.
[b] In the presence of cimetidine.

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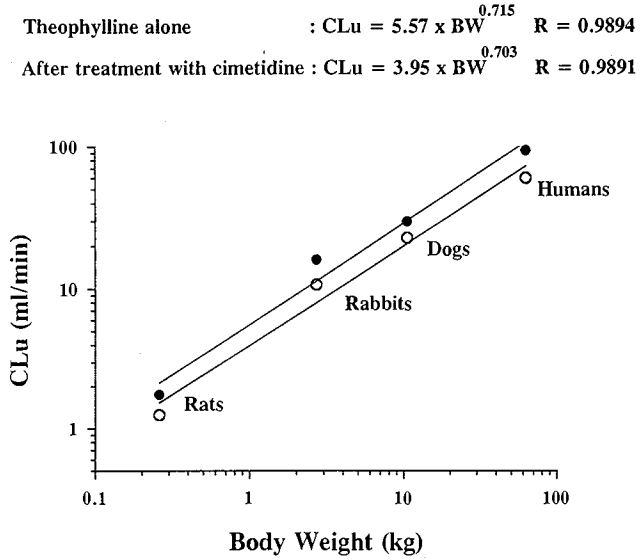

Fig. 1. Allometric relationship between unbound plasma clearance (CLu) of theophylline alone (●) or after treatment with cimetidine (○) and the body weight (BW) of four species.

The CLu_{int} has been commonly used as a parameter to measure the intrinsic activity of the liver to metabolize a drug (1,7,8). This parameter is usually calculated based on a well-defined hepatic model that assumes well-stirring and lack of existence of any concentration gradients in the entire liver (8). The above basic assumptions are contradictory to the anatomy and physiology of the liver as well as the observed distribution profiles of drugs and metabolites in the liver (8,9 and references therein). Since many reported kinetic data can be adequately explained by the model-derived equations, this is then considered as supporting the validity of the model (8). Such an argument is no longer valid because the same mode-derived equation can also be used to accurately or satisfactorily explain the absorption kinetics of drugs in a single-pass perfused intestinal loop (10) or the dialysis kinetics of compounds in a single-pass, artificial, rigid dialyzer (11,12). Both the perfused intestine and dialyzer are virtually unstirred preparations and their concentration gradients along the path of perfusion are well known. As expected, their absorption or dialysis kinetics can also be satisfactorily described by the classical tube model (10–12). If one accepts the notion (a reasonable one) that the liver more closely resembles the tube model than the well-stirred model, the CLu_{int} determined based on the well-stirred model may be much higher than the true CLu_{int}, or that based on the tube mode (11). In view of the above discussions it appears that one should be cautious in the use of CLu_{int} in pharmacokinetics studies. The difficulty of estimating accurate CLu_{int} has been extensively discussed (2). Furthermore, the role of neoteny in human evolution (13) and drug metabolism (14) has been seriously challenged. Thus, the apparent success of using $CLu_{int} \times MPL$ approach in interspecies correlation of drug metabolism may need to be re-examined. This is interesting in view of some success of using the simple CLu approach for scale-up or correlation. This approach may be particularly valuable for comparison or correlation between humans and rats (2–5 and unpublished data).

REFERENCES

1. A. R. Gascon, B. Calvo, R. M. Hernandez, A. Dominquez-Gill, and J. L. Pedraz. Interspecies scaling of cimetidine-theophylline pharmacokinetics interaction: Interspecies scaling in pharmacokinetics interactions. Pharm. Res. 11:945–950 (1994).
2. W. L. Chiou and F. H. Hsu. Correlation of unbound plasma clearance of fifteen extensively metabolized drugs between humans and rats. Pharm. Res. 5:668–672 (1988).
3. F. H. Hsu. "Absorption and Disposition of Chlorothiazide in Rats." Ph.D. thesis, University of Illinois at Chicago, 1987.
4. F. H. Hsu and W. L. Chiou. A simple and useful approach to interspecies scaling in pharmacokinetics: Unbound plasma clearance based on body surface area or body weight. Pharm. Res. 5:S2–11 (1988).
5. T. M. Chen, L. X. Li and W. L. Chiou. Extrapolation of oral bioavailability and unbound plasma clearance of hydrochlorothiazide from rat to human. Pharm. Res. 5:S-168 (1988).
6. P. Manipisikul and W. L. Chiou. Intravenous verapamil kinetics in rats: Marked arterialvenous concentration difference and comparison with humans. Biopharm. Drug Disp. 14:555–566 (1994).
7. H. Boxenbaum. Interspecies variation in liver weight, hepatic blood flow, and antipyrine intrinsic clearance: extrapolation of data to benzodiazepines and phenytoin. J. Pharmacok. Biopharm. 8:165–176 (1980).
8. W. L. Chiou. A new model-independent physiological approach to study hepatic drug clearance and its applications. Int. J. Clin. Pharmacol. Ther. Toxicol. 22:577–590 (1984).
9. R. A. Weisiger, C. M. Mendel, and R. R. Cavalieri. The hepatic sinusoid is not well-stirred: Estimation of the degree of axial mixing by analysis of lobular concentration gradients formed during uptake of thyroxine by the perfused rat liver. J. Pharm. Sci. 75:233–237 (1986).
10. W. L. Chiou. The effect of change in luminal perfusion rate on intestinal drug absorption studied by a simple unified organ clearance approach. Pharm. Res. 6:1056–1059 (1989).
11. W. L. Chiou and H. J. Lee. Effect of change in blood flow on hemodialysis clearance studied by a simple unified organ clearance approach. Res. Commun. Chem. Pathol. Pharmacol. 65: 393–396 (1989).
12. H. J. Lee and W. L. Chiou. Effect of change in blood flow on hemodialysis clearance of salicylic acid, creatinine and acetaminophen: Satisfactory fitting into the unified organ clearance model and the parallel-tube clearance model. Pharm. Res. 8:S-317 (1991).
13. B. T. Shea. Heterochrony in human evolution: The case for neoteny reconsidered. In "Yearbook of Physical Anthropology" 32:69–101 (1989).
14. H. Boxenbaum. Hypothesis on mammalian aging, toxicity and longevity hormesis: Explication by a generalized Gompertz function. In "Biological Effects of Low Level Exposures to Chemicals and Radiation." ed. by E. J. Calabrese, Lewis Publishers, Boca Raton, Florida, 1992. Chapter 1, pp. 1–39.