Selection of the First-Time Dose in Humans: Comparison of Different Approaches Based on Interspecies Scaling of Clearance

Iftekhar Mahmood, PhD, Martin David Green, PhD, and J. Edward Fisher, PhD

The authors describe four approaches to selecting a safe starting dose for humans in clinical drug trials based on interspecies scaling of clearance. Human clearance was predicted by scaling for 10 example drugs for which animal clearance values were available in the literature. The predicted human clearance values were then used to select the estimated starting dose in humans. These doses were then compared with the actual doses given to humans during clinical trials. All four approaches used to estimate the first-time dose in humans provided values that were within the dose range given to humans from Phases I to III. This work demonstrates that animal pharmacokinetic data can be used to estimate a suitable human starting dose, provided the data have been obtained from a dose that produces no adverse effects.

Keywords: *Interspecies scaling; first-time dose; drug development; allometric scaling; predicted human clearance; toxicity*

Journal of Clinical Pharmacology, 2003;43:692-697

Interspecies scaling is frequently used to predict pharmacokinetic parameters from animals to humans during drug development and is becoming a useful tool especially for the selection of the first-time dose in humans.[1] Estimation of a starting dose for "first-in-human" clinical trials of new molecular entities in healthy volunteers is very important since a low starting dose will prolong dose optimization, and a high starting dose may cause serious toxicity. But despite the importance of this task from a drug development standpoint, there is no consensus regarding the best approach for estimating the starting dose.[2]

From the Division of Clinical Trial Design and Analysis, Center for Biologics Evaluation and Research (I. Mahmood, M. D. Green) and the Division of Neuropharmacological Drug Products, Center for Drug Evaluation and Research (J.E. Fisher), Food and Drug Administration (FDA), Rockville, Maryland. The views expressed in this article are those of the authors and do not reflect the official policy of the FDA. No official support or endorsement by the FDA is intended or should be inferred. Submitted for publication December 22, 2002; revised version accepted April 12, 2003. Address for reprints: Iftekhar Mahmood, Division of Clinical Trial Design and Analysis, Office of Therapeutic Research and Review, Clinical Pharmacology and Toxicology Branch (HFD-579), Center for Biologics Evaluation and Research, Food and Drug Administration, Woodmont Office Center I, Suite 200N, 1401 Rockville Pike, Rockville, MD 20852.
DOI: 10.1177/0091270003254631

One of the most commonly used methods for selecting the starting dose has involved the conversion of an animal no observed adverse effect level (NOAEL) to the human equivalent dose (HED) using appropriate scaling factors, followed by application of a safety factor (SF). This procedure is described in detail in a recently issued Food and Drug Administration (FDA) draft guidance, which outlines an algorithmic process for selecting the maximum recommended starting dose (MRSD) for healthy adult volunteers based on animal toxicology data and administered doses.[3] Although this method has proven generally adequate, it presents a number of problems for the toxicologist. Determination of the appropriate animal NOAEL is a difficult and time-consuming task, depending on a number of key study variables, including duration of treatment, dose selection, and species. The choice of an appropriate scaling factor also involves considerable uncertainty. For most systemically administered drugs, conversion to the HED is typically based on the normalization of doses to body surface area.[4,5] However, the applicability of the data used to derive this scaling factor (i.e., the two-thirds power of body weight) to risk assessment for noncytotoxic agents and the largely unknown impact of experimental conditions on dose scaling across spe-

cies have been widely discussed.[6-8] As has been pointed out repeatedly, the choice of an SF is almost entirely arbitrary and without scientific justification.

In those cases for which adequate data exist, animal pharmacokinetics may aid in determining initial clinical doses. Although not without their own set of limitations and assumptions, pharmacokinetically guided approaches to dose extrapolation such as those described herein should provide a more rational basis for calculating an appropriate starting dose. In 1986, Collins et al[9] proposed a pharmacokinetically guided dose escalation scheme for anticancer drugs. To select the first-time dose in humans, Reigner and Blesch[2] suggested the use of the lowest AUC at the NOAEL when a drug is given to several species as well as the predicted human clearance (dose in humans = AUC × predicted human clearance). Therefore, for this approach, it is essential that the clearance be predicted with reasonable accuracy in humans. Over the years, many different approaches have been suggested to improve the prediction of clearance in humans.[10-14] With the introduction of the rule of exponents by Mahmood and Balian,[10] the probability of predicting clearance with reasonable accuracy has vastly improved. The objective of this report is to propose four different approaches based on the predicted human clearance and their suitability to select a safe first-time dose in humans for the Phase I study.

METHODS

A literature search was conducted to obtain clearance values for 10 drugs[15-33] that have been studied in at least three animal species (mice, rat, rabbit, monkey, or dog). These drugs are eliminated renally or by extensive metabolism. Drugs used in this study were given either intravenously or orally. The first step was to predict clearance in humans. Scaling of clearance was performed using the following three methods. Human data were not included in the scaling. In the case when several doses were given to animals, the lowest dose was selected for scaling.

Prediction of Clearance

Method I. Clearance of each drug was plotted against the body weight on a log-log scale, and the following allometric equation was used to predict clearance in humans.

$$CL = a(W)^b, \quad (1)$$

where W is the body weight and a and b are the coefficient and exponent of the allometric equation, respectively.

Method II. The observed clearance values in the different animal species were multiplied by their respective maximum life span potential (MLP) and plotted as a function of body weight on a log-log scale. From the allometric equation, clearance × MLP was estimated in humans and the result was then divided by the MLP of humans (8.18×10^5 h) to predict the clearance in man.

$$CL = a(MLP \times Clearance)^b/8.18 \times 10^5. \quad (2)$$

MLP in years was calculated from the following equation, as described by Sacher[34]:

$$MLP\ (years) = 185.4\ (BW)^{0.636}\ (W)^{-0.225}, \quad (3)$$

where both brain weight (BW) and body weight (W) are in kilograms.

Method III. In this approach, clearance of animal species was multiplied by the brain weight of the species, and the product was plotted as a function of body weight on a log-log scale. The allometric equation (equation (4)) was then used to predict the clearance in humans using the human brain weight (1.53 kg).

$$CL = a(CL \times BW)^b/1.53, \quad (4)$$

where BW is the brain weight in kilograms.

Selection of Dose

Based on the predicted human clearance, the following four approaches were used to select the dose in humans. The predicted dose was then compared with the lowest and highest doses given to humans during the clinical trials (from Phase I to Phase III).

Approach I. In this approach, the clearances of the species (used in the prediction of clearance for humans) were plotted on linear scale against the dose given to the species. The resultant equation was then used to recommend the starting dose in humans as follows:

$$Dose = a + b(x), \quad (5)$$

where a is the intercept, b is the slope, and x is the predicted clearance in humans.

Approach II. In this approach, the dose given to each species was multiplied by the HED and then plotted against clearance in each species on a linear scale. The resultant equation was then used to select the dose, as

Table I Names of the Studied Drugs and the Species Used in the Allometric Scaling

Drugs	Species Used	Route of Administration[a]	Reference Animals	Reference Humans
Topiramate	m, r, d	Oral	15, 16	17
Moxifloxacin	m, r, mk, d	IV	18	19
Zonisamide	r, d, mk	Oral	20	20
Troglitazone	m, r, mk, d	Oral	21	21
Venlafaxine	m, r, d, mk	Oral	22	23
Morphine	r, rb, d	IV	24-26	27
Felbamate	r, rb, d	Oral	28	29
Bepridil	m, r, mk	Oral	30	30
Stavudine	m, r, rb, mk	IV	31	32
Zenarestat	m, r, d	Oral	33	33

m, mouse; r, rat; rb, rabbit; mk, monkey; d, dog.
a. The route of administration in animals and humans was same.

described in equation (5). HED in a given species was estimated as follows[3]:

$$\text{HED} = \text{animal dose in mg/kg} \times (\text{animal weight in kg/human weight in kg})^{0.33}.$$

Approach III. This approach is a slightly modified version of the pharmacokinetically guided approach. No safety factor was used in this dosing recommendation based on the assumption that the dose given to animals is much lower than the NOAEL. Since the AUC values for a given drug were available in more than one species, the recommended dose was estimated using the lowest AUC observed in a given species as follows:

$$\text{Dose (mg)} = \text{AUC in animal } (\mu g \bullet h/mL) \times \text{predicted clearance in humans (L/h)}.$$

Approach IV. This mathematically manipulated approach can be used to recommend the first-time dose in humans as follows.

First, one selects the species whose clearance (per kg body weight) is nearest to the predicted human clearance (based on kg body weight). A correction factor is then obtained by dividing the clearance of the chosen species by the predicted human clearance. Then the recommended dose can be selected according to the following equation:

$$\text{Dose (mg)} = (\text{AUC in the chosen animal } (\mu g \bullet h/mL) \times \text{predicted clearance in humans (L/h)})/\text{correction factor}.$$

Example: For felbamate, the observed clearance in rat, rabbit, and dog was 2.54, 0.98, and 1.55 mL/min/kg, respectively. In man, the predicted clearance was 0.3 mL/min/kg. Based on the clearance value, rabbit was the closest species to man. The estimated correction factor was 3.27 (0.98/0.3), and the dose was calculated as follows:

$$\text{Dose (mg)} = (474\ \mu g \bullet h/mL \times 1.26\ L/h)/3.27.$$

Thus, the recommended starting dose of felbamate in humans was 183 mg.

RESULTS

Table I is the summary of the drugs and species used in this study as well as the route of administration of these drugs to animals and humans. The exponents of the simple allometry and the correlation coefficient between body weight and clearance are summarized in Table II. Table II also compares the predicted and observed clearance of the studied drugs.

A good correlation between body weight and clearance was observed for most of the drugs tested. The results of this study (as in the previous study[10]) indicate that there are specific conditions under which only one of the three methods can be used for improved prediction of clearance. When the exponents of the simple allometry ranged from 0.55 to 0.70, the simple allometry was considered suitable for the prediction of clearance in humans. When the exponents of the simple allometry ranged from 0.70 to 0.99, the MLP approach was found to be appropriate for the prediction of clearance in humans. The product of clearance and brain weight was considered suitable for the prediction of clearance in humans when the exponents of the simple allometry were ≥ 1.0. It can be seen from Table II that simple allometry was not adequate for the prediction of clearance for all drugs, but the use of the rule of exponents vastly improved the prediction of these drugs.

In this study, however, there were two drugs whose predicted clearances were many times higher than the observed clearances. Zenarestat's exponent was 1.340, but as mentioned previously,[10] if the exponent of the

Table II Observed versus Predicted Clearance (mL/min) in Humans

Drugs	Exponent	Correlation Coefficient (*r*)	Observed CL	Predicted CL (SA)	Predicted CL (RE)
Topiramate	0.557	0.864	22-36	51	51
Moxifloxacin	0.603	0.969	154	166	166
Zonisamide	0.735	0.987	16	22	20
Troglitazone	0.633	0.984	751-891	793	793
Venlafaxine	0.782	0.866	2240	4874	2268
Morphine	0.777	0.985	1300	2714	910
Felbamate	0.823	0.979	30	59	21
Bepridil	0.842	0.995	1085	12,886	6535
Stavudine	0.901	0.999	572	961	400
Zenarestat	1.340	0.994	47	688	155

SA, simple allometry; RE, rule of exponents.

allometry is > 1.30, the predicted clearance may be many times higher than the observed clearance, and indeed this was the case with zenarestat. In a previous paper,[35] Mahmood mentioned that the prediction of oral clearance would be erratic when the oral clearance of the species used in the scaling is either equal to or greater than the liver blood flow and the observed human clearance is less than the liver blood flow. This observation was found to be true with bepridil. Bepridil's oral clearance in the mouse, rat, and monkey was greater than their respective blood flow, resulting in a much higher prediction of oral clearance (observed human CL = 1085 mL/min, which is less than human liver blood flow) in humans (predicted CL = 6535 mL/min).

The results obtained by the four approaches to selecting the first-time dose in humans are compared with the doses actually given to humans from Phase I to Phase III in Table III. The clinical dose range shown extends from the first human dose to the highest dose used in the definitive efficacy trials, which can be considered a well-tolerated but not necessarily a maximum-tolerated dose. The method of dose selection in the original trials is unknown. Approach I was the most aggressive approach and may not be suitable for the selection of the first-time dose in humans. Approach III was the most conservative method and, like Approach I, may be unsuitable. Approaches II and IV were more moderate and could be useful in estimating a safe and efficient dose for the first-time administration of a drug to humans. It should be noted, however, that with the exception of zenarestat, even the dose arrived at by Approach I did not exceed the highest dose given to humans for any of the studied drugs.

DISCUSSION

Interspecies scaling is based on the assumption (a correct assumption) that there are anatomical, physiological, and biochemical similarities among animals, which can be described by mathematical models. It is now a well-established fact that many physiological processes and organ sizes exhibit a power-law relationship with the body weight of species. This relationship is the scientific basis of allometry.

Pharmacokinetics play an important role during drug development. Characterization of absorption, distribution, metabolism, and excretion (ADME) in animals is of fundamental importance. The pharmacokinetic parameters, especially clearance, can be extrapolated to humans for the selection of a safe dose for the first-dosing trials in humans. Two of the widely used methods of first-time dose selection are based on the NOAEL or toxicokinetic studies of a drug in one to three species. There are several disadvantages to these approaches. In the NOAEL approach, it becomes necessary to select a NOAEL, which is a tedious and time-consuming process. In reality, one may never find an absolute NOAEL in a given species. In toxicokinetic studies, animals are given a very high dose chronically, and if the resultant toxicity does not kill the animal, it may alter the physiology of the animal. This change in the physiology of the animal may have an impact on the pharmacokinetics of a given drug. Overall, both the NOAEL and toxicokinetic approaches for the first-time selection of a dose to humans are slow and very conservative approaches. In fact, there is no need to select the first dose in humans based on NOAEL or

Table III Recommended First-Time Dose in Humans by Different Approaches

Drugs	Approach I	Approach II	Approach III	Approach IV	Dose Given
Topiramate	175	95	36	44	100-1200
Moxifloxacin	107	86	23	80	84-400
Zonisamide	595	329	265	490	200-800
Troglitazone	90	37	35	85	100-600
Venlafaxine	60	23	22	60	25-150
Morphine	9.3	5.3	2.5	3	7.5-10
Felbamate	145	80	122	183	100-800
Bepridil	400	177	161	176	200-400
Stavudine	243	86	170	134	47-280[a]
Zenarestat	845	460	313	353	150-600

Approach I = dose versus clearance (CL); Approach II = human equivalent dose (HED) dose versus CL; Approach III = no observed adverse effect level (NOAEL); Approach IV = correction factor.

a. Given orally, but the recommended dose is based on the scaling of IV data as the absolute bioavailability is 1 in humans. The initial IV dose in humans was 70 mg.

toxicokinetics. One can achieve this goal by giving a safe low dose to animals and, based on the prediction of clearance, selecting a safe and suitable dose in humans as described in this study. Nevertheless, this does not necessarily mean that one should not try to determine the NOAEL or conduct a toxicokinetic study as these endpoints provide information that is often useful in characterizing toxicity.

In this report, we have proposed several methods that can be used to administer a first-time dose to humans that is not only safe but also avoids many unnecessary low-dose schemes. Even when the predicted clearance is many times higher than the observed clearance, as seen with bepridil (sixfold higher) and zenarestat (threefold higher), the doses selected by Approaches II, III, and IV were well below the highest well-tolerated doses given to humans. It is, however, not known that these clinical doses represent the maximum tolerated dose or whether one could give even higher doses to humans without producing any significant toxicity. Approach III is, in fact, a modified version of NOAEL or toxicokinetic methods for the selection of the first-time dose in humans. In this approach, a safety factor was not used since the animal doses were low and without any side effects.

An important caveat is that the above-mentioned approaches ignore the fact that there may be a toxic metabolite of a drug in humans that is not formed in animals. Considering that current standards of drug development require a thorough investigation of metabolites formed in animals and humans, such a case is highly unlikely to occur.[2] Another important point worth considering is that genetic polymorphism, as in the case of 2D6, may occur. One may then require developing two different starting doses, one for poor metabolizers and one for extensive metabolizers.[2]

The main objective of this work is to describe different approaches that can help to select a first dose in humans that is not only safe but also efficient (neither very low nor very high). These suggested approaches provide rational alternatives to the somewhat arbitrary dose selection process often used. Having a clear set of methods rather than relying on some fuzzy approach should be an important advantage in the bigger context of drug development. Although various safety factors used in the first-time dose in humans have no scientific basis, one can tailor these factors based on the need or the characteristics of a given drug. It should also be noted that there is no right or wrong method, and one can select one of the many approaches available by using scientific judgment and the ease of the method. Our proposed methods are one of the many approaches that may be used to select a first-time dose to humans. Other approaches may be considered in relationship to the severity and incidence of toxicity. For example, a conservative approach is suitable for drugs likely to have a narrow therapeutic index.

REFERENCES

1. Boxenbaum H, Dilea C: First-time-in-human dose selection: allometric thoughts and perspectives. *J Clin Pharmacol* 1995;35:957-966.

2. Reigner BG, Blesch KS: Estimating the starting dose for entry into humans: principles and practice. *Eur J Clin Pharmacol* 2002;57:835-845.

3. U.S. Food and Drug Administration: Draft guidance for industry and reviewers: estimating the safe starting dose in clinical trials for

therapeutics in adult healthy volunteers. *Fed Reg* 2003;68:2340-2341.

4. Freireich EJ, Gehan EA, Rall DP, Schmidt LH, Skipper HE: Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey, and man. *Cancer Chemother Rep* 1966;50:219-244.

5. Shein PS, Davis RD, Carter S, Newman J, Shein DR, Rall DP: The evaluation of anticancer drugs in dogs and monkeys for the prediction of qualitative toxicities in man. *Clin Pharmacol Therap* 1979; 11:3-40.

6. Travis CC, Bowers JC: Interspecies scaling of anesthetic potency. *Toxicol Indust Health* 1991;7:249-260.

7. Watanabe K, Bois FY, Zeise L: Interspecies extrapolation: a reexamination of acute toxicity data. *Risk Anal* 1992;2:301-310.

8. Rhomberg LR, Wolff SK: Empirical scaling of single oral lethal doses across mammalian species based on a large database. *Risk Anal* 1998;18:741-753.

9. Collins JM, Zaharko S, Dedrick RL, Chabner BA: Potential roles for preclinical pharmacology in phase I clinical trials. *Cancer Treat Rep* 1986;70:73-80.

10. Mahmood I, Balian JD: Interspecies scaling: predicting clearance of drugs in humans. Three different approaches. *Xenobiotica* 1996;26:887-895.

11. Boxenbaum H, Fertig JB: Scaling of antipyrine intrinsic clearance of unbound drug in 15 mammalian species. *Eur J Drug Metab Pharmacokin* 1984;9:177-183.

12. Lave TH, Dupin S, Schmitt C, Chou RC, Jaeck D, Coassolo PH: Integration of in vitro data into allometric scaling to predict hepatic metabolic clearance in man: application to 10 extensively metabolized drugs. *J Pharm Sci* 1997;86:584-590.

13. Obach RS, Baxter JG, Liston TE, Silber BM, Jones C, Macintyre F, et al: The prediction of human pharmacokinetic parameters from pre-clinical and in vitro metabolism. *J Pharmacol Exp Ther* 1997; 283:46-58.

14. Boxenbaum H: Interspecies pharmacokinetic scaling and the evolutionary-comparative paradigm. *Drug Metab Rev* 1984;15:1071-1121.

15. Streeter AJ, Stahle PL, Holland ML, Pritchard JF, Takacs AR: Pharmacokinetics and bioavailability of topiramate in the beagle dog. *Drug Metab Dispos* 1995;23:90-93.

16. Streeter AJ, Stahle PL, Hills JF, Lucas PN, McKown LA, Nese SL, et al: Pharmacokinetics of topiramate in the rat. *Pharm Res* 1994; 11(Suppl.):S372.

17. Rosenfeld WE: Topiramate: a review of preclinical, pharmacokinetic, and clinical data. *Clin Ther* 1997;19:1294-1308.

18. Siefert HM, Domdey-Bette A, Henninger K, Hucke F, Kohlsdorfer, Stass HH: Pharmacokinetics of the 8-methoxyquinolone, moxifloxacin: a comparison in humans and other mammalian species. *J Antimicrob Chemotherap* 1999;43(Suppl. B):69-76.

19. Stass H, Kubitza D: Pharmacokinetics and elimination of moxifloxacin after oral and intravenous administration in man. *J Antimicrob Chemotherap* 1999;43(Suppl. B):83-90.

20. Matsumoto K, Miyazaki H, Fuji T, Maeda T, Hashimoto M: Absorption, distribution and excretion of 3-(sulfanoyl [14C] methyl)-1,2-benzisoxazole-(AD-810) in rats, dogs and monkeys and of AD-810 in men. *Arzneim-Forsch* 1983;33:961-967.

21. Izami T, Enomoto S, Hosiyama K, Sasahara K, Shibukawa A, Nakagawa T, et al: Pharmacokinetics of troglitazone, a new and extensively metabolized antidiabetic agent, after oral administration, with an animal scale-up approach. *J Pharmacol Exp Ther* 1996; 277:1630-1641.

22. Howell SR, Hicks DR, Scatina JA, Sisenwine SF: Pharmacokinetics of venlafaxine and o-desmethylvenlafaxine in laboratory animals. *Xenobiotica* 1994;24:315-327.

23. Klamerus KJ, Maloney K, Rudolph RL, Sisenwine SF, Jusko WJ, Chiang ST: Introduction of a composite parameter to the pharmacokinetics of venlafaxine and its active o-desmethyl metabolite. *J Clin Pharmacol* 1992;32:716-724.

24. Bhargava HN, Villar VM, Gulati A, Chari G: Analgesic and hyperthermic effects of intravenously administered morphine in the rat are related to its serum levels. *J Pharmacol Exp Therap* 1991; 258:511-516.

25. Matsuzawa T, Wada Y, Shimoyama M, Nakajima K, Seki T, Sugibayashi K, et al: The effect of different routes of administration on the metabolism of morphine: the disposition of morphine and its metabolites after topical application. *Biopharm Drug Disp* 1994; 15:665-678.

26. Merrell WJ, Gordon L, Wood AJ, Shay S, Jackson EK, Wood M: The effect of halothane on morphine disposition: relative contributions of the liver and kidney to morphine glucuronidation in the dog. *Anesthesiology* 1990;72:308-314.

27. Miline RW, Nation RL, Somogyi AA: The disposition of morphine and its 3-and 6-glucuronide metabolites in humans and animals and the importance of the metabolites to the pharmacological effects of morphine. *Drug Metab Rev* 1996;28:345-472.

28. Adusumalli VE, Yang JT, Wong KK, Kucharczyk N, Sofia RD: Felbamate pharmacokinetics in the rat, rabbit, and dog. *Drug Metab Disp* 1991;19:1116-1125.

29. *Physician's Desk Reference*. 56th ed. Montvale, NJ: Medical Economics Company, 2002.

30. Wu WN, Pritchard JF, Hills JF, Uetz JA, Yorgey KA, McKown LA, et al: Disposition of bepridil in laboratory animals and man. *Xenobiotica* 1992;22:153-169.

31. Kaul S, Dandekar KA, Schilling BE, Barbhaya RH: Toxicokinetics of 2', 3'-didehydro-3'-deoxythymidine, stavudine (D4T). *Drug Metab Disp* 1999;27:1-12.

32. Rana KZ, Dudley MN: Clinical pharmacokinetics of stavudine. *Clin Pharmacokin* 1997;33:276-284.

33. Tanaka Y, Shimojyo H, Hata T, Hashimoto M, Noguchi H: Toxicokinetics of zenarestat, an aldose reductase inhibitor in animals and man. *Xenobiotica* 1994;24:461-471.

34. Sacher G: Relation of lifespan to brain weight and body weight in mammals, in: Wolstenholme GEW, O'Connor M (eds.), *CIBA Foundation Colloquia on Aging*. London: Churchill, 1959;115-133.

35. Mahmood I: Interspecies scaling: predicting oral clearance in humans. *American J Therap* 2002;9:35-42.