Available online at www.sciencedirect.com
ScienceDirect
Advanced Drug Delivery Reviews 59 (2007) 1177–1192
Advanced DRUG DELIVERY Reviews
www.elsevier.com/locate/addr

Application of allometric principles for the prediction of pharmacokinetics in human and veterinary drug development ☆,☆☆

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Received 9 March 2007; accepted 5 May 2007
Available online 16 August 2007

Abstract

The concept of correlating pharmacokinetic parameters with body weight (termed as pharmacokinetic interspecies scaling) from different animal species has become a useful tool in drug development. Interspecies scaling is based on the power function, where the body weight of the species is plotted against the pharmacokinetic parameter of interest. Clearance, volume of distribution, and elimination half-life are the three most frequently extrapolated pharmacokinetic parameters. The predicted pharmacokinetic parameter clearance can be used for estimating a first-in-human dose. Over the years, many approaches have been suggested to improve the prediction of aforementioned pharmacokinetic parameters in humans from animal data. A literature review indicates that there are different degrees of success with different methods for different drugs. Interspecies scaling is also a very useful tool in veterinary medicine. The knowledge of pharmacokinetics in veterinary medicine is important for dosage selection, particularly in the treatment of large animals such as horses, camels, elephants, or other large zoo animals. Despite the potential for extrapolation error, the reality is that interspecies scaling is needed across many veterinary practice situations, and therefore will be used. For this reason, it is important to consider mechanisms for reducing the risk of extrapolation errors that can seriously affect animal safety and therapeutic response. Overall, although interspecies scaling requires continuous refinement and better understanding, the rationale approach of interspecies scaling has a lot of potential during the drug development process.
Published by Elsevier B.V.

Keywords: Pharmacokinetic interspecies scaling; clearance; volume of distribution; elimination half-life; first-in-human dose; veterinary medicine; large animals

Contents

☆ The views expressed in this article are those of the author and do not reflect the official policy of the FDA. No official support or endorsement by the FDA is intended or should be inferred.

☆☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Prediction of Therapeutic and Drug Delivery Outcomes using Animal Models".

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0169-409X/$ - see front matter. Published by Elsevier B.V.
doi:10.1016/j.addr.2007.05.015

1. Introduction

Similarities in structure and form in animals have been studied and reported for at least three hundred years [1]. The simple hypothesis of scaling was that all physiological parameters were proportional to body size or body mass. In 1838, Sarrus and Rameaux developed their theory of 'surface law' for the energy metabolism rates of mammals [3] and in 1936, Huxley and Tessier coined the word "allometry". Allometry is the study of size and its consequences [2]. Allometry is opposite to isometry. Isometry means 'by the same measure' whereas allometry means 'by a different measure'. In isometric system the proportion remains same but in allometric system the proportions are altered in a regular manner. In other words, this change in a specific parameter correlates with differences in size of the organism.

Interspecies allometric 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 the species. This relationship is the scientific basis of allometric scaling [3].

Interspecies pharmacokinetic scaling can be described [3] as an operation when a pharamcokinetic parameter of interest can be scaled across species in an orderly manner (change in a parameter correlates with body weight). Allometric equations represent quantitative trends over orders of magnitude of body weight and provide a method to estimate or predict a physiological process (blood flow, creatinine clearance, heart rate, liver weight, kidney weight, and glomerular filtration rate etc) of several species including humans. Extrapolation of animal data to predict pharmacokinetic parameters in humans is becoming an important tool during drug development. This extrapolation is helpful in facilitating the process of dosing transitions from animals to man and accelerating the drug testing and approval process. The ultimate goal of interspecies pharmacokinetic scaling is to select the first-in-human dose based on predicted pharmacokinetic parameters in humans. Allometric scaling is equally useful in veterinary medicine not only for the prediction of pharmacokinetic parameters in animals but also for the first-in-animal dose selection.

The advantages of interspecies pharmacokinetic scaling are that the approach [4]:

- Is simple and easy to use.
- Requires blood or plasma or serum concentration-time data from which pharmacokinetic parameters can be calculated.
- Knowledge of elimination pathways, plasma protein binding or binding with blood components is helpful but not necessary.
- Data analysis time is short.

The anatomical, physiological, and biochemical similarities among animals can be generalized and expressed mathematically by the allometric equation. The allometric approach has been based on the power function, as the body weight from several species is plotted against the pharmacokinetic parameter of interest on a log–log scale. The power function can be written as follows:

$$Y = aW^b \tag{1}$$

where Y is the parameter of interest, W is the body weight, and a and b are the coefficient and exponent of the allometric equation, respectively. The log transformation of Eq. (1) is represented as follows:

$$\log Y = \log a + b \log W \tag{2}$$

where $\log a$ is the y-intercept, and b is the slope. The slope (b) of the equation indicates the rate of change between a parameter of interest and body weight.

There are several caveats with using the allometric equations [5]. First, in order to derive the allometric equation, one should use certain range of body weights. Calder [6] recommended at least three orders of magnitude. Second, the allometric equations should be used between rather than within species. Third, because the allometric equations are derived using animals not closely related, the equations carry both measurement error as well as biological variables. As a result, the allometric equations may not predict a pharmacokinetic parameter accurately. However, with proper understanding of the nature of allometric equations (slope and intercept), one can use these equations to great advantage for prediction purposes.

In this review, methods for interspecies pharmacokinetic scaling, their shortcomings and advantages as well as many wrong notions which prevail in allometric scaling are discussed.