Physiologically Based Pharmacokinetic Tissue Compartment Model Selection in Drug Development and Risk Assessment

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Received 17 June 2011; revised 31 August 2011; accepted 2 September 2011

Published online 3 October 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.22768

ABSTRACT: A well-stirred tank (WST) has been the predominant flow-limited tissue compartment model in physiologically based pharmacokinetic (PBPK) modeling. Recently, we developed a two-region asymptotically reduced (TAR) PBPK tissue compartment model through an asymptotic approximation to a two-region vascular–extravascular system to incorporate more biophysical detail than the WST model. To determine the relevance of a flow-limited TAR (F-TAR) approach, 75 structurally diverse drugs were evaluated herein using a priori predicted tissue:plasma partition coefficients along with hybrid and whole-body PBPK of eight rat tissues to determine the impact of model selection on simulation and optimization. Simulations showed that the F-TAR model significantly improved the ability to predict drug exposure, with hybrid and whole-body WST model error approaching 50% for tissues with larger vascular volumes. When optimization was used to fit F-TAR and WST models to pseudo data, WST-optimized drug partition coefficients more appropriately represented curve-fitting parameters rather than biophysically meaningful partition coefficients. Median F-TAR-optimized error ranged from −0.4% to +0.3%, whereas WST-optimized median error ranged from −22.2% to +1.8%. These studies demonstrated that the use of F-TAR represents a more accurate, biophysically realistic PBPK tissue model for predicting tissue exposure to drug and that it should be considered for use in drug development and regulatory review. © 2011 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:424–435, 2012

Keywords: pharmacokinetics; physiological model; well stirred model; tissue partition; *in silico* modeling; physicochemical; singular perturbation; asymptotic matching; flow-limited; compartmental modeling

INTRODUCTION

In contrast to classic compartmental pharmacokinetics, physiologically based pharmacokinetic (PBPK) model structure is rooted in anatomic (e.g., volumes and tissue compartment connectivity) and physiologic (e.g., flows and clearance) attributes of the species with consideration of the physicochemical nature of drug partitioning and binding, composition of bodily tissues (e.g., lipids and water), and rates associated with the metabolism of drug by tissues.[1] Through this detailed, mechanism-based approach, simulations of drug absorption, distribution, metabolism, and excretion are constrained by the biophysical characteristics of the system, allowing an understanding of pharmacodynamic and/or adverse effects through evaluation of tissue exposure to a drug or toxin. For these reasons, PBPK has found use in drug development and regulatory review, where large numbers of new chemical entities/investigational new drugs must be evaluated, relying on the integration of many types of data,[2] such as from physicochemical [e.g., a priori predicted tissue:plasma partition coefficients ($P_{t:p}$)], *in vitro* (e.g., rates of metabolism by hepatocytes), and preclinical animal models, to assess dosing and risk in large heterogeneous populations. In addition to improving the ability to predict drug disposition and evaluating the findings from preclinical and clinical studies,[3] the development of physiological models to study drug kinetics allows the translation of findings

Abbreviations used: FBV, fractional blood volume; F-TAR, flow-limited two-region asymptotically reduced; PBPK, physiologically based pharmacokinetics; $P_{t:p}$, tissue:plasma partition coefficient; PLT, permeability-limited two-subcompartment; P-TAR, permeability-limited two-region asymptotically reduced; TAR, two-region asymptotically reduced; WST, well-stirred tank.

Additional Supporting Information may be found in the online version of this article. Supporting Information

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Journal of Pharmaceutical Sciences, Vol. 101, 424–435 (2012)

across species,[4] between normal and altered physiologic and pathophysiologic states,[5] and between child and adult populations.[6] These examples highlight the critical need to continue to develop and improve existing PBPK models to predict the disposition of drugs in human subjects.

A recently published[7] two-region asymptotically reduced (TAR) PBPK tissue compartment model was shown to theoretically improve the standard flow-limited tissue compartment model. Herein, the potential influence and role of the TAR model in drug development and risk assessment is evaluated with both hybrid and whole-body PBPK modeling approaches in eight rat tissues using a group of 75 structurally unrelated compounds, thereby providing a feasible range of $P_{t:p}$ and tissue vascular volumes over which tissue compartment models could be assessed through simulation and optimization.

THEORY

The building block of modeling drug distribution with PBPK is the tissue compartment model. PBPK tissue compartment models are primarily described as being either flow-limited or diffusion-limited. Application of a flow-limited tissue compartment model as a general approach to PBPK modeling for drug discovery and development was presented by Poulin and Theil,[3] and in the field of toxicology, the same flow-limited model is extensively employed to study toxicokinetics.[8] The standard flow-limited (or perfusion-limited) approach models the tissue as a single-compartment, well-stirred tank (WST), defined by the mass balance differential equation:

$$\frac{dc}{dt} = \frac{F}{V}\left(c_{in} - \frac{c}{P_{t:p}}\right) \quad (1)$$

where c is the concentration of drug in the well-stirred compartment, c_{in} is the inflow concentration of drug, F is tissue blood flow, and V is the total volume of the tissue. The tissue:plasma partition coefficient is abbreviated as $P_{t:p}$ and defined in the literature as the ratio of the tissue concentration of drug to the arterial concentration of drug at equilibrium.[9] Equation 1 is equivalently referred to as the WST model and the venous equilibrium model, in which the venous outflow concentration, c_v, is the concentration in the outflowing blood:

$$c_v = \frac{c}{P_{t:p}} = c_{out} \quad (2)$$

For the rest of the presentation, the flow-limited model of Eq. 1 will be referred to as the WST model.

The other PBPK tissue compartment model, though less commonly employed, is important for use in tissues where mass transfer out of the vascular space and into the extravascular space is limited by a permeability barrier and is, therefore, permeation- or diffusion-limited. Tissues possessing a permeability barrier, such as brain, may require the tissue compartment to be modeled with two subcompartments, dependent on the drug lipophilicity.[10] Two ordinary differential equations define the standard diffusion-limited model:

$$\frac{dc_1}{dt} = \frac{F}{V_1}(c_{in} - c_1) - \frac{PS}{V_1}\left(c_1 - \frac{c_2}{P_{t:p}}\right) \quad (3)$$

$$\frac{dc_2}{dt} = +\frac{PS}{V_2}\left(c_1 - \frac{c_2}{P_{t:p}}\right) \quad (4)$$

where c_1 is the concentration of drug in the vascular space, V_1 is the vascular volume, c_2 is the concentration of drug in the extravascular space, V_2 is the extravascular volume, and PS is the permeability–surface area product. Equations 3 and 4 can be thought of as an extension of the WST model (Eq. 1) with addition of permeation between two well-stirred subcompartments. This model will be referred to as the permeability-limited two-subcompartment (PLT) model. Together, Eqs. 1, 3, and 4 represent the vast majority of PBPK tissue compartment models used in the literature[1] because they provide a framework for analyzing physiologically rich experimental data sets and predicting *in vivo* kinetics, especially exposure of the target tissue to drug.

Motivation for Development of TAR Model Equations

In the WST model, drug is assumed to instantaneously mix and, therefore, drug concentration is homogeneous throughout the entire compartment. Though the WST model has been implemented in evaluating a range of drugs and toxins, it does not account for potential regional variation in vascular–extravascular concentration as a result of drug-specific physicochemical and tissue-specific properties. As a result, selection of the most appropriate model may not simply depend on successful fitting of drug time courses, but rather on the basis of the model parameters possessing more biophysical, mechanistic meaning. Analysis of the WST and TAR models reveals that the TAR formulation more closely approximates the behavior of the PLT model in the flow-limited regime of $PS/F \to \infty$ and is, therefore, a first-order improvement over the WST model.[7]

TAR Model Equations

Because the permeability-limited (P-TAR) and flow-limited TAR (F-TAR) PBPK models agree with the PLT model over a wider range of physiological and physicochemical parameter values than the WST