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The Presence of Phases and the Inability of the Classical Compartment Models to Provide Pharmacokinetic Parameters of Physiological Significance for Lipophilic Drugs

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Abstract

The first biphasic open one-compartment pharmacokinetic model is described. Its analytical solutions to drug concentration were developed from parameters of an open two-compartment pharmacokinetic model. The model is used to explain the unusually large compartment volumes and apparent volumes of distribution of lipophilic drugs, as well as to identify which of the pharmacokinetic parameters of the classical compartment models are biologically relevant.

Keywords

Lipophilic Drugs, Pharmacokinetic Compartment Model, Apparent Volume of Distribution, Clearance, Prazosin, Doxazosin, Digoxin, Pindolol

1. Introduction

In our recent work, we have defined the apparent volume of distribution anew and we were able to use this concept to fully explain the classical pharmacokinetic compartment models for hydrophilic drugs. In addition, we have proven that the calculated apparent volume of distribution reflects the extent of the true distribution of hydrophilic drugs in the body and stated that lipophilic drugs that do not follow a one-compartment model are unlikely to be fully described by the theory of the classical pharmacokinetic compartment models [1] [2] [3]. Lipophilic drugs exhibit an apparent volume of distribution that is much larger than the volume of total body fluids. If their distribution/binding to tissues outside the blood circulation is very rapid and comparable to the kinetics of mixing

of the drug in the plasma, the central compartment of the pharmacokinetic model will be composed of more than one phase. In this paper, firstly, we have processed clinical data of the drug Prazosin, clearly, a drug that follows an open two-compartment pharmacokinetic model, using an open biphasic one-compartment model [4]-[9]. The intent is to develop the model and derive explicit solutions to drug concentration in two immiscible phases at equilibrium within a single compartment. Such a model could help us better understand the disposition of drugs in the body that has an apparent volume of distribution larger than the volume of the total body fluids. Secondly, we have used published clinical data of Doxazosin, Digoxin and Pindolol to demonstrate the inability of the classical compartment models to extract pharmacokinetic parameters of physiological significance for lipophilic drugs.

2. Methods

Doxazosin, Prazosin, Digoxin and Pindolol plasma drug concentrations were extracted from published work using the graph reader tool provided by the graphreader.com. Pharmacokinetic compartment modeling of the clinical data was conducted using methods described elsewhere [3] [9].

3. Results and Discussion

It was demonstrated in our recent work that the apparent volume of distribution of Prazosin as determined from an open two-compartment model is the true distribution volume of the drug in the body [9]. It is well established that the elimination half-life of the drug regardless of the mode of drug administration is about 2.5 h whereas after an intravenous bolus injection the drug is distributed to the peripheral compartment with an average half-life of about 10 minutes. Figure 1 displays patient HA's plasma Prazosin concentration as a function of time as reported in the work of Grahnen [4]. If the initial three blood samples after 5, 10 and 20 minutes were not collected, the drug disposition would have followed a one-compartment pharmacokinetic model, and we would have calculated from the parameters given by the best fit equation (C_0 = 10.6 ng/mL) and the intravenous dose (500 μg), an apparent volume of distribution also known as

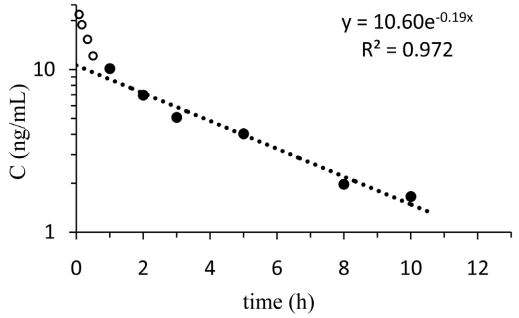


Figure 1. Plasma drug concentration as a function of time for patient HA [4]. The drug was administered by an 0.5 mg rapid intravenous push and data from 1 to 10 hours were fitted using an open one-compartment pharmacokinetic model.

the extrapolated volume of distribution ($V_{d,extrap}$) equal to 47.2 L. This value is very close to the total body water of 70-kg regular human subject. It is well known that the distribution of a drug in two kinetic compartments which is controlled by the intercompartmental distribution rate constants k_{12} and k_{21}, is complete in the terminal or β elimination phase. In that pharmacokinetic phase, the two compartments behave as a single one and the established pseudoequilibrium in plasma drug concentration is controlled only by the rate of drug elimination. The hypothesis of the first part of this work is the potential modeling of the β elimination phase or period of a two-compartment model drug using a biphasic one-compartment pharmacokinetic model.

In the system of Figure 2 (right), we have a single compartment composed of two immiscible phases at equilibrium. Ideally, all the drug is added directly to the blood which is part of the chemical phase 1 and drug distribution in the one-compartment model from the blood to all other body tissues (phase 2) is instantaneous. The distribution of Prazosin in the body, however, being a two-compartment model drug, doesn't reach completion until its disposition enters the terminal elimination phase. As with the one-compartment pharmacokinetic model, an important condition of the biphasic one-compartment model is the instantaneous drug distributional equilibrium between the two phases upon any drug addition into the system. Thus, to establish the pseudoequilibrium conditions of the two-compartment model from time zero in our biphasic single compartment system we have to rapidly introduce part of the dose in phase 2.

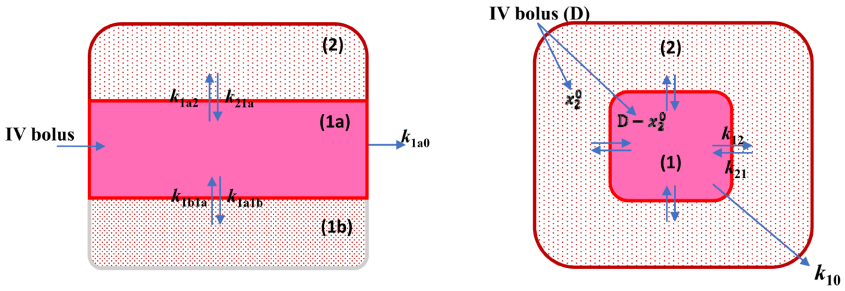


Figure 2. (Left) Open two-compartment mammillary pharmacokinetic model for Doxazosin after a single intravenous bolus injection into a biphasic central compartment. The symbols 1, 2, 1a, 1b, k_{1b1a}, k_{1a1b}, k_{1a2}, k_{21a} and k_{1a0} are the central compartment, the peripheral compartment, the plasma or extracellular fluid which is part of the central compartment, other tissues which are also kinetically part of the central compartment, in contact and immiscible with the phase 1a, the transfer rate constant of drug from phase 1b to phase 1a within the central compartment, the transfer rate constant of the drug from phase a to phase b of the central compartment, the transfer rate constant of the drug from compartment 1 phase 1a to compartment 2, the transfer rate constant of drug from compartment 2 to phase 1a, and the elimination rate constant of the drug from phase 1a of the central compartment, respectively. **(Right)** Biphasic open one-compartment pharmacokinetic model. Equilibrium between the two phases in the system upon rapid addition of the solute in the two phases is instantaneous. The solute distribution rate constants k_{12} and k_{21} have the same values as originally calculated from the two-compartment model of prazosin [9]. k_{10} is the elimination rate constant of the drug from phase 1.

A system of differential equations can be written with the intravenous drug dose as D and the amount of drug in phase 2 at time zero as x_2^0.

$$\dot{x}_1 = -\left(k_{10} + k_{12}\right) \cdot x_1 + k_{21} \cdot x_2;\ \ x_1\left(0\right) = D - x_2^0 \tag{1}$$

$$\dot{x}_2 = k_{12} \cdot x_1 - k_{21} \cdot x_2;\ \ x_2\left(0\right) = x_2^0 \tag{2}$$

The analytical solutions to the drug amount in the two phases as a function of time are,

$$x_1\left(t\right) = D \cdot \left(\frac{\alpha - k_{21}}{\alpha - \beta} \cdot \mathrm{e}^{-\alpha \cdot t} + \frac{k_{21} - \beta}{\alpha - \beta} \cdot \mathrm{e}^{-\beta \cdot t} \right) - x_2^0 \cdot \left(\frac{\alpha}{\alpha - \beta} \cdot \mathrm{e}^{-\alpha \cdot t} - \frac{\beta}{\alpha - \beta} \cdot \mathrm{e}^{-\beta \cdot t} \right) \tag{3}$$

where $\alpha + \beta = k_{10} + k_{12} + k_{21}$ and $\alpha \cdot \beta = k_{10} \cdot k_{21}$.

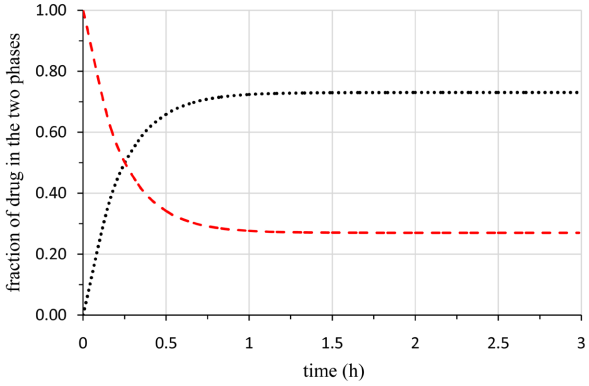
Substituting Equation (3) into Equation (1) and differentiating,

$$x_2\left(t\right) = k_{12} \cdot D \cdot \left(-\frac{\mathrm{e}^{-\alpha \cdot t}}{\alpha - \beta} + \frac{\mathrm{e}^{-\beta \cdot t}}{\alpha - \beta} \right) + x_2^0 \cdot \left(\frac{\alpha - k_{10}}{\alpha - \beta} \cdot \mathrm{e}^{-\alpha \cdot t} - \frac{k_{10} - \beta}{\alpha - \beta} \cdot \mathrm{e}^{-\beta \cdot t} \right) \tag{4}$$

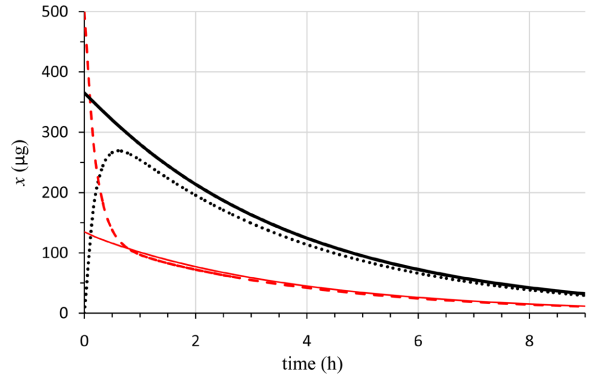
Our next task is to choose the value of x_2^0. As it can be seen from **Figure 3(a)**, pseudoequilibrium conditions in a two-compartment pharmacokinetic model are reached at around one hour after which time the fractional concentrations f_{x_1} and f_{x_2} reach the constant values of 0.27 and 0.73, respectively. It must be noted that these calculations were carried out using the average pharmacokinetic parameters of four patients (not just patient HA) [9]. Under the pseudoequilibrium conditions, the amount of drug in each compartment varies but the fractional concentration stays constant. The fractional ratio in the two compartments at pseudoequilibrium conditions is equal to 2.71. Using the pharmacokinetic parameters described in our recent work, 1.03 μg of prazosin, 0.278 μg x_1 and 0.752 μg x_2, are removed from the system per minute during the pseudoequilibrium conditions [9]. Thus, the biphasic one-compartment model requires 365.177 μg to be introduced into phase 2 at time zero (x_2^0) and the remaining from the 500 μg total dose to be added in phase 1 ($x_1^0 = 134.823$ μg).

The mono-exponential decay pattern of the simulations shown in **Figure 3(b)** verifies that the biphasic single compartment system is always at equilibrium. The simulations shown in **Figure 3(c)** were conducted at x_2/x_1 fractional ratios of 9, 2.71 and 0.41. It is quite interesting to note that the second part of Equation (3) is negative at early times while the second part of Equation (4) is always positive ($\alpha > k_{10} > \beta$), suggesting that equilibrium conditions require initial removal of drug from phase 1 into phase 2. Of course, as x_2^0 tends toward the value of zero both equations are converted back to the original explicit solutions of the two-compartment pharmacokinetic model. If Prazosin followed a one-compartment biphasic model instead of the two-compartment model, one would have calculated an initial plasma concentration C_1^0 from the average pharmacokinetic parameters of all four patients (not just patient HA) and a volume of phase 1 or compartment 1, $V_1 = 11.2$ L, equal to 12.0 ng/mL instead of 44.5 ng/mL.

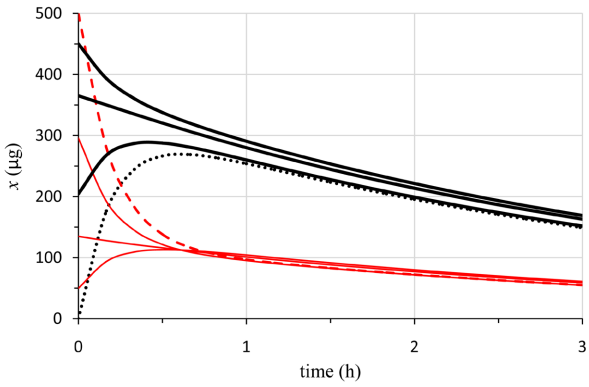
Vincent and coworkers have studied the pharmacological effects of doxazosin that was administered by intravenous bolus injection in six healthy volunteers



(a)



(b)



(c)

Figure 3. (a): Fractional concentration of Prazosin in kinetic compartment 1 (f_{x_1} , dashed line) and in compartment 2 (f_{x_2} , dotted line) using the two-compartment kinetic model described elsewhere [9]. (b): The dashed line represents Prazosin amount x_1 in kinetic compartment 1, and dotted line represents drug amount x_2 in compartment 2, which were calculated from the clinical data of four patients (not only patient HA) using Equation (7) and Equation (8) of the published article of Savva and coworkers [9]. Thin and thick continuous lines are the drug quantities x_1 and x_2, respectively, that were calculated using the biphasic one-compartment model explicit solutions to drug amount (Equations (3) and (4)). (c): Thick and thin continuous lines are x_2 and x_1 simulations that were carried out using Equation (4) and Equation (3) of the biphasic open one-compartment pharmacokinetic model, respectively, at x_2-to-x_1 fractional ratios of 9, 2.71 and 0.41, for both thick lines (top to bottom) and thin lines (bottom to top), respectively.

[10]. Our analysis of their data extracted from **Figure 1** in their respective publication using an open two-compartment mammillary model, was carried out using the methods described elsewhere, and yielded k_{12}, k_{21}, k_{10}, α, β, V_1, $V_{d,1}$ and $V_{d,extrap}$ equal to 3.6226 h^{-1}, 2.0413 h^{-1}, 0.2211 h^{-1}, 5.8073 h^{-1}, 0.07771 h^{-1}, 34.6 L, 96.1 L and 99.9 L, respectively (**Figure 4**) [9]. The term $V_{d,1}$ stands for the apparent volume of distribution associated with the central compartment as determined by the Riggs equation. We have recently shown that this term is equal to the so-called steady-state volume of distribution, $V_{d,ss}$ [2] [11]. In agreement with our estimates, the same group of investigators has calculated an elimination $t_{1/2,z}$ of 562 minutes and an average value of $V_{d,ss}$ of 110 L in twelve elderly volunteers [12].

Despite the perfect fit of the raw data to the two-compartment model, an estimated value of the volume of the central compartment so close to the volume of the total body water suggests that the model lacks physiological significance. It is possible that the more lipophilic than prazosin, quinazoline derivative, partitions into tissues other than plasma as soon as it is injected into the bloodstream. In this case, the central compartment is at least biphasic (**Figure 2**, left). One of the possibilities is that the drug enters the system via an intravenous push into phase 1a of the central compartment, it is distributed in phase 1b within the central compartment and to the peripheral compartment and it is eliminated out of the system from the central compartment. The drug transfer rate constants k_{1b1a} and k_{1a1b} in the two phases 1a and 1b of the central compartment are extremely high and practically unmeasurable in the time domain of sample collection as suggested by the excellent goodness of fit of plasma drug concentrations by the two-compartment model (**Figure 4**). Phase 1b is not in contact and is not related in any way to the peripheral compartment. The drug can be distributed to phase 1b and to the peripheral compartment only from phase 1a. Drug distribution upon its entry from phase 1a into the tissues that make up phase 1b within the central compartment is considered to be instantaneous. Contrary to that, the rate of drug distribution from phase 1a into the tissues comprising the peripheral compartment, and vice versa, takes place at a slower rate and is measurable in the system.

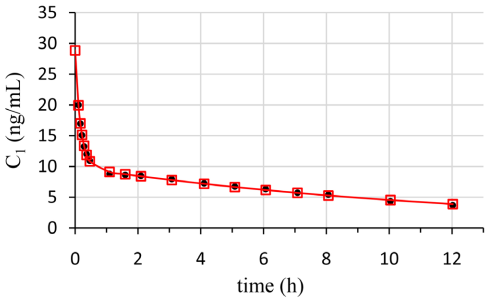


Figure 4. Measured Doxazosin blood concentration of subject 6 (•) and simulated drug concentration in the central compartment (□) joined with a continuous line as a function of time. The experimental Doxazosin concentration measurements were taken from **Figure 1** of the published work of Vincent *et al.* [10].

The chemical equilibrium constant of the two consecutive reversible reactions (R1) is related to the partition coefficients of the drug in the three phases at equilibrium. The drug dose (D) is added into phase 1a and instantly the drug diffuses and reaches equilibrium in phase 1b.

$$C_{1b} \leftrightarrows C_{1a} \leftrightarrows C_2 \tag{R1}$$

Initial conditions:

$$C_{1b}(0) = \frac{x_{1b}}{V_{1b}}; C_{1a}(0) = (D - x_{1b})/V_{1a}; C_2(0) = 0$$

At equilibrium:

$$C_{1b,eq} = \left[\frac{x_{1b} - x_{2b}}{V_{1b}}\right]; C_{1a,eq} = \left[\frac{D - x_{1b} - x_{2a}}{V_{1a}}\right]; C_{2,eq} = \left[\frac{x_{2a} + x_{2b}}{V_2}\right];$$

Partition coefficients:

$$K_{1b,1a} = \frac{C_{1b,eq}}{C_{1a,eq}} = \frac{\left[\frac{x_{1b} - x_{2b}}{V_{1b}}\right]}{\left[\frac{D - x_{1b} - x_{2a}}{V_{1a}}\right]} \tag{5}$$

$$K_{2,1a} = \frac{\left[\frac{x_{2a} + x_{2b}}{V_2}\right]}{\left[\frac{D - x_{1b} - x_{2a}}{V_{1a}}\right]} \tag{6}$$

The chemical equilibrium constant, K of the process is,

$$K = \left[\frac{x_{1b} - x_{2b}}{V_{1b}}\right] \cdot K_{2,1a} \tag{7}$$

The apparent volume of distribution with respect to the phase 1a of the central compartment $V_{d,1a}$, which plasma is definitely part of it, and like the partition coefficient is also an equilibrium quantity, can be described at distribution equilibrium with phase 1b and the peripheral compartment, using the mass balance equations (Equation (8)).

$$V_{d,1a} = \frac{x_{s,eq}}{C_{1a,eq}} \tag{8}$$

Substituting $x_s = x_{1a} + x_{1b} + x_2$ onto Equation (8) we get,

$$V_{d,1a} = V_{1a} + K_{b,a} \cdot V_{1b} + K_{2,1a} \cdot V_2 \tag{8a}$$

At zero time, all the drug is in the central compartment and has reached equilibrium in both phases 1a and 1b. No drug has yet been eliminated out of the system or distributed into the peripheral compartment. Thus, at $t = 0$ we can consider the central compartment as being a closed and isolated system where all the drug is located. This unique situation can be described by Equation (8b) and Equation (8c).

$$V'_{d,1a} = V_{1a} + K_{b,a} \cdot V_{1b} \tag{8b}$$

$$V'_{\mathrm{d,1a}} = \frac{D}{C_{\mathrm{1a,0}}} \tag{8c}$$

Hence, according to the multiphasic compartment model, the volume 34.6 L which is determined from the intercept of the line derived after application of the method of residuals, is not the real volume of the central compartment V_1. It is rather the apparent volume of distribution of doxazosin with respect to phase 1a when phase 1a is at equilibrium with phase 1b within the central compartment. $V'_{\mathrm{d,1a}}$ suggests that at time zero it would require 34.6 L of plasma to accommodate 1 mg of Doxazosin in the absence of the peripheral compartment. As soon as the drug starts getting distributed in the peripheral compartment, the apparent volume of distribution of Doxazosin with respect to the plasma changes and becomes equal to $V_{\mathrm{d,1a}}$ (Equation (8a)) which can only be estimated at the time of momentary distribution equilibrium between the three phases, if only we knew how much drug is initially distributed in the two phases within the central compartment. The problem is that the analytical solution to drug concentration in the central compartment will always be a function of the unknown initial quantity of the drug in phase 1b. It is also important to understand that since the system undergoes two totally different conditions, $V'_{\mathrm{d,1a}}$ is only valid at zero time and is totally unrelated to $V_{\mathrm{d,1a}}$.

Even if the system in **Figure 2** is set up as a three-compartment kinetic model, it may not be feasible to collect plasma drug concentrations at earlier times to distinguish kinetically compartment 1a from compartment 1b. Kramer *et al.*, have studied the pharmacokinetics of Digoxin using a two- and a three-compartment model. They have reported an average value of V_1 in a two- and a three-compartment model equal to 58 L and 46 L, respectively [13]. We have carried out our own analysis on the clinical data of patient TF in an open three-compartment mammillary pharmacokinetic model [13] [14] [15] [16]. The initial value problem for the system of differential equations was set up with all the drug being in the central compartment at time zero. After applying the method of residuals twice, C_0 was calculated to be 26.28 ng/mL and $V_1 = 38$ L. These volumes cannot be the real volumes of the central compartment. They are rather the digoxin apparent volumes of distribution $V'_{\mathrm{d,1a}}$ at zero time. This initial rapid distribution phase was also reported by Doherty [17]. Although these investigators were collecting blood samples every 2 minutes, as early as 2 minutes after intravenous injection, it was not possible to resolve the digoxin distribution kinetics in the different tissues, hence different phases, that comprise the central compartment. Two more studies have reported a V_1 of 37 L while a third one reported a V_1 equal to 110 L [18] [19] [20]. The $V_{\mathrm{d,ss}}$ of digoxin is reported to be larger than 350 L. None of these volumes has physiological significance. Digoxin has an aqueous solubility of 65 μg/mL. It is not very lipophilic ($\log P = 1.26$) and it is not freely permeable through plasma membranes (MW = 781). Yet, it is extensively distributed at high concentrations in heart, kidney and liver and at lower concentrations essentially in all human tissues, apart from the brain, at very early times

after administration [21]. The average concentration of digoxin in the human heart, myocardium and atrium is reported to be 20 - 35 times, 65 times and 365 times higher than its plasma concentration [21] [22] [23]. Steiness and Valentin have measured high digoxin concentration in dogs as early as 10 minutes after intravenous administration for at least 90 minutes. They have also described consistent tissue redistribution of digoxin within the myocardium 30 minutes after an intravenous push of the drug [24]. It appears that as soon as the drug is injected into the blood it is instantly distributed to other tissues of vital organs. Thus, the central compartment is composed of multiple tissues/organs while it is possible that the peripheral compartments are the result of drug redistribution in the same organs of the central compartment. Although drug transfer into these tissues is kinetically indistinguishable from the mixing of the drug in the vascular fluid, they have a different affinity for the drug and they are immiscible with the vascular and extravascular fluid thereby forming different phases within the central compartment. The volume estimated at zero time after applying the method of residuals is not the volume of the central compartment but it is rather the apparent volume of distribution of the drug associated with the plasma, $V'_{\mathrm{d,1a}}$, at zero time prior to the distribution of the drug in the peripheral compartments. In order to calculate the volume of the central compartment, we would have to provide estimates of the various tissue volumes and their distribution coefficients relative to plasma (Equation (8d)). Also, the possible redistribution of drug within these phases may cause inconsistency and variability in the volume of the kinetic compartments.

$$V'_{\mathrm{d,1a}} = V_{\mathrm{1a}} + \sum_{i=1\mathrm{b}}^{n} V_i \cdot K_{i,\mathrm{1a}} \tag{8d}$$

Clearly, the compartment volumes and the apparent volumes of distribution for doxazosin and digoxin and by extension for other lipophilic drugs are not biologically relevant but multicompartment pharmacokinetic models can still adequately describe the time course of disposition of lipophilic drugs in the body. The hybrid rate constant β which is also called disposition rate constant is biologically relevant since it is the only pharmacokinetic parameter that is determined from the slope of the raw experimentally measured plasma drug concentration with time during the elimination phase of the drug. Furthermore, although the volume of the central compartment and the elimination rate constant of the drug from the central compartment are not biologically relevant, their product is physiologically relevant.

Gugler *et al.*, studied the pharmacokinetic of Pindolol in man using an open two-compartment model [25]. They have calculated after an intravenous infusion of the drug over 3 hours, from the intravenous dose, the disposition rate constant β and the AUC, a total drug clearance equal to 483 ± 79.6 mL·min^{-1}. The rate of drug elimination $\frac{\mathrm{d}x_{\mathrm{s}}}{\mathrm{d}t}$, where $x_{\mathrm{s}} = x_1 + x_2$ in a two-compartment model after an intravenous bolus administration is,

$$\frac{dx_s}{dt} = \frac{dx_1}{dt} + \frac{dx_2}{dt} = k_{10} \cdot x_1 \quad \text{and} \quad x_1 = V_1 \cdot C_1 \quad \Rightarrow$$

$$\frac{dx_s}{dt} = k_{10} \cdot V_1 \cdot C_1 \tag{9}$$

V_1 and k_{10} in Equation (9) are constants, C_1 is the only parameter that changes with time.

By arbitrarily defining Clearance as the volume of plasma cleared of drug per unit time,

$$CL = k_{10} \cdot V_1 \tag{10}$$

and

$$\frac{dx_s}{dt} = CL \cdot C_1 \tag{9a}$$

Nagashima, Gibaldi and coworkers have shown that [26] [27],

$$k_{10} = \frac{\beta}{f_{x_1}} \tag{11}$$

and

$$V_\beta = \frac{V_1}{f_{x_1}} \tag{12}$$

Therefore,

$$CL = \beta \cdot V_\beta \tag{10a}$$

We have verified the validity of Equation (11) and Equation (12) within the time domain of the drug elimination phase, where f_{x_1}, β and V_β are relatively constant, in our work with Sisomicin that was administered by an intermittent intravenous infusion and Prazosin that was administered by an intravenous bolus (results not shown) [3] [9].

Hicks and coworkers have conducted clinical studies of pindolol administered by an intravenous push to four normal subjects. They have published the mean plasma levels of pindolol but did not carry out pharmacokinetic analysis [28]. We have extracted the published mean plasma levels of pindolol using methods described elsewhere and determined the pharmacokinetic parameters of Pindolol using an open two-compartment model (**Table 1** and **Figure 5**) [9].

The average value of total clearance of Pindolol using Equation (10) was calculated to be 443.00 mL/min, which in agreement with that calculated by Gugler

Table 1. Average pharmacokinetic parameters after administration of a single rapid intravenous injection of 0.6 mg Pindolol using an open two-compartment model. Plasma pindolol concentration-time points were extracted from the article of Hicks. k_{10} is the elimination rate constant.

α (h^{-1})	β (h^{-1})	k_{12} (h^{-1})	k_{21} (h^{-1})	k_{10} (h^{-1})	V_1 (L)	$V_{d,ss}$ (L)
4.8889	0.1983	2.2253	2.4693	0.3926	67.7	128.7

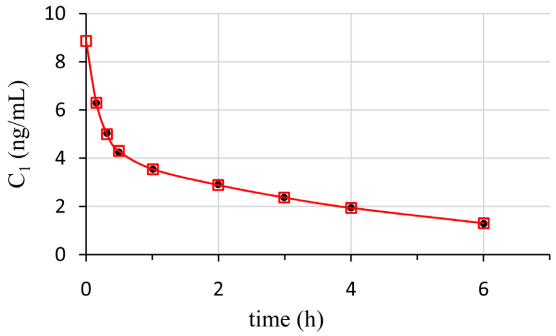


Figure 5. Mean plasma Pindolol concentration extracted from the work of Hicks *et al.*, (•) and simulated drug concentration in the central compartment (□) as a function of time using an open two-compartment model.

and al. From these two independent works on Pindolol, it becomes clear that although k_{10} and V_1 (or $V'_{d,1}$) are of no physiological significance their product is the very physiologically relevant total drug clearance.

4. Conclusion

The elimination phase of any open two-compartment pharmacokinetic model can be described by an open biphasic one-compartment model. This provides proof that the very large apparent volumes of distribution of lipophilic drugs that do not follow a one-compartment model have been miscalculated due to the presence of different phases within the central compartment. Despite the lack of physiological significance of the central and peripheral compartment volumes, the apparent volume of distribution, the intercompartmental distribution constants and elimination rate constant, multicompartment pharmacokinetic models for lipophilic drugs can still provide valuable information about the systematic half-life and the total drug clearance, and they can still be used to provide accurate simulations of plasma drug concentration with time.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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