



Current PBPK Models: Are They Predicting Tissue Drug Concentration Correctly?

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Physiologically based pharmacokinetic (PBPK) models have been receiving extensive attention from biomedical scientific journals for the last 15 years. Even though the concept was first introduced by Teorell [1], recent improvements in computing power have led to an explosive development and implementation of several software platforms containing such models at their core [2–5]. These tools are being increasingly implemented in drug discovery and development, as both the industry and the regulating agencies embrace their application for specific assessments such as drug–drug interactions and dosage recommendations in specific sub-populations [6, 7]. The reason for such interest is that PBPK models have been established as valid tools in the instrumentation of “bottom-up” and “middle-out” approaches, where the pharmacokinetic profile of a compound for a non-explored scenario can be simulated using previous knowledge of the drug and the organism, eventually integrating in-vitro experiments. This allows prior evaluation of several factors that can affect drug pharmacokinetics such as the dosage form, administration route, food intake, and comedication, and individual characteristics such as ethnicity, age, sex, and disease state [8].

Parameter optimization in PBPK modeling is routinely carried out by the adjustment of simulated concentrations to the experimental blood or plasma concentration–time profiles. Commonly, drug blood concentrations displayed in these platforms belong to both the central vein and the artery but not to peripheral veins, which are the usual sampling site in clinical trials. Several researchers became aware of this aspect and proposed some modifications to the model for the purpose of estimating the correct arteriovenous difference of drug concentrations [9–11].

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Nevertheless, the most important concentration to be assessed in silico, and then correlated with the in vivo profile, should be the extravascular concentration, at the site where most drugs will be acting to produce either therapeutic or toxic effects. These sites could be located in the interstitial space (external face of the cell membrane) or in the intracellular space. Hence, a better pharmacokinetic/pharmacodynamic relationship could be attained from concentrations at the action sites and not from peripheral veins. In fact, this should be the main goal for such PBPK modeling: to predict effective and safe treatments and not to forecast plasma drug concentrations anywhere along the circulatory system. Unfortunately, even though great efforts have been made to predict extravascular tissue drug concentrations using perfusion and permeability rate-limited models with appropriate tissue/plasma partition coefficients, these models are still unable to provide accurate predictions for an individual under different physiologic (i.e., circadian rhythm of the cardiac output distribution) or physiopathologic (i.e., ischemia) states.

Several reports about the refractoriness to antimicrobial treatments were published in some populations [12, 13] and in the same individual under different clinical states [14], or with altered blood perfusion in a region of their bodies [15, 16]. These reports provided evidence of dissimilar drug access to the interstitial space of tissues in relation to healthy tissues. Our research group intended to simulate ciprofloxacin in ischemic and healthy tissues with lower blood perfusion [16] in respect to healthy tissues with normal blood flow using the software given in a recent publication [17]. We were unable to detect any change in the amount of drug partitioned into both tissues (ischemic and healthy) except for their time-dependent profile. However, when we modified the algorithm of the program accordingly to the proposal displayed below, simulated extravascular tissue concentrations of ciprofloxacin exhibited a good correlation with the experimental healthy and ischemic tissues obtained using a microdialysis technique [16].

In our view, the origin of such predictive failures lies in the method of exchange of substances between intra- and extravascular spaces proposed in these models. Here, we retrieve the differential equations dealing with the systemic amount (X) balance and the exchange of a drug at a non-eliminating tissue (T):

$$\frac{dX_{\text{Artery}}}{dt} = k_{VA} \cdot X_V - \left(\sum_j^n k_{AT,j} \right) \cdot X_A \quad (1)$$

$$\frac{dX_{\text{Intravascular}}}{dt} = k_{AT} \cdot X_A - k_{Tivev} \cdot X_{Tiv} + k_{Teviv} \cdot X_{Tev} - k_{TV} \cdot X_{Tiv} \quad (2)$$

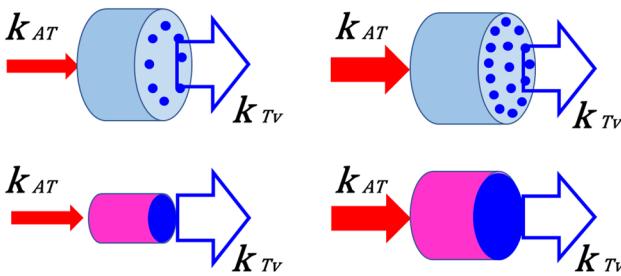


Fig. 1 Graphical representation of a tissue under low (left side) or high (right side) consumption of oxygen in a hypothetical constant cardiac output. Blood flowing through a higher fraction of the capillary bed could be viewed as a wider cylinder of constant length voiding its content at the same rate as the thinner cylinder, which would void to tissue vein the blood coming from a lower fraction of perfused capillaries. The first-order rate constant for the tissue output (hollow blue arrows) is only dependent on the blood speed flowing through the tissue but not on the extent of the perfused area

$$\frac{dX_{\text{Extravascular}}}{dt} = k_{Tivev} \cdot X_{Tiv} - k_{Teviv} \cdot X_{Tev} \quad (3)$$

$$\frac{dX_{\text{veinfromT}}}{dt} = k_{TV} \cdot X_{Tiv} - k_{vTV} \cdot X_{vT} \quad (4)$$

$$\frac{dX_{\text{Vein}}}{dt} = k_{vTV} \cdot \left(\sum_j^n X_{vT,j} \right) - k_{VA} \cdot X_V \quad (5)$$

Figures 1 and 2 allow the readers to understand the meaning of first-order rate constants at the tissue level (Eqs. 2–3). The same principle would be applied for the eliminating tissues, by adding into Eq. 3 the kinetic of elimination from their extravascular spaces.

First-order rate constants, k_{TV} and k_{vTV} , remain invariant for a given cardiac output (CO), independently of the actual CO fraction supplied (σ_T). First-order input rate constants served to any tissue, k_{AT} , are dependent on both CO and their particular σ_T . k_{AT} accounts for the fraction of mass of the drug delivered from the arterial central compartment to a given tissue per time. By moving the notation from the first-order rate constant to clearance, it adopts the following expression: $\sigma_T \cdot CO/V_a$, with V_a being the arterial volume invariant.

Otherwise, both k_{TV} and k_{vTV} are always invariant for a given CO and for all body tissues. In other words, whatever the actual σ_T supplied, those first-order output rate constants from tissues would adopt the same value. This is because circulating blood volume in veins, and in the intravascular space of tissues, comes from those capillaries that are perfused to supply the oxygen demand of the

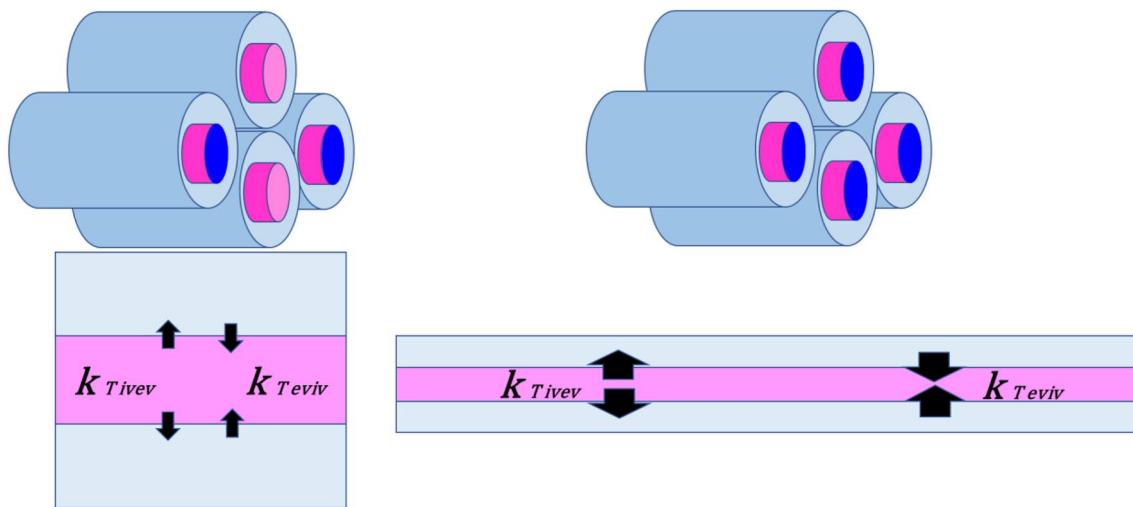


Fig. 2 Perfused capillaries are represented by cylindric tubes ended with blue surfaces. Extravascular surrounding areas exchange their solutes with the intravascular space of the tissue when the blood alternately flows through the perfused capillaries from the whole cap-

illary bed. This is viewed as a bidimensional diagram in the bottom of the panel. Once the tissue consumption of oxygen increases (right side), both the number of perfused capillaries and the intra-extravascular interphase area increase, leading to a faster exchange of solutes

extravascular space of tissues [18]. Consequently, there is a unique value for the output no matter which tissue is considered, and it depends only on CO:

$$k_{vTV} = \sigma_T \cdot \frac{CO}{V_{\text{vein from } T}} = \sigma_T \cdot \frac{CO}{V_{\text{perfused capillaries of } T}} = k_{TV} \quad (6)$$

Equation 6 enables us to conclude that k_{TV} equals k_{vTV} , as blood volumes that circulate through capillaries and the vein of tissues are equal. As the actual σ_T determines the number of capillaries perfused, it can be stated that there would be a constant $\sigma_T/V_{\text{perfused } T}$ ratio. Considering that cardiac output distribution is better known at a resting state, this basal state of individuals could be adopted to define the first-order output rate constant:

$$k_{TV} = \sigma_{T \text{ basal}} \cdot \frac{CO}{V_{\text{perfused capillaries of } T \text{ basal}}} = \sigma_{T \text{ basal}} \cdot \frac{CO}{V_{\text{vein from } T \text{ basal}}} \quad (7)$$

Figure 1 illustrates these concepts for a given tissue under low (left) or high (right) consumption of oxygen. It is important to bear in mind that a constant tissue blood flow implies that blood flows harmoniously through a given fraction of the capillaries, alternating the vessels of the capillary bed in accordance with the oxygen/carbonic anhydride balance at each site, among other mechanisms [19]. Then, diffusion of a drug between intra- and extravascular spaces within the tissue may diminish or increase in both senses (k_{Tivev} and k_{Teviv}), depending on whether σ_T diminishes or increases. Hence, exchanges proceed with slower or faster velocity in response to whether the interphase area decreases or increases, respectively. Figure 2 illustrates the effect on the speed of the drug exchange once the tissue goes from states of low (left) to high (right) consumption of oxygen. This does not imply, however, that the amount of drug partitioned into the tissue from the central artery compartment remains unchanged, as such a partition does not depend on the velocity of the exchange, but on the σ_T delivered to the tissue instead.

The previous comments are independent of the type of transfer that takes place at the capillary membrane, whether by simple diffusion, by facilitated or active transport. Any modification in the cardiac output fraction that feeds a tissue only modifies the capillary transfer area; therefore, no transport of limited capacity could be affected as the concentration of drug in the blood remains unchanged. This is the main issue of our proposal because before the drug molecules can be transferred to the extravascular space of a certain tissue, they must first arrive at the tissue capillaries with the potentiality that the physiological or pathophysiological conditions determine. Our point is located before permeating the capillary membrane; it is in how much transfer area is present to fulfill such permeation.

Perfusion rate-limited models, the most broadly used in PBPK modeling, assume instantaneous distribution of a drug into the whole tissue (intra- and extravascular spaces) and between capillaries and venous sections, thus Eqs. 3 and 4 equal zero. Equation 2 can be then simplified as:

$$\frac{dX_T}{dt} = k_{AT} \cdot X_A - k_{vTV} \cdot X_{vT} \quad (8)$$

$$\text{Being, } X_{vT} = \frac{k_{Teviv} \cdot X_{Tev}}{k_{Tivev}}. \quad (9)$$

Equation 10 is obtained by rewriting Eq. 8 in terms of clearance, or blood flow, and concentrations (C):

$$V_T \cdot \frac{dC_T}{dt} = \sigma_T \cdot CO \cdot C_A - \sigma_{T \text{ basal}} \cdot CO \cdot C_{vT}. \quad (10)$$

This precedent equation for non-eliminating tissues has a substantial difference from the current equation, in which the same actual σ_T is employed in both terms of the right side of the equation. It has an important therapeutic impact as the free drug concentration in blood would not reflect the concentration present in the extravascular space of the target tissue.

The same reasoning could be made for deducing the equation for eliminating tissues; however, it should not be assumed, as it is currently done [20], that the free drug concentration at the extravascular site is equal to the free concentration in the venous plasma leaving the tissue. This is because the $\sigma_T/\sigma_{T \text{ basal}}$ ratio determines a change in the real tissue drug bioavailability in comparison with the basal state. It is easy to understand this fundamental concept if we are aware that physiological changes in blood perfusion of the tissue take place precisely to restore the intracellular oxygen content following its disappearance due to increased cell activity. Drugs, even they are not required by tissue cells, follow the time course of physiological needs for oxygen. Hence, more molecules would enter the cells and would be eliminated from the body if this site had the enzymes or transporters to clear them.

More evidence of dissimilar free drug concentrations between the inside and outside parts of the vessels [21] is provided to change the way we conceive PBPK modeling. We are aware of the importance of such models and the power of their findings, but they need to keep improving so that this useful pharmacokinetic/pharmacodynamic tool is managed with the maximum of certainty.

It should be borne in mind that the previous equations refer to free drug molecules, the only molecules capable of being transferred through capillary membranes. Blood flow distribution among tissues does not alter the free drug concentration in plasma, it just modifies the volume of arterial fluid in tissues, and hence, the amount of drug in

contact with them. In other words, arterial blood increases the exchange surface in some tissues while decreasing it in others; therefore, free drug molecules at the extravascular spaces are transferred from low- to high-perfused tissues.

Most of the concepts stated here were communicated previously [22–25], nevertheless, PBPK modeling provided us the opportunity to retrieve them and put them into practice without the need to perform clinical trials. We are confident that readers will take our point into account in clarifying the way drug molecules travel in living bodies and will be able to write appropriate algorithms to reproduce this in silico.

Declarations

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Consent to participate Not applicable.

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