Advancing Prediction of Tissue Distribution and Volume of Distribution of Highly Lipophilic Compounds from a Simplified Tissue-Composition-Based Model as a Mechanistic Animal Alternative Method

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ABSTRACT: It has been reported that values of tissue–plasma ratios (K_p) and resulting volume of distribution at steady state (V_{ss}) are substantially overpredicted for several highly lipophilic drugs. This effect was observed particularly with the published version of the tissue-composition-based model, which used experimentally determined unbound fraction in plasma (fu_p) as input for drugs. The reasons for the unreasonably high V_{ss} predictions were investigated in this study for 14 highly lipophilic compounds with a log *n*-octanol–water partition coefficient (log P_{ow}) of at least 5.8. Here, we argue that the experimentally determined fu_p is inaccurate for these compounds, which affected the prediction of K_p and V_{ss}. Alternatively, the tissue-plasma ratio of neutral lipids (nl) equivalent was used as the main factor governing K_p, and hence V_{ss}, in addition to log P_{ow}. The average fold error of deviation between the predicted and observed human V_{ss} is 124 for the published model, whereas it significantly decreased to 1.5 for the proposed model. The sensitivity analysis confirmed the importance of nl content and drug lipophilicity. Overall, this study proposes a generic and simplified tissue-composition-based model for highly lipophilic drugs and chemicals, which is a step forward toward improving prediction of V_{ss} into physiologically based pharmacokinetic (PBPK) models. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:2250–2261, 2012
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INTRODUCTION

The volume of distribution at steady state (V_{ss}) and clearance processes characterize the disposition of drugs. Thus, the estimation of V_{ss} is essential. An approach that has gained popularity in recent years is to use *in vitro* and physicochemical data for a particular compound to estimate its tissue–plasma ratio (K_p) and by accounting for the volumes of different tissues and their composition.[1–19] This information is integrated in a physiological manner to predict V_{ss} of a compound referring to plasma pharmacokinetics (Eq. 1)[7,16,20]:

$$V_{ss} = (\Sigma V_t \times K_p) + V_p \quad (1)$$

where V is the fractional body volume (L/kg), t is tissue, and p is plasma. By definition, K_p is the numerical value representing the ratio of concentration in tissues and plasma at equilibrium. There is a conceptual difference between chemicals and drugs because the traditional tissue-composition-based equations in the literature predict tissue partitioning of chemicals on the basis of total concentration (i.e., K_p), whereas the most advanced equations predict tissue

Abbreviations used: fu_p, unbound fraction in plasma; fu_t, unbound fraction in tissue; nl, neutral lipids; apl, acidic phospholipids; *I*, ionization term; K_p, tissue–plasma ratio; K_{pu}, tissue—plasma ratio for the unbound drug; P_{ow}, *n*-octanol–water PC; P_{vow}, vegetable oil–water PC; PC, partition coefficient; PCB, polychlorinated biphenyl; V_{ss}, volume of distribution at steady state.

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partitioning of drugs principally for the unbound concentration (i.e., the tissue-to-water partitioning; K_{pu}).[1–19] The later provides K_p estimates from the product of K_{pu} and unbound fraction in plasma (fu_p).

It has been reported that the resulting values of V_{ss} was substantially overpredicted by using the tissue-composition-based model for highly lipophilic drugs, which have a log *n*-octanol–water (log P_{ow}) partition coefficient (PC) greater than 5.8.[2,20] However, initial validations of such model contained few drugs of high lipophilicity. Nevertheless, there are a number of possible reasons that may explain the inaccuracies with V_{ss} of highly lipophilic drugs. Among the most probable reasons are significant errors in experimental assessment of essential input parameters on physicochemical properties (e.g., log P_{ow}) and/or fu_p. This was illustrated by a simulation conducted with the tissue-composition-based model, where both the total and unbound V_{ss} increased exponentially when the value of log P_{ow} exceeds the range 3–6.[16] The general perception behind the tissue-composition-based model is a proportional increase in K_p values, and hence V_{ss}, as a function of lipophilicity.[16] However, it might be that this effect may not be entirely true above a certain log P_{ow} value.[7,18,19]

In this context, some comparisons of observed adipose K_p versus log P_{ow} have indicated that K_p, and hence V_{ss}, might not increase exponentially with log P_{ow}, but might plateau instead. This has been actually demonstrated in environmental sciences with respect to the K_p of adipose tissue of highly lipophilic neutral pollutants.[18] In the case of adipose tissue, it is not the adipose tissue *per se* that accounts for chemical storage, but rather its neutral lipid (nl) portion. Because the distribution in the nl equivalent is likely to be the same for adipose tissue lipids and blood lipids, it has been demonstrated that the adipose K_p values is relatively equal to the ratio of lipid content between the adipose tissue and blood under *in vivo* conditions for several highly lipophilic pollutants.[18] This observation suggests that there is a theoretical upper limit of the K_p value of both the nonadipose and adipose tissues, and hence of V_{ss} value, for highly lipophilic organic compounds.[7,18,19]

As highly lipophilic drugs tend to be commonplace in discovery and development, improvement in prediction methods of tissue distribution would be advantageous. Therefore, the reasons for the unreasonable overpredictions of V_{ss} for highly lipophilic drugs were investigated. This study basically intended to demonstrate that K_p and V_{ss} values might be restricted by the physiology above a certain log P_{ow} value.

METHODS

The overall strategy is divided into four steps. The first step consists of presenting the original tissue-composition-based model. The second step presents the simplified (adjusted) model to reflect the limitations of K_p and V_{ss} by the physiology, and the third step evaluates the performance of both the published and simplified model using the same dataset of highly lipophilic compounds. Finally, a sensitivity analysis is presented to demonstrate the importance of the physicochemical properties (P_{ow}), binding parameters (fu_p), and tissue partitioning (K_p) reflective of specific mechanistic determinants relevant to prediction of V_{ss} values of highly lipophilic drugs and chemicals.

Presentation of the Original Tissue-Composition-Based Model

A model unifying the principles of different tissue-composition-based models was used for the purpose of this study.[3,4] In other words, the unified model adequately reproduced the values predicted previously by diverse tissue-composition-based models published in the literature either based on K_{pu} or K_p data. The overall K_p is determined by the ratio between fu_p and the unbound fraction for a tissue (fu_t). Therefore, the partitioning into each matrix is determined from a combination of drug distribution in the water spaces, specific binding to proteins and acidic phospholipids (apl), and nonspecific binding to nl equivalent at equilibrium[3,4] (Eqs. 2 and 3):

$$fu_p = \left\{ (1+I_w) \Big/ \begin{array}{r} (1+I_{up})\cdot F_{wp} + P_{nlw}\cdot F_{nlp} \\ + I_{up}\cdot P_{aplw}\cdot F_{aplp} \\ + (1+I_{up})\cdot P_{prw}\cdot F_{prp} \end{array} \right\} \quad (2)$$

$$fu_t = \left\{ (1+I_w) \Big/ \begin{array}{r} (1+I_{wt})\cdot F_{wt} + P_{nlw}\cdot F_{nlt} \\ + I_t\cdot P_{aplw}\cdot F_{aplt} \\ + (1+I_{wt})\cdot P_{prw}\cdot F_{prt} \end{array} \right\} \quad (3)$$

where F_w is the fractional volume of water equivalent, F_{nl} is the fractional volume of nl equivalent, F_{apl} is the fractional volume of apl, F_{pr} is the fractional volume of binding proteins, I_w is the ionization term for the water (aqueous) phase in tissue or extracellular water, P_{nlw} is nl–water PC, P_{aplw} is apl–water PC, and P_{prw} is protein–water PC. Accordingly, the value of K_p was obtained by the ratio of fu_p and fu_t at the organ level (Eq. 4)[3,4]:

$$Kp = \left\{ \begin{array}{l} (1+I_{wt})\cdot F_{wt} + P_{nlw} \\ \cdot F_{nlt} + I_{wt}\cdot P_{aplw} \\ \cdot F_{aplt} + (1+I_{wt}) \\ \cdot P_{prw}\cdot F_{prt} \end{array} \Big/ \begin{array}{l} (1+I_{up})\cdot F_{up} + P_{nlw} \\ \cdot F_{nlp} + I_{up}\cdot P_{aplw} \\ \cdot F_{aplp} + (1+I_{up}) \\ \cdot P_{prw}\cdot F_{prp} \end{array} \right\} \quad (4)$$

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