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Prediction of Clearance, Volume of Distribution and Half-life by Allometric Scaling and by use of Plasma Concentrations Predicted from Pharmacokinetic Constants: a Comparative Study

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Abstract

Pharmacokinetic parameters (clearance, CL, volume of distribution in the central compartment, Vd_C, and elimination half-life, $t_{½\beta}$) predicted by an empirical allometric approach have been compared with parameters predicted from plasma concentrations calculated by use of the pharmacokinetic constants A, B, α and β, where A and B are the intercepts on the Y axis of the plot of plasma concentration against time and α and β are the rate constants, both pairs of constants being for the distribution and elimination phases, respectively.

The pharmacokinetic parameters of cefpiramide, actisomide, troglitazone, procaterol, moxalactam and ciprofloxacin were scaled from animal data obtained from the literature. Three methods were used to generate plots for the prediction of clearance in man: dependence of clearance on body weight (simple allometric equation); dependence of the product of clearance and maximum life-span potential (MLP) on body weight; and dependence of the product of clearance and brain weight on body weight. Plasma concentrations of the drugs were predicted in man by use of A, B, α and β obtained from animal data. The predicted plasma concentrations were then used to calculate CL, Vd_C and $t_{½\beta}$. The pharmacokinetic parameters predicted by use of both approaches were compared with measured values. The results indicate that simple allometry did not predict clearance satisfactorily for actisomide, troglitazone, procaterol and ciprofloxacin. Use of MLP or the product of clearance and brain weight improved the prediction of clearance for these four drugs. Except for troglitazone, Vd_C and $t_{½\beta}$ predicted for man by use of the allometric approach were comparable with measured values for the drugs studied. CL, Vd_C and $t_{½\beta}$ predicted by use of pharmacokinetic constants were comparable with values predicted by simple allometry. Thus, if simple allometry failed to predict clearance of a drug, so did the pharmacokinetic constant approach (except for actisomide).

The results of this study indicate that caution should be employed in interpreting plasma concentrations predicted for a drug in man by use of pharmacokinetic constants obtained in animals.

Prediction of pharmacokinetic parameters in man from data obtained in lower animals can be of considerable importance in the process of drug development. Such extrapolation, known as interspecies scaling, can be used to predict pharmacokinetic parameters on the basis of body weight. Clearance (CL), volume of distribution of the central compartment (Vd_C), and elimination half-life ($t_{½\beta}$) are three important pharmacokinetic parameters. Many theories and different approaches have been proposed for improving the predictive performance of allometry for CL, Vd_C and $t_{½\beta}$ (Dedrick 1973; Boxenbaum 1982, 1984; Houston 1994; Mahmood & Balian 1996a, b). Besides predicting CL, Vd_C and $t_{½\beta}$, attempts have also been made to predict the plasma concentrations of drugs. One approach in this direction is the use of ''species-invariant time''. This concept was first applied by Dedrick et al (1970) to methotrexate in five mammalian species after intravenous

administration. By transforming chronological time to equivalent time, plasma concentrations of methotrexate were superimposable for all species. Boxenbaum (1982) refined the concept of equivalent time by introducing two new units of pharmacokinetic time, kally-nochrons and apolysichrons. In another approach Swabb & Bonner (1983) and Mordenti (1985) predicted the plasma concentrations of aztreonam and ceftizoxime, respectively, by use of allometric relationships between pharmacokinetic parameters and pharmacokinetic constants A, B, α and β, where A and B are the intercepts on the Y axis of the plot of plasma concentration against time and α and β are the rate constants, both pairs of constants being for the distribution and elimination phases, respectively. Because this approach of predicting plasma concentrations by use of pharmacokinetic constants has not been systematically evaluated, the objective of this study was to compare CL, Vd_C and $t_{1/2\beta}$ predicted by the allometric approach with values obtained from plasma concentrations predicted by use of pharmacokinetic constants. This comparison might also indicate if the pharmacokinetic parameters (CL, Vd_C and $t_{1/2\beta}$) predicted for man from plasma concentrations generated from pharmacokinetic constants from animals are more accurate than the direct allometric approach.

Materials and Methods

Drug selection

A literature search was conducted to obtain values for the pharmacokinetic parameters (CL, Vd_C and $t_{1/2\beta}$) for cefpiramide, actisomide, troglitazone, procaterol, moxalactam and ciprofloxacin. Although these drugs were selected randomly, the selection criteria were based on their different routes of elimination (e.g. metabolism, renal excretion). Moxalactam and ciprofloxacin are mainly eliminated by the renal route. Troglitazone and procaterol are extensively metabolized, whereas about 25% cefpiramide and 33% actisomide are excreted unchanged in the urine. After intravenous administration in animals the pharmacokinetics of all six drugs can be described by a two-compartment model. Intravenous data for troglitazone and procaterol were not available for man. These two drugs were chosen because there might be situations where man cannot be exposed to an intravenous dose of a drug and yet extrapolation of pharmacokinetic parameters from animals to man (given an oral dose) might be warranted. The absolute bioavailability of troglitazone and procaterol were assumed to be 20% (Izumi et al 1996) and 30% (Eldon et al 1993), respectively.

Allometric scaling

Clearance. The allometric equation for clearance was generated by three methods by use of at least three animal species, and the values predicted were compared with those reported for man. A difference of 30% or less (arbitrarily selected) between predicted and observed values was considered a good prediction.

Method I. Clearance of each compound was plotted against the body weight on a log-log scale and clearance in man was predicted by use of equation 1:

$$CL = aW^b \quad (1)$$

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

Method II. The observed clearance values in the different animal species were multiplied by their respective maximum life-span potential (MLP) and were plotted as a function of body weight on a log-log scale. From the allometric equation, the product clearance × MLP was estimated for man and the result was then divided by the MLP of man ($8{\cdot}18 \times 10^5$ h) for prediction of clearance. The maximum life-span potential (MLP) in years was calculated from equation 2 as described by Sacher (1959):

$$\text{MLP (years)} = 185 \cdot 4(BW)^{0{\cdot}636}(W)^{-0{\cdot}225} \quad (2)$$

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

$$CL = aW^b/8 \cdot 18 \times 10^5 \quad (3)$$

Method III. Clearance for each animal 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 was then used to predict the clearance in man by use of brain weight (1·53 kg).

$$CL = aW^b/1 \cdot 53 \quad (4)$$

Volume of distribution and elimination half-life. Volume of distribution and elimination half-life were also plotted as a function of body weight on a log-log scale. The allometric equation thus generated was used to predict volume and half-life in man.

Allometric scaling of pharmacokinetic model parameters

Equation 5, which represents a two-compartment model after intravenous administration, was used to generate plasma concentration data in man from the pharmacokinetic constants predicted from animals:

$$C = Ae^{-\alpha t} + Be^{-\beta t} \quad (5)$$

where A and B are the intercepts on the Y axis of the plot of plasma concentration against time and α and β are the rate constants, both pairs of constants being for the distribution and elimination phases, respectively.

The pharmacokinetic constants (A, B, α and β) were plotted as a function of body weight on a log-log scale. The allometric equation thus generated was used to predict pharmacokinetic constants in man. To predict plasma concentration in man the predicted pharmacokinetic constants were used. It should be noted that pharmacokinetic constants A and B were normalized according to the dose. For example, if the animals were given 5 mg kg^{-1} dose and the dose in man was 1 mg kg^{-1}, the values for A and B were reduced to one-fifth with no change in α and β. Plasma concentration–time data were generated from the pharmacokinetic constants, and these concentrations were then used to predict clearance, volume and half-life.

The predicted clearance, volume and half-life from both approaches were compared with the observed values, where the observed value is the value reported in the literature for man.

Results

Table 1 summarizes the exponents and correlation coefficients of the allometric equations for CL, Vd_C, $t_{1/2\beta}$, A, B, α and β for the six drugs; the table also lists the species used in the scaling. Correlation between body weight and CL, Vd_C and $t_{1/2\beta}$ across species was good whereas that between body weight and A, B, or α was poor. Although prediction of A and B was occasionally within the acceptable range despite poor correlation between body weight and A or B, prediction of α was in gross error; β was predicted with reasonable accuracy. These predicted pharmacokinetic

Table 1. The exponents and correlation coefficients of the pharmacokinetic parameters for the six drugs.

Parameter	Ciprofloxacin	Moxalactam	Troglitazone	Procaterol	Actisomide	Cefpiramide
Clearance						
Exponent	0·822	0·558	0·801	0·824	1·045	0·443
Correlation	0·999	0·995	0·995	0·995	0·998	0·724
Volume of distribution in the central compartment						
Exponent	0·50	0·967	1·0	0·952	0·568	0·883
Correlation	0·931	0·999	0·998	0·993	0·994	0·915
Elimination half-life						
Exponent	0·289	0·278	0·300	0·232	−0·222	0·346
Correlation	0·813	0·999	0·949	0·956	0·468	0·805
A						
Exponent	0·071	−0·062	−0·005	0·049	0·433	0·127
Correlation	0·087	0·776	0·07	0·384	0·982	0·390
B						
Exponent	−0·057	0·161	−0·184	0·034	0·426	0·138
Correlation	1·0	0·965	0·731	0·223	0·989	0·256
α						
Exponent	−0·149	−0·323	−0·279	−0·007	0·289	0·030
Correlation	0·103	0·973	0·999	0·138	0·979	0·434
β						
Exponent	−0·275	−0·283	−0·300	−0·232	0·023	−0·342
Correlation	0·828	1·0	0·949	0·956	0·490	0·804

The species used in the scaling were: ciprofloxacin: rabbit, dog, pig; moxalactam: rat, dog, monkey; troglitazone: mouse, rat, dog, monkey; procaterol: rat, rabbit, dog; actisomide: rat, dog, monkey; cefpiramide: rat, rabbit, dog, monkey. Data for the six drugs were obtained from: ciprofloxacin, Drusano et al (1986), Nouws et al (1988), Abadia et al (1994) and Aramayona et al (1996); moxalactam, Sugeno et al (1980) and Yamada et al (1980); troglitazone, Izumi et al (1996); procaterol, Ishigami et al (1979) and Eldon et al (1993); actisomide, Cook et al (1993); and cefpiramide, Matsui et al (1982) and Nakagawa et al (1984).

constants were used to predict plasma concentrations in man. Plasma concentrations were then used to predict CL, Vd_C, and $t_{½\beta}$ in man.

Table 2 summarizes the predicted and observed values of the pharmacokinetic parameters for the six drugs in man. The results indicate that although simple allometry did not predict clearance satisfactorily for actisomide, troglitazone, procaterol and ciprofloxacin, utilization of MLP or the product of clearance and brain weight, as suggested by Mahmood & Balian (1996b) improved the prediction of clearance for these four drugs. The exponent of moxalactam and cefpiramide was less than 0·7, hence according to Mahmood & Balian (1996b) simple allometry should predict the clearance of these two drugs with reasonable accuracy. The clearance of moxalactam was predicted fairly well but the predicted clearance of cefpiramide was more than twice the observed clearance. The predicted volume of distribution (except troglitazone) and elimination half-life in man using the allometric approach were comparable with the observed values for the drugs studied.

When pharmacokinetic constants were used, only clearance of actisomide was predicted accurately from plasma concentrations. Predicted clearances of ciprofloxacin, troglitazone and procaterol were in error when calculated from plasma concentrations generated by pharmacokinetic constants. Both volume of distribution and half-life were predicted with the same accuracy as by simple allometry. The exception was ciprofloxacin, for which the volume of distribution predicted from pharmacokinetic constants was over twice the observed volume.

Discussion

Interspecies scaling is becoming an important scientific tool during drug development. Its importance obviously lies in first-time dosing to man. The common practice in interspecies scaling is to predict CL, Vd_C, and $t_{½\beta}$ using an empirical approach, i.e. dependence on body weight of the pharmacokinetic parameter of interest. Because prediction of pharmacokinetic parameters might not be always accurate and predictions can deviate manyfold from observed values, constant efforts have been made to improve the prediction of pharmacokinetic parameters and many different approaches have been made in this direction. One early attempt was to predict plasma concentrations by use of species-invariant time (Dedrick et al 1970). Unfortunately, the concept of

Table 2. Predicted and observed pharmacokinetic parameters for the six drugs, in man.

Parameter	Ciprofloxacin	Moxalactam	Troglitazone	Procaterol	Actisomide	Cefpiramide
Clearance ($mL\,min^{-1}$)						
Observed	423	82	178[a]	296[a]	424	18
Simple allometry	1085	55	359	984	825	42
MLP × CL	270	28	178	308	574	18
Brain wt × CL	116	22	101	182	473	14
Predicted[b]	986	54	309	800	387	33
Volume of distribution in the central compartment (L)						
Observed	33·0	3·7	96·0	24·0	7·0	3·3
Predicted	26·3	6·4	21·0	32·5	6·7	4·7
Predicted[b]	75·0	6·0	22·5	32·7	6·7	4·0
Elimination half-life (h)						
Observed	4·1	1·3	7·0	4·2	1·9	3·9
Predicted	3·9	1·8	7·8	3·0	1·2	3·4
Predicted[b]	3·7	1·9	7·7	3·0	1·2	3·3
A ($\mu g\,mL^{-1}$)						
Observed	2·95	173·3	NA[c]	NA	6·77	179·4
Predicted[b]	1·10	63·7			6·45	156·0
B ($\mu g\,mL^{-1}$)						
Observed	0·44	97·0	NA	NA	0·45	123·8
Predicted[b]	0·23	102·4			1·05	96·9
α (h^{-1})						
Observed	7·05	9·0	NA	NA	6·5	1·94
Predicted[b]	3·64	3·37			39·4	7·40
β (h^{-1})						
Observed	0·17	0·53	0·10	0·17	0·39	0·18
Predicted[b]	0·19	0·37	0·09	0·23	0·58	0·21

[a]Oral clearance of troglitazone and procaterol was 891 $mL\,min^{-1}$ and 988 $mL\,min^{-1}$, respectively. The clearance values in the table for troglitazone and procaterol are after adjusting for absolute bioavailability (20 and 30%, respectively). [b]Predicted from pharmacokinetic constants. The values for A and B are after adjustment for the dose for man. NA = no observed values available.

species-invariant time has not been thoroughly investigated.

By using pharmacokinetic constants Swabb & Bonner (1983) and Mordenti (1985) accurately predicted plasma concentrations of aztreonam and ceftizoxime, respectively. Like the species-invariant time method this approach also has not been systematically evaluated. This report describes an attempt to compare pharmacokinetic parameters predicted by the allometric approach with those predicted by use of plasma concentrations in turn predicted from pharmacokinetic constants. This report also examines whether the use of pharmacokinetic constants helps improve the predictive performance of allometric scaling.

The results of this study indicate that the use of pharmacokinetic constants is not necessarily an improvement on the conventional allometric approach. Although values of CL, Vd_C and $t_{½\beta}$ predicted by simple allometry were comparable with those obtained from pharmacokinetic constants, CL predicted by simple allometry was too high by more than a factor of two for five of the six drugs. Although the pharmacokinetic constants provided an accurate prediction of the clearance of actisomide, overprediction of the clearance of troglitazone, procaterol and ciprofloxacin indicates that predicted plasma concentrations of these three drugs were less than observed concentrations by a factor of two or more. Prediction of clearance by simple allometry was improved by use of the approach of Mahmood & Balian (1996b), who suggested that if the exponent of simple allometry is between 0·7 and 1·0 the MLP approach is suitable for accurate prediction of clearance, whereas prediction of clearance can be improved by integrating brain weight in clearance if the exponent of simple allometry is ≥ 1. Indeed this was so for actisomide (exponent = 1·045), troglitazone (exponent = 0·801), procaterol (exponent = 0·824), and ciprofloxacin (exponent = 0·822). The clearance of actisomide was predicted accurately by using brain weight, whereas accurate prediction of the clearance for troglitazone, procaterol and ciprofloxacin was obtained by using MLP (Table 2).

The correlation between body weight and A, B or α was unpredictable. Overall, poor correlation was obtained between body weight and pharmacokinetic constants. The prediction of α was in gross error whereas β was predicted with reasonable accuracy. Despite the poor correlation, the predicted values of A and B for some drugs were comparable with observed values. This resulted in a predicted value of Vd_C comparable with that obtained by simple allometry, although ciprofloxacin was an exception. It should be emphasized that the similar predicted and observed values of Vd_C might be by chance rather than reflecting real dependence and caution must be employed when interpreting such predictions from pharmacokinetics constants (A and B).

Furthermore, plasma concentrations of the evaluated drugs could not be predicted with accuracy because of errors in the predicted values of A, B and α. Values of α, in particular, deviated from observed values by at least a factor of two. Although the macrokinetic constants method might provide some indication of plasma concentrations, the accuracy of the method for predicting plasma concentrations in man is questionable.

References

Abadia, A. R., Aramayona, J. J., Munoz, M. J., Pladelfina, J. M., Saez, M. P., Bregante, M. A. (1994) Disposition of ciprofloxacin following intravenous administration in dogs. J. Vet. Pharmacol. Ther. 17: 384–388

Aramayona, J. J., Mora, J., Fraile, L. J., Garcia, M. A., Abadia, A. R., Bregante, M. A. (1996) Penetration of enrofloxacin and ciprofloxacin into breast milk, and pharmacokinetics of the drugs in lactating rabbits and neonatal offspring. Am. J. Vet. Res. 57: 547–553

Boxenbaum, H. (1982) Interspecies scaling, allometry, physiological time and the ground plan of pharmacokinetics. J. Pharmacokin. Biopharm. 10: 201–227

Boxenbaum, H. (1984) Interspecies pharmacokinetic scaling and the evolutionary-comparative paradigm. Drug. Metab. Rev. 15: 1071–1021

Boxenbaum, H., Fertig, J. B. (1984) Scaling of antipyrine intrinsic clearance of unbound drug in 15 mammalian species. Eur. J. Drug. Metab. Pharmacokin. 9: 177–183

Cook, C. S., Rozek, L. F., Stolzenbach, J., Anderson, S., Schoenhard, G. L., Karim, A. (1993) Pharmacokinetics of a novel antiarrhythmic drug, actisomide. Pharm. Res. 10: 427–433

Dedrick, R. L. (1973) Animal scale-up. J. Pharmacokin. Biopharm. 1: 435–461

Dedrick, R. L., Bischoff, K. B., Zaharko, D. Z. (1970) Interspecies correlation of plasma concentration history of methotrexate (NSC-740). Cancer. Chemother. Rep. (Part 1) 54: 95–101

Drusano, G. L., Plaisance, K. I. A., Standiford, H. C. (1986) Dose ranging study and constant infusion evaluation of ciprofloxacin. Antimicrob. Agents. Chemother. 30: 440–443

Eldon, M. A., Battle, M. M., Coon, M. J., Nordblom, G. D., Sedman, A. J., Colburn, W. A. (1993) Clinical pharmacokinetics and relative bioavailability of oral procaterol. Pharm. Res. 10: 603–605

Houston, J. B. (1994) Utility of in vitro drug metabolism data in predicting in vivo metabolic clearance. Biochem. Pharmacol. 47: 1469–1479

Ishigami, M., Saburomaru, K., Niino, K., Kido, M., Morita, S., Miyamoto, G., Kohri, H. (1979) Pharmacokinetics of procaterol in the rat, rabbit and beagle dog. Arzneim. Forsch. 29: 266–270

Izumi, T., Enomoto, S., Hosiyama, K., Sasahara, K., Shibukawa, A., Nakagawa, T., Sugiyama, Y. (1996) Prediction of the human pharmacokinetics of troglitazone, a new and extensively metabolized antidiabetic agent, after oral administration, with an animal scale-up approach. J. Pharmacol. Exp. Ther. 277: 1630–1641

Mahmood, I., Balian, J. D. (1996a) Interspecies scaling: predicting pharmacokinetic parameters of antiepileptic drugs in man from animals with special emphasis on clearance. J. Pharm. Sci. 85: 411–414

Mahmood, I., Balian, J. D. (1996b) Interspecies scaling: predicting clearance of drugs in man. Three different approaches. Xenobiotica 26: 887–895

Matsui, H., Yano, K., Okuda, T. (1982) Pharmacokinetics of cephalosporin SM-1652 in mice, rats, rabbits, dogs, and rhesus monkey. Antimicrob. Agents Chemother. 22: 213–217

Mordenti, J. (1985) Pharmacokinetic scale-up: accurate prediction of human pharmacokinetic profiles from human data. J. Pharm. Sci. 74: 1097–1099

Nakagawa, K., Koyama, M., Matsui, H., Ikeda, C., Yano, K., Nakatsuru, N., Yoshinaga, K., Noguchi, T. (1984) Pharmacokinetics of cefpiramide (SM-1652) in man. Antimicrob. Agents Chemother. 25: 221–225

Nouws, J. F. M., Mevius, D. J., Vree, T. B., Baars, A. M., Laurensen, J. (1988) Pharmacokinetics, renal clearance and metabolism of ciprofloxacin following intravenous and oral administration to calves and pigs. Vet. Quarterly 10: 156–163

Sacher, G. (1959) In: Wolstenholme, G. E. W., O'Connor, M. (eds) CIBA Foundation Colloquia on Aging, Churchill, London, pp 115–133

Sugeno, K., Okabe, H., Tanaka, H., Norikura, R. (1980) Disposition of 6059-S in rats, dogs and monkeys. Chemotherapy 28 (Suppl. 7): 194–195

Swabb, E., Bonner, D. (1983) Prediction of aztreonam pharmacokinetics in man based on data from animals. J. Pharmacokinet. Biopharm. 11: 215–223

Yamada, H., Yoshida, T., Oguma, T., Kimura, Y., Tochino, Y., Kurihara, T., Nagatake, F. (1980) Clinical pharmacology of 6059-S in healthy volunteers. Chemotherapy 28 (Suppl. 7): 251–262