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Vertical allometry: Fact or fiction? ☆

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ABSTRACT

In pharmacokinetics, vertical allometry is referred to the clearance of a drug when the predicted human clearance is substantially higher than the observed human clearance. Vertical allometry was initially reported for diazepam based on a 33-fold higher human predicted clearance than the observed human clearance. In recent years, it has been found that many other drugs besides diazepam, can be classified as drugs which exhibit vertical allometry.

Over the years, many questions regarding vertical allometry have been raised. For example, (1) How to define and identify the vertical allometry? (2) How much difference should be between predicted and observed human clearance values before a drug could be declared 'a drug which follows vertical allometry'? (3) If somehow one can identify vertical allometry from animal data, how this information can be used for reasonably accurate prediction of clearance in humans?

This report attempts to answer the aforementioned questions. The concept of vertical allometry at this time remains complex and obscure but with more extensive works one can have better understanding of 'vertical allometry'.

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1. Introduction

To develop a new therapeutic compound for human use, relevant pharmacological, pharmacokinetics, and toxicological studies are initially conducted in small laboratory animals such as mice, rats, rabbits, dogs, or monkeys. These initial studies are helpful in screening the potential therapeutic compounds in the process of drug development. Pharmacokinetic 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.

Interspecies allometric scaling is based on the assumption that there are anatomical, physiological, and biochemical similarities among animals, which can be described by mathematical models (Boxenbaum, 1984). Similarities in structure and form in animals have been studied and reported for at least three hundred years. The simple hypothesis of scaling was that all physiological parameters were proportional to body size or body mass (Boxenbaum, 1984).

Clearance (CL) is the most important pharmacokinetic parameter. The knowledge of clearance for a drug is very important during drug discovery or screening process because clearance can be used to select first-in-human dose from animals (Boxenbaum, 1984). The inverse of the clearance indicates the total exposure (area under the curve (AUC) of a drug (AUC = Dose/CL). Those drugs which are eliminated quickly may have a low absolute bioavailability and shorter duration in the systemic circulation resulting in a short duration or lack of efficacy. Due to this importance of clearance, over the years enormous attention has been given to predict clearance from animals to humans.

When anthropoid primate brain mass was allometrically plotted against body mass, it was noted that human brain mass was almost 3.4 times greater than the allometrically predicted human brain mass (predicted = 0.45 kg, observed = 1.53 kg) (Boxenbaum and Dilea, 1995). The larger human brain than other species may be due to special capability of adaptation and Calder (1984) called this special adaptation process 'vertical allometry'. In pharmacokinetics, vertical allometry is referred to the clearance of a drug when the predicted human clearance is substantially higher than the observed human clearance.

Vertical allometry was initially noted for human clearance of diazepam (Boxenbaum and Dilea, 1995). The predicted clearance of diazepam in humans (860 mL/min) is 33-fold higher than the observed clearance (26 mL/min) (Klotz et al., 1976). In recent years, it has been found that many other drugs besides diazepam, can be

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classified as drugs which exhibit vertical allometry. The predicted clearances of drugs like valproic acid (Loscher, 1978), tamsulosin (Hoogdalem et al., 1997), susalimod (Pahlman et al., 1998), GV 150526 (Ivarone et al., 1999), and UCN-01 (Fuse et al., 2005) are 29, 16, 11, 54, and 3200 times higher than the observed human clearances, respectively. The role and importance of vertical allometry in allometric scaling is not known but it certainly complicates the prediction of human drug clearance.

2. Objectives

Vertical allometry has been observed with only a handful of drugs and the reason(s) for the occurrence of vertical allometry are not known. The major problems in allometric scaling associated with vertical allometry are:

- To define and identify vertical allometry in the absence of human data.
- The magnitude of difference between predicted and observed human clearance values before a drug could be declared 'a drug which follows vertical allometry'.
- If somehow one can identify vertical allometry from animal clearance values then how this information can be used for reasonably accurate prediction of clearance in humans?

This report attempts to answer the aforementioned questions. In this report, we also assess the impact on the volume of distribution of drugs which are known to follow vertical allometry based on the prediction of human drug clearance.

3. Definition of vertical allometry

Generally, the clearance (after human data are available) of a drug is used to describe if the drug follows vertical allometry. There is no clear definition of vertical allometry and at this time it is not possible to identify a priori (before the availability of human data) which drug will follow vertical allometry? A drug is considered to follow vertical allometry when its predicted clearance is several times (no clear understanding of how many times, may be $\geqslant$5 times or 10 times) higher than the observed human clearance. In this report, we will consider a drug following vertical allometry if the predicted clearance is $\geqslant$5-fold higher than the observed clearance (Tang and Mayersohn, 2006a,b). We will acknowledge that this cut off point is arbitrary.

4. Methods

From the literature, ten drugs were selected for this study. These drugs were diazepam (Klotz et al., 1976), valproic acid (Loscher, 1978), tamsulosin (Hoogdalem et al., 1997), GV 150526 (Ivarone et al., 1999), and UCN-01 (Fuse et al., 2005), susalimod (Pahlman et al., 1998), warfarin (Nagashima and Levy, 1969; Sakai et al., 1983; Thjjssen et al., 1983), antipyrine (Bachmann, 1989; Balani et al., 2002), compounds #36 and #108 (Jones et al., 2011; Ring et al., 2011). All drugs were given to animals and humans by intravenous route.

4.1. Prediction of human clearance

The human clearance was predicted by simple allometry (Mahmood and Balian, 1996), the rule of exponents (Mahmood and Balian, 1996), fu corrected intercept method (FCIM) (Tang and Mayersohn, 2006a,b), and unbound clearance using the rule of exponents where necessary.

4.1.1. Simple allometry

In this approach, clearances of different species were plotted against body weights on a log–log scale (Eq. (1))

$$\log Y = \log a + b \log W \tag{1}$$

where 'a' is the intercept, 'b' is the slope of the line, and 'W' is the body weight.

4.1.2. Rule of exponents

The rule of exponents includes simple allometry (Section 4.1.1) and two correction factors in terms of maximum life span potential (MLP) or brain weight (Mahmood and Balian, 1996). Based on the exponents of the simple allometry, Mahmood and Balian (1996) proposed the following conditions under which only one of the three methods can be used for the prediction of human drug clearance. The proposed methods (as outlined below) help in improving the prediction of human drug clearance as compared to a single simple allometric approach.

1. Simple allometry will predict human drug clearance more accurately than CL $\times$ MLP or CL $\times$ brain weight if the exponent of the simple allometry is within 0.55–0.70.
2. CL $\times$ MLP will predict human drug clearance more accurately compared to simple allometry or CL $\times$ brain weight if the exponent of the simple allometry lies between 0.71 and 0.99.
3. CL $\times$ brain weight will predict human drug clearance more accurately compared to simple allometry or CL $\times$ MLP when the exponent of the simple allometry is $\geqslant$1.0.
4. If the exponents of allometry are <0.55 then it is possible that the predicted clearance will be lower than the observed clearance. This under-prediction of clearance however, may not be of any practical significance. On the other hand, if the exponents of allometry are >1.3 then the predicted clearance, despite the application of brain weight as a correction factor, will be over-predicted and in some instances may be of practical significance.

Susalimod is excreted by biliary excretion and for this kind of drugs a physiological correction factor has been suggested (Mahmood, 2005a,b). Therefore, for the prediction of susalimod clearance, this correction factor was applied with the ROE (exponent of the simple allometry was 0.749).

4.1.3. Product of maximum life-span potential (MLP) and clearance

In this approach, the observed clearance values of at least three animal species are multiplied by their respective maximum life-span potential and are plotted as a function of body weight (Eq. (1)). From the allometric equation, human clearance x MLP value is estimated and then divided by the MLP in humans (8.18×10^5 h) to predict human drug clearance.

$$\mathrm{CL} = \frac{a * (\text{human body weight})^b}{8.18 \times 10^5} \tag{2}$$

where, 'a' is the coefficient and 'b' is the exponent obtained from the plot of body weight and product of MLP and clearance. In Eq. (2), the human MLP value (8.18×10^5) has been given in hours but one can use any unit of time (e.g. years, months, days) provided the unit of time for clearance is consistent across the species for a given drug.

4.1.4. Product of brain weight and clearance

In this approach, the clearances of at least three animal species are multiplied by the brain weight of the species and the product is plotted as a function of body weight on a log–log scale (Eq. (1)). From the allometric equation, human clearance $\times$ brain weight value is estimated and then divided by the human brain weight