PHARMACOKINETICS, PHARMACODYNAMICS AND DRUG METABOLISM

Prediction of Drug Tissue to Plasma Concentration Ratios Using a Measured Volume of Distribution in Combination With Lipophilicity

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Received 3 January 2007; revised 9 May 2007; accepted 13 June 2007

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.21130

ABSTRACT: One of the drug specific parameters needed in physiologically based pharmacokinetic (PBPK) models is the tissue to plasma drug concentration ratios (K_p values). The aim of this study was to develop an empirical method for predicting K_p values using a preclinically determined *in vivo* volume of distribution, in combination with descriptors for drug lipophilicity. Pharmacokinetic data in laboratory animals for a wide range of drug compounds were collected. Obtained correlations between K_p values for muscle and other tissues, in a training set of 49 compounds, were used to predict K_p values for a test set of 22 compounds, based on their volume of distribution and lipophilicity. Predicted K_p values agreed well with experimentally determined values ($n = 118$), especially for noneliminating tissues ($r^2 = 0.81$) with 72% and 87% being within a factor ± 2 and ± 3, respectively. In conclusion, we present an empirical method based on a measured volume of distribution and a drug lipophilicity descriptor, which can be used to predict tissue K_p values with reasonable accuracy. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:2324–2339, 2008

Keywords: physiochemical properties; tissue partition; computational ADME; pharmacokinetics; physiological model; distribution; preclinical pharmacokinetics; log P; clinical pharmacokinetics; ADME

INTRODUCTION

Physiologically based pharmacokinetic models (PBPK), in contrast to compartmental models, describe the complex processes of drug flux in the body based on physiological blood flows and the anatomical structure of the studied species. A PBPK model can therefore be applicable to other species, including human beings, by insertion of the appropriate physiological parameters. In contrast to scaling by allometry, PBPK models also offer the possibility to predict multiphasic disposition profiles.

Despite their potential as a useful tool in the drug development process,[1–3] PBPK models have not yet been extensively implemented in the preclinical development phase and for candidate drug selection.[4,5] One of the reasons is the time-consuming and laborious effort it takes to acquire the drug-specific model parameters, in partic-

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Journal of Pharmaceutical Sciences, Vol. 97, 2324–2339 (2008)

ular the tissue-to-plasma concentration ratios ($K_{p\,tissue}$). To extend the use of PBPK model simulations in the drug development process it is essential that the model parameters required can be more conveniently obtained.

Mechanistic based models to predict K_p values based on tissue composition, the physico-chemical properties and plasma protein binding of the compound have been developed by Poulin et al.[6–8] and recently further extended by incorporating electrostatic interactions, using blood cell partitioning, by Rodgers et al.[9,10] With these methods 45–89% of predicted K_p values lie within a factor of ±3 compared to experimental values, although highly depending on datasets evaluated.[7,9–11] These tissue composition based (TCB) methods have their place in the early stages of drug discovery as they enable an initial prediction of K_p values, and hence volume of distribution, to enable simulations of pharmacokinetic profiles prior to performing *in vivo* studies.

On the other hand, once an *in vivo* estimate of the volume of distribution has been obtained it would appear reasonable to use this information if it leads to an improved prediction of tissue partitioning. Predicted K_p values thus obtained can be used in PBPK models, which, after adjustment for species differences in plasma protein binding, can be scaled to other species, including man.

An empirical method using the volume of distribution, and in the case of adipose tissue log *D*, for prediction of tissue K_p values has been presented by Arundel.[12] This approach was recently modified and used when TCB equations gave poor predictions of Vss.[2] Both models were developed based on a limited sample of 10–15 structurally unrelated compounds.

The novel approach presented here, based on a measured volume of distribution and the lipophilicity of the compound, offers an alternative way to predict K_p values.

THEORY

Correlation of K_p Values between Tissues

It has previously been found that K_p values for nonadipose tissues correlate with $K_{p\,muscle}$ and it has been suggested that the latter can be used as a predictor for other tissues.[7,13]

The correlation between muscle and other tissues has previously been described by Björkman[13] by linear regression as:

$$K_{p\,tissue} = a_{tissue} \times K_{p\,muscle} + \text{intercept}_{tissue} \quad (1)$$

where a_{tissue} = slope for tissue.

Poulin and Theil[7] correlated log transformed K_p values:

$$\log K_{p\,tissue} = a_{tissue} \times \log K_{p\,muscle} + \text{intercept}_{tissue} \quad (2)$$

This transformation results in a more even distribution of data and was used in the present study. The correlation between $K_{p\,muscle}$ and other tissues might be improved by adding a drug lipophilicity parameter to the equation:

$$\log K_{p\,tissue} = a_{tissue} \times \log K_{p\,muscle} + b_{tissue} \times \log X_{drug} + \text{intercept}_{tissue} \quad (3)$$

where b_{tissue} = slope for $\log X_{drug}$.

$\text{Log}X_{drug}$ is a compound-specific lipophilicity parameter such as the logarithmic value of octanol:water partitioning (log *P*), adjusted for ionization at physiological pH 7.4 (log *D*), or the vegetable oil:water partitioning adjusted for ionization at pH 7.4 (log $K_{7.4}$). If the log $K_{7.4}$ value has not been experimentally determined it can be calculated by solvent regression equations and the log *P* and pK_a value.[7,14]

Whether to include (Eq. 3) or exclude a lipophilicity descriptor (Eq. 2) can be evaluated by an *F*-test. The descriptor returning the lowest sum of squared residuals is selected. For any new compound its $K_{p\,tissue}$ values can thus be predicted from an estimate of its $K_{p\,muscle}$ value and, when applicable, a lipohilicity descriptor by rearrangement of Eqs. (2) and (3) respectively (Eqs. 4 and 5):

$$K_{p\,tissue} = 10^{a_{tissue} \times \log K_{p\,muscle} + \text{intercept}_{tissue}} \quad (4)$$

$$K_{p\,tissue} = 10^{a_{tissue} \times \log K_{p\,muscle} + b_{tissue} \times \log X_{drug} + \text{intercept}_{tissue}} \quad (5)$$

Predicting K_p Values Based on a Measured Volume of Distribution

The volume of distribution at distributional steady state (Vss) is dependent on the plasma volume and the sum of apparent volumes of each tissue:[15]

$$\text{Vss} = V_{plasma} + \sum_{i=1}^{n} V_{tissue,i} \times \text{K}_{p\,tissue,i} \quad (6)$$

where V_{plasma} = physiological plasma volume, $V_{tissue,i}$ = physiological volume of each tissue.