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Estimation of the minimum permeability coefficient in rats for perfusion-limited tissue distribution in whole-body physiologically-based pharmacokinetics

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ABSTRACT

The objective of the current study was to determine the minimum permeability coefficient, *P*, needed for perfusion-limited distribution in PBPK. Two expanded kinetic models, containing both permeability and perfusion terms for the rate of tissue distribution, were considered: The resulting equations could be simplified to perfusion-limited distribution depending on tissue permeability. Integration plot analyses were carried out with theophylline in 11 typical tissues to determine their apparent distributional clearances and the model-dependent permeabilities of the tissues. Effective surface areas were calculated for 11 tissues from the tissue permeabilities of theophylline and its PAMPA *P*. Tissue permeabilities of other drugs were then estimated from their PAMPA *P* and the effective surface area of the tissues. The differences between the observed and predicted concentrations, as expressed by the sum of squared log differences with the present models were at least comparable to or less than the values obtained using the traditional perfusion-limited distribution model for 24 compounds with diverse PAMPA *P* values. These observations suggest that the use of a combination of the proposed models, PAMPA *P* and the effective surface area can be used to reasonably predict the pharmacokinetics of 22 out of 24 model compounds, and is potentially applicable to calculating the kinetics for other drugs. Assuming that the fractional distribution parameter of 80% of the perfusion rate is a reasonable threshold for perfusion-limited distribution in PBPK, our theoretical prediction indicates that the pharmacokinetics of drugs having an apparent PAMPA *P* of 1×10^{-6} cm/s or more will follow the traditional perfusion-limited distribution in PBPK for major tissues in the body.

1. Introduction

PBPK is a modeling technique that can be used to estimate the concentration-time relationship for a drug in the body using anatomical (e.g., tissue volume) and physiological variables (e.g., the perfusion rate, intrinsic clearance) [1,2]. Using this model, it is possible to calculate concentration-time relationships for a given species and/or tissue(s). In line with this, it was recently shown that the steady state tissue-to-plasma concentration ratio (K_p), one of the crucial terms required in PBPK calculations, could be empirically estimated from physicochemical variables (e.g., pK_a, the octanol-to-water partition coefficient, free fraction in the plasma, blood-to-plasma concentration ratio) [3,4]. In addition, key pharmacokinetic properties of compounds such as microsomal

Abbreviations: ABC, ATP-binding cassette; BCA, bicinchoninic acid; BCRP, breast cancer-resistance protein; DPBS, Dulbecco's phosphate-buffered saline; log P_{oct}, octanol-to-water partition coefficient; MDCK, Madin-Darby canine kidney; MDR, multidrug resistance protein; MeOH, methanol; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; *P*, permeability coefficient; PAMPA, parallel artificial membrane permeability assay; PBPK, physiologically-based pharmacokinetics; PBS, phosphate buffered saline; *R*, blood-to-plasma concentration ratio; SLC, solute carrier; SSLD, sum of squared log differences.

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stability [5,6] and free fraction in the plasma [7,8] can be predicted from information obtained from their chemical structure. These techniques permitted concentration-time relationships in animals and humans to be estimated with only very limited [9,10], in some cases without any [11,12], *in vitro*/*in vivo* experimental data. An experimentally-based determination of these pharmacokinetic variables would have necessitated a series of *in vitro*/*in vivo* studies.

Despite the practical merit of PBPK modeling as a predictive tool in pharmacokinetics, however, estimating the rate of drug distribution to tissues may require further refinement. Pharmacokinetic theory states that the rate of tissue distribution is related to both perfusion and permeability. However, the distribution rate in PBPK is assumed to be governed only by perfusion [perfusion-limited model [13]] for a drug with a sufficient permeability, while the rate is described only by the permeability [membrane-limited model [14]] when the drug has insufficient permeability. The literature is not clear on the determining the conditions for tissue permeability between the two possible models. Despite the lack of the clear determinant, however, the perfusion-limited model is typically used in PBPK studies, probably because of the fact that tissue sampling at an early time, where the tissue distribution kinetics is the major component, is not routinely carried out and/or that tissue permeability is often difficult to determine/estimate. Simulations using the perfusion-limited model are frequently done, even in situations where the assumption may not be adequate (e.g., in the early phases of drug discovery programs): In such cases, the prediction might well be significantly inaccurate. In line with this, drug transporters are now becoming increasingly evident as the underlying mechanism for tissue distribution [15,16]. Since the involvement of drug transporters in distribution would imply temporal changes in tissue permeability, the conditions for the appropriate model for tissue distribution may also change with time. Under those circumstances, the selection of the mathematical model to be used for the rate of tissue distribution may become problematic in PBPK.

The objective of the current study was to determine the threshold condition that governs the kinetics of drug distribution to tissues. Thus, tissue distribution models were expanded to include both permeability and perfusion terms in the resulting equation so that threshold condition between the two traditional models can be theoretically estimated. In this study, we attempted to estimate the threshold value in terms of the permeability coefficient (P) measured in a parallel artificial membrane permeability assay (PAMPA), since this value would be readily obtained experimentally [17,18] or computationally [19,20], and, thus, may be relevant in estimating the kinetics of distribution of other drugs to tissues. We report that the pharmacokinetics of a drug having an apparent PAMPA P of 1×10^{-6} cm/s or more may be described by the traditional perfusion-limited tissue distribution in PBPK for major tissues.

2. Theoretical approach

In this theoretical consideration, simple passive diffusion was assumed to be involved for transport processes both into and out of tissues. In this study, the presence of the extracellular space was not taken into consideration, since the volume of the space is generally less than 20% (for the case of the skin, 30.2% [21]) of the tissue volume. Furthermore, the presence of this compartment does not appear to be kinetically crucial in tissue kinetics in the range of permeability from 0.01 to 1000 mL/min (Fig. S1, Supplementary information). Under these assumptions, the following models may be applicable for describing the rate of tissue distribution by perfusion and permeability:

2.1. Model 1

In the literature, the 'capillary permeability model' [22], a kinetic model that simultaneously handles both permeability and perfusion terms for the rate of tissue distribution, was previously considered by Morgan and Huang [23] in compartment models. This approach may also be applied to PBPK (Fig. 1a). Under the assumption of the 'permeable capillary' (Model 1, Fig. 1b; for derivation see Appendix A), the equations for the outflow blood concentration of capillary [Eq. (1)] and for the rate of drug distribution to the tissue [Eq. (2)] may be written as follows;

$$C_{out} = C_{in} \cdot e^{-\frac{f_{up} \cdot PS}{R Q_T}} + \frac{C_T \cdot R}{K_p}\left(1 - e^{-\frac{f_{up} \cdot PS}{R Q_T}}\right) \tag{1}$$

$$V_T \frac{dC_T}{dt} = Q_T\left(1 - e^{-\frac{f_{up} \cdot PS}{R Q_T}}\right) \cdot \left(C_{art,blood} - \frac{C_T \cdot R}{K_p}\right) \tag{2}$$

where V_T is the volume of each tissue; Q_T, the blood flow rate to the tissue; $C_{art,blood}$ and C_T are the drug concentration in arterial blood and tissue, respectively; P and S are the permeability coefficient and surface area across the interface between the systemic circulation and tissue; f_{up}, the free fraction of drug in the plasma; R, the blood-to-plasma concentration ratio; K_p, the tissue-to-plasma concentration ratio; C_{in} and C_{out} are the inflow and outflow blood concentrations of capillary, respectively. Eq. (2) was obtained from Eq. (1) and Fick's law of perfusion.

2.2. Model 2

The 'well-stirred' assumption may also be applicable to tissue distribution in PBPK as described by Thompson and Beard [24] (Model 2, Fig. 1c). This model is essentially identical to the membrane-limited model [14], since the extracellular space was not taken into consideration in this study (Fig. S1, Supplementary information). The equation for the rate of drug distribution to tissue may be defined as (see Appendix B):

$$V_T \frac{dC_T}{dt} = \frac{Q_T \cdot f_{up} \cdot PS/R}{Q_T + f_{up} \cdot PS/R} \cdot \left(C_{art,blood} - \frac{C_T \cdot R}{K_p}\right) \tag{3}$$

The physiological and biopharmaceutical variables appeared in the Eq. (3) are identical to those found in Model 1.

2.3. Steady state tissue-to-plasma concentration ratio

For both models, the steady state tissue-to-plasma concentration ratio (K_p) could be expressed in terms of the ratio of influx and efflux transport rates. Assuming symmetrical transport rates into and out from tissues via simple diffusion, the following relationship may be obtained;

$$K_p = \frac{C_{T,ss}}{C_{p,ss}} = \frac{PS \cdot f_{up}}{PS \cdot f_{uT}} = \frac{f_{up}}{f_{uT}} \tag{4}$$

where $C_{T,ss}$ and $C_{p,ss}$ are the drug concentration at the steady state in tissue and plasma, respectively.

2.4. Limiting conditions

When a drug has a very small PS term, Q_T would become much larger than PS/R. Under this condition, Eq. (2) could be simplified using the Taylor expansion as follows;

$$\begin{aligned} V_T \frac{dC_T}{dt} &= Q_T\left[1 - \left(1 - \frac{f_{up} \cdot PS}{R \cdot Q_T}\right)\right] \cdot \left(C_{art,blood} - \frac{C_T \cdot R}{K_p}\right) \\ &= f_{up} \cdot PS/R \cdot \left(C_{art,blood} - \frac{C_T \cdot R}{K_p}\right) \end{aligned} \tag{5}$$