Prediction of Human Drug Clearance from Animal Data: Application of the Rule of Exponents and 'fu Corrected Intercept Method' (FCIM)

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ABSTRACT: The objective of this study is to evaluate the predictive performance of the rule of exponents (ROE) and 'fu Corrected Intercept Method' (FCIM) for the human drug clearance. Different classes of drugs such as extensively metabolized, renally excreted, renally secreted, and biliary excreted drugs were used in this analysis. The results of the study indicated that both these methods under given conditions are extremely useful for the prediction of human drug clearance. There are certain situations under which one of these methods is more suited than the other method. Overall, it appears that a rational use of FCIM and the ROE can help a great deal in obtaining a better estimate of the human drug clearance for a wide variety of drugs. The advantages and disadvantages of these two methods are also discussed. J Pharm Sci 95:1810–1821, 2006

Keywords: allometric scaling; preclinical pharmacokinetics; clearance; protein binding; biliary excretion; renal clearance; vertical allometry

INTRODUCTION

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.[1–3] Since clearance is an important pharmacokinetic parameter, a lot of emphasis has been given to the prediction of clearance from animals to man. Over the years, many different approaches have been suggested to improve the prediction of clearance in humans.[4–10]

It is now well established that simple allometry (SA) is not adequate for the prediction of clearance for drugs and based on the exponents of the SA, one may require correction factors (CF)[4,11] to improve the prediction of human drug clearance. In order to improve the prediction of human drug clearance from animal data, Mahmood and Balian,[4] developed the "rule of exponents." The rule of exponents (ROE) was developed from real observations and behavior of the allometric exponents. The ROE has helped a great deal in improving the human drug clearance over SA and it has also provided the guidelines for the selection of CF such as the maximum life span potential (MLP) and brain weight (BW) (before the ROE these CF were applied randomly). However, the ROE is not rigid and there are many examples where predictions obtained from this method was not accurate but produced less prediction error than SA for the same drug. Although not perfect, at this time ROE remains the method of choice for the prediction of human drug clearance for a wide variety of drugs following both intravenous and oral administration.[12]

In a recent paper, Tang et al.[13] have suggested a new approach to improve the prediction of human

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drug clearance. Using 61 drugs, the authors have derived a universal equation (as shown in Eq. 1) to predict human clearance for a wide variety of drugs without the need of any CF. One of the hallmarks of this work is that the method predicts the clearance of drugs with high degree of accuracy which are known to follow vertical allometry (although at this time it is not exactly known how to define vertical allometry). The authors also compared their universal equation with ROE and concluded that their method predicts the clearances of most of the drugs with more accuracy than ROE. This comparison, however, is based on the back extrapolation of the same data. In other words, the authors have used 61 drugs to develop their model and then have used the same 61 drugs to validate their model. This approach is highly likely to give the best result for any model developed in this way. Furthermore, the comparison was based on two methods of calculation of percent error. For example, if the observed value is 40 and the prediction from method A is 65 and method B is 15 then the prediction error according to the authors, is 62.5% (denominator is 40) by method A and 166.7% (denominator is 15) by method B. In both cases the prediction error is off by 25 units. Therefore, this method of calculation of percent error introduces substantial bias for one method over other.

As mentioned above, the ROE is not rigid and under some circumstances the ROE is either not applicable or requires additional physiological CF. For example, the ROE is not applicable to renally secreted drugs,[11] and physiological CF along with the ROE are needed[11] to improve the prediction of human drug clearance for biliary excreted drugs. Furthermore, it was noticed that those drugs that have exponents less than 0.55 are generally underpredicted, although not necessarily the predicted clearance value is in gross error. It was also noted by Mahmood and Balian[4] if the exponents of the SA is >1.3 it is highly likely that the predicted clearance may be several times higher than the observed clearance. Considering that the proposed method by Tang et al.[13] predicted the clearance of drugs known to follow vertical allometry and several drugs fairly accurately, the objectives of this study are as follows:

- To evaluate the performance of Tang et al.'s method (onward this method will be called 'fu Corrected Intercept Method' (FCIM) by using those drugs which were not included in the derivation of Eq. 1.
- To evaluate if FCIM can predict the clearance of renally secreted drugs with more accuracy than the proposed CF (not based on ROE) by Mahmood.
- To evaluate if FCIM can predict the clearance of biliary excreted drugs with more accuracy than the proposed CF (ROE + phyphysiological CF) by Mahmood.
- To evaluate if one can achieve improved prediction of human drug clearance by the method of Tang et al. when the exponents of allometry are either <0.55 or >1.3.

METHODS

A literature search was conducted and clearance values for 40 drugs that were studied in at least three animal species (mice, rat, rabbit, monkey, or dog) were obtained. Since for some drugs, the data were available for both intravenous and oral administration, the total number of observations was 45. Human data were not included in the scaling and the predictions were made using human body weight of 70 kg. The following two methods were used to predict human clearance from animal data:

fu Corrected Intercept Method

$$\text{Predicted human drug CL} = 33.35 \times \left(\frac{a}{\text{Rf}_\text{u}}\right)^{0.77} \quad (1)$$

where a = intercept obtained from the log-log plot of CL versus body weight using at least three animal species; Rf_u = ratio of unbound fraction in plasma between rats and humans. The constant of the equation is 33.35 and the exponent is 0.77.

The Rule of Exponents

The following three methods were used to predict human drug clearance from laboratory animals (mice, rat, rabbit, dog, and monkey). The predicted human clearance using one of the methods (according to the ROE) was then compared with the observed human clearance.

Simple Allometry

The clearance of each drug is plotted against the body weight on a log-log scale (where logs are