Scientific Research Publishing

Journal of Biosciences and Medicines, 2022, 10, 108-140
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

A Reevaluation of Prazosin Pharmacokinetics in a Two-Compartment Model, the Apparent Volume of Distribution and Comparative Simulations in the One-Compartment Model

Michalakis Savva[1*], Xudong Yuan[2]

[1]South University, Savannah, USA
[2]Acon Pharmaceuticals, Cranbury, USA
Email: *msavva@southuniversity.edu, *micsavva@gmail.com

How to cite this paper: Savva, M. and Yuan, X.D. (2022) A Reevaluation of Prazosin Pharmacokinetics in a Two-Compartment Model, the Apparent Volume of Distribution and Comparative Simulations in the One-Compartment Model. *Journal of Biosciences and Medicines*, **10**, 108-140.
https://doi.org/10.4236/jbm.2022.101010

Received: December 17, 2021
Accepted: January 23, 2022
Published: January 26, 2022

Abstract

Published clinical data of Prazosin were reevaluated pharmacokinetically using explicit solutions to drug concentration as a function of total time for IV bolus injection, intermittent intravenous infusion and oral routes of administration in an open two-compartment model. In a novel way, the apparent volume of distribution was estimated from a two-compartment model and found to be close to the total body water suggesting that Prazosin is distributed in all tissues both extracellularly and intracellularly. In addition, extracting the value of the apparent volume of distribution from a two-compartment model allowed comparative simulations in the one-compartment model. It is shown that dosage calculations of Prazosin intermittent infusion can be safely performed using the simpler one-compartment model equations. Lastly, several additional time-dependent pharmacokinetic parameters e.g., the peak time in the central and peripheral compartment and non-steady state and steady state peak concentration and AUC were determined using series equations for all three routes of administration, as a function of dose number and total time upon multiple drug administrations in the two-compartment model. It is also the first time that steady-state plasma drug concentration equations were derived in a two-compartment mammillary model.

Keywords

Prazosin, Pharmacokinetics, Intravenous Bolus, Intermittent Infusion, Oral Dose, Multiple Doses, Compartment Model, Apparent Volume of Distribution

1. Introduction

Despite their primary role in estimating pharmacokinetic parameters that can be used to design optimum dosing regimens to achieve plasma drug concentrations within therapeutic range, it is generally believed that the apparent volume of distribution cannot be estimated in multi-compartment models and that the compartment volumes of multi-compartment pharmacokinetic models bear no physiological significance. This is no longer true [1] [2] [3]. The volume of distribution of a substance in a phase is the volume of that phase in the system. The apparent volume of distribution (V_d) of a solute associated with a solvent in a two-phase system on the other hand, can be determined at equilibrium using a mass balance equation (Equation (1)).

$$V_{d,1} = V_1 + K_{2,1} \cdot V_2 \tag{1}$$

In pharmacokinetic modeling, each compartment has its own solute's V_d only when the compartments constitute different phases. Chemically or compositionally similar, kinetically different, compartments have the same V_d which is equal to the total volume of the kinetically different compartments. As with the partition coefficient, there are as many solute V_d as the number of phases in a system. Unlike the partition coefficient, however, the value of the V_d of a substance is dependent on the actual phase volumes, and at constant phase volumes, phase solute concentrations are directly proportional to the total mass of the solute x_s in the system as shown by Equation (2), below:

$$V_{d,1} = \frac{x_s}{x_1} \cdot V_1 \tag{2}$$

$$V_{d,2} = \frac{x_s}{x_2} \cdot V_2 \tag{2a}$$

In vivo, the apparent volume of distribution of a drug can be defined as the volume of the assayed phase that is needed to dissolve the whole drug dose and achieve the measured drug concentration in the assayed phase. Its value depends on the physicochemical properties of the drug and the body's physiology which regulates the chemical constituency and the actual fluid volumes of the pharmacokinetic compartments. The presence of disease states and other pathological conditions may cause deviations from what we usually measure in normal healthy individuals. Under constant conditions, the apparent volume of distribution is a constant parameter and thus, in accordance with Equation (2) increasing or decreasing a dose (x_s) will result in an increase or decrease of plasma drug concentration, respectively. Drug concentrations are usually measured in plasma but the V_d of a drug is related to the whole compartment that contains the plasma along with other body fluids. Since changes in drug dose are reflected in changes of drug concentration in the assayed compartment, Equation (2) can be used to compute the V_d from the administered dose and the measured drug concentration in the assayed compartment. We have carried out such an analysis on clinical data of the drug sisomicin in an open two-compartment pharmacoki-

netic model and have determined the apparent volume of distribution of the drug. In addition, we were able to show that the volumes of the central and peripheral compartment are approximately equal to the extracellular fluid volume and thus, they represent the true distribution of sisomicin in the body [3].

Prazosin was first used in the mid-seventies as an antihypertensive agent due to its alpha-1 receptor blocking properties in vascular smooth muscle of arteries and veins [4]. A number of clinical studies assessed some of the pharmacokinetic properties of the drug [5]-[13]. Most of the single-dose studies support a two-compartment open model for prazosin's *in vivo* disposition. One of the early clinical studies of Prazosin was that of Bateman and coworkers. These investigators have determined pharmacokinetic micro rate constants and the hybrid distribution and elimination rate constants in a two-compartment model but they were unable to discern the physiological relevance of the central and peripheral compartment volumes in their model. Although the drug was administered by a 10-minute intermittent infusion, results were analyzed using the explicit solution to drug concentration after IV bolus administration and only for the central compartment using the so-called mid-point of the infusion rule. The only pharmacokinetic parameters extracted from clinical studies conducted with an oral dosage form (Hypovase) were the bioavailability factor and the half-life of drug elimination [5]. The investigators were neither able to assess parameters of the peripheral compartment nor time-dependent pharmacokinetic parameters, such as, the peak time and peak concentration in the central and peripheral compartments. Similarly, a clinical study conducted with a single intravenous bolus dose of prazosin concluded that the drug follows a two-compartment kinetic model [6]. Several useful pharmacokinetic parameters were determined but not the V_d, the V_2, the drug concentration, AUC, peak time and peak concentration in the peripheral compartment.

We have recently derived series equations for various routes of drug administration that simulate drug concentration not just within the first dosing interval, but in the whole time-domain of therapy [3] [14] [15]. We have additionally produced herein, the real-time explicit solutions to drug concentration for multiple IV boluses and multiple oral doses in a two-compartment model and utilized them along with the analytical solutions of the multiple intermittent infusions that we have reported elsewhere to analyze published clinical data of prazosin. The goal was to assess various primary and secondary time-dependent pharmacokinetic parameters, as well, as to simulate non-steady state and steady state concentration-time curves in both central and peripheral compartments upon administration of multiple doses. In particular, we have achieved the construction of the accumulation phase of the intermittent intravenous infusion of Prazosin from pharmacokinetic parameters extracted from the elimination phase of the drug. In addition, the assessment of Prazosin's apparent volume of distribution from a two-compartment model enabled comparative simulations of the one-compartment open model for all three routes of drug administration.

2. Methods

2.1. Explanation of Terms

V_d : Drug apparent volume of distribution

CL: Drug clearance

k: Drug first-order elimination rate constant

τ : dosing interval

D: Drug dose

n: number of doses

$x_{1,1}$: Drug amount in central or compartment 1 during the first dose ($0 \le t \le \tau$).

$x_{1,2}$: Drug amount in compartment 1 during the second dose ($\tau \le t \le 2 \cdot \tau$).

$x_{2,1}$: Drug amount in the peripheral or compartment 2 during the first dose ($0 \le t \le \tau$).

$C_{1,1,\max}$: Maximum drug concentration in compartment 1 after administration of the first dose.

$C_{2,3,\max}$: Maximum drug concentration in compartment 2 after administration of the third dose.

$C_{1,3,\min}$: Minimum drug concentration in compartment 1 after the third dose at $t = 3 \cdot \tau$.

$C_{2,4,\min}$: Minimum drug concentration in the peripheral compartment at the end of the fourth dosing interval ($t = 4 \cdot \tau$).

$C_{2,n,ss,t}$: Steady state drug concentration in the peripheral compartment as a function of dose number and total time.

2.2. Compartment Models

Explicit solutions to concentration were developed for multiple IV boluses and multiple oral administration in an open two-compartment mammillary model (**Figure 1**) following an approach that was recently described elsewhere [3] [14] [15].

2.2.1. Multiple Intravenous Boluses in an Open Two-Compartment Mammillary Model

Differential equations for inputs and outputs:

Input: The whole drug dose (*D*) is transferred into the central compartment instantly.

Output: First-order drug elimination from the central compartment.

$$\dot{x}_1 = -\left(k_{10} + k_{12}\right) \cdot x_1 + k_{21} \cdot x_2; \quad x_1(0) = D \tag{3}$$

$$\dot{x}_2 = k_{12} \cdot x_1 - k_{21} \cdot x_2; \quad x_2(0) = 0 \tag{4}$$

Analytical solutions to drug amount in the central and peripheral compartments after a single intravenous bolus injection

Using Laplace transform to the initial value problem and writing X_1 and X_2 for $\mathcal{L}\{x_1(t)\}$ and $\mathcal{L}\{x_2(t)\}$, we obtain:

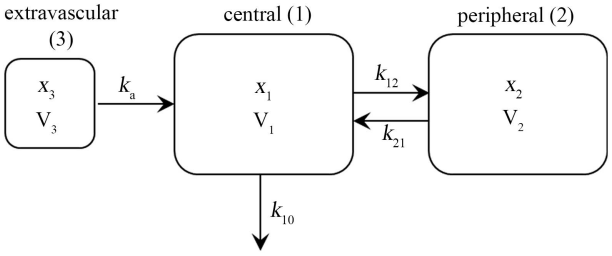

Figure 1. Extravascular drug administration in a two-compartment mammillary model. Drug absorption and elimination is described by first-order kinetics into and out of the central compartment, respectively.

$$\left(s+k_{10}+k_{12}\right)\cdot X_1 - k_{21}\cdot X_2 = D \tag{5}$$

$$-k_{12}\cdot X_1 + \left(s+k_{21}\right)\cdot X_2 = 0 \tag{6}$$

Solving Equation (6) for X_1 and substituting on Equation (5),

$$X_2 = \frac{D\cdot k_{12}}{\left(s^2+\left(k_{10}+k_{12}+k_{21}\right)\cdot s + k_{10}\cdot k_{12}\right)}$$

Let $\lambda_1+\lambda_2 = k_{10}+k_{12}+k_{21}$ and $\lambda_1\cdot\lambda_2 = k_{10}\cdot k_{21}$

$$X_2 = \frac{D\cdot k_{12}}{\left(s+\lambda_1\right)\cdot\left(s+\lambda_2\right)} = \frac{A}{\left(s+\lambda_1\right)} + \frac{B}{\left(s+\lambda_2\right)}$$

Using the method of partial fraction decomposition,

$$A = \frac{D\cdot k_{12}}{\left(\lambda_2-\lambda_1\right)};\quad B = -\frac{D\cdot k_{12}}{\left(\lambda_2-\lambda_1\right)}$$

$$X_2 = \frac{D\cdot k_{12}}{\left(\lambda_2-\lambda_1\right)}\cdot\left(\frac{1}{s+\lambda_1}-\frac{1}{s+\lambda_2}\right)$$

Taking the inverse transform,

$$\mathcal{L}^{-1}\left\{X_2(s)\right\} = x_2(t) = D\cdot k_{12}\cdot\left(A_2\cdot e^{-\lambda_1\cdot t} + B_2\cdot e^{-\lambda_2\cdot t}\right) \tag{7}$$

$$A_2 = \frac{1}{\left(\lambda_2-\lambda_1\right)};\quad B_2 = \frac{1}{\left(\lambda_1-\lambda_2\right)}$$

Substituting $x_2(t)$ on Equation (4),

$$x_1(t) = D\cdot\left(A_1\cdot e^{-\lambda_1\cdot t} + B_1\cdot e^{-\lambda_2\cdot t}\right) \tag{8}$$

$$A_1 = \frac{\lambda_1-k_{21}}{\left(\lambda_1-\lambda_2\right)};\quad B_1 = \frac{k_{21}-\lambda_2}{\left(\lambda_1-\lambda_2\right)};$$

$$C_1(t) = \frac{x_1(t)}{V_1} \tag{8a}$$

Terms of the mathematical sequence for multiple IV doses administered with a dosing interval τ.

$$\left\{C_{1,n}\right\} = \left\{\frac{D}{V_1}\cdot\left(A_1\cdot e^{-\lambda_1\cdot t} + B_1\cdot e^{-\lambda_2\cdot t}\right), \frac{D}{V_1}\cdot\left(A_1\cdot e^{-\lambda_1\cdot t} + B_1\cdot e^{-\lambda_2\cdot t}\right)\right.$$

$$\left. + \frac{D}{V_1}\cdot\left(A_1\cdot e^{-\lambda_1\cdot(t-\tau)} + B_1\cdot e^{-\lambda_2\cdot(t-\tau)}\right), \cdots\right\}$$

Pattern of Sequence

$$\left\{C_{1,n}\right\}=\left\{\frac{D}{V_1}\cdot\left(A_1\cdot \mathrm{e}^{-\lambda_1\cdot\left(t-(n-1)\cdot\tau\right)}+B_1\cdot \mathrm{e}^{-\lambda_2\cdot\left(t-(n-1)\cdot\tau\right)}\right)\right\}$$

where, t is the total time.

Partial sums and formula of the mathematical Series for repetitive IV bolus doses

$$C_{1,n,t}=\sum_{n=1}^{\infty}\frac{D}{V_1}\cdot\left(A_1\cdot \mathrm{e}^{-\lambda_1\cdot\left(t-(n-1)\cdot\tau\right)}+B_1\cdot \mathrm{e}^{-\lambda_2\cdot\left(t-(n-1)\cdot\tau\right)}\right)$$

Multiplying and dividing the two terms of the above equation with $\left(1-\mathrm{e}^{\lambda_1\cdot\tau}\right)$ and $\left(1-\mathrm{e}^{\lambda_2\cdot\tau}\right)$, respectively,

$$C_{1,n,t}=\frac{D}{V_1}\cdot\left\{A_1\cdot\frac{\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}\cdot \mathrm{e}^{-\lambda_1\cdot\left(t-(n-1)\cdot\tau\right)}+B_1\cdot\frac{\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\cdot \mathrm{e}^{-\lambda_2\cdot\left(t-(n-1)\cdot\tau\right)}\right\} \quad (9)$$

$$C_{2,n,t}=\frac{D\cdot k_{12}}{V_2}\cdot\left\{A_2\cdot\frac{\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}\cdot \mathrm{e}^{-\lambda_1\cdot\left(t-(n-1)\cdot\tau\right)}+B_2\cdot\frac{\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\cdot \mathrm{e}^{-\lambda_2\cdot\left(t-(n-1)\cdot\tau\right)}\right\} \quad (10)$$

The corresponding steady-state concentrations of the drug in the two compartments are,

$$C_{1,n,ss,t}=\frac{D}{V_1}\cdot\left\{\frac{A_1}{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}\cdot \mathrm{e}^{-\lambda_1\cdot\left(t-(n-1)\cdot\tau\right)}+\frac{B_1}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\cdot \mathrm{e}^{-\lambda_2\cdot\left(t-(n-1)\cdot\tau\right)}\right\} \quad (11)$$

$$C_{2,n,ss,t}=\frac{D\cdot k_{12}}{V_2}\cdot\left\{\frac{A_2}{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}\cdot \mathrm{e}^{-\lambda_1\cdot\left(t-(n-1)\cdot\tau\right)}+\frac{B_2}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\cdot \mathrm{e}^{-\lambda_2\cdot\left(t-(n-1)\cdot\tau\right)}\right\} \quad (12)$$

Notice that the drug concentrations at time zero after administration of the first dose ($n=1$) in the central and peripheral compartments are,

$$C_{1,1,0}=C_{1,1,\max}=\frac{D}{V_1} \quad (9a)$$

$$C_{2,1,0}=0 \quad (10a)$$

Trough concentrations can be obtained from Equations (9)-(12) at $t=n\cdot\tau$.

$$C_{1,n,\min}=\frac{D}{V_1}\cdot\left\{A_1\cdot\frac{\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}\cdot \mathrm{e}^{-\lambda_1\cdot\tau}+B_1\cdot\frac{\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\cdot \mathrm{e}^{-\lambda_2\cdot\tau}\right\} \quad n\in[0,\infty) \quad (13)$$

$$C_{2,n,\min}=\frac{D\cdot k_{12}}{V_2}\cdot\left\{A_2\cdot\frac{\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}\cdot \mathrm{e}^{-\lambda_1\cdot\tau}+B_2\cdot\frac{\left(\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)\right)}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\cdot \mathrm{e}^{-\lambda_2\cdot\tau}\right\} \quad n\in[0,\infty) \quad (14)$$

$$C_{1,\min,ss}=\frac{D}{V_1}\cdot\left\{\frac{A_1}{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}\cdot \mathrm{e}^{-\lambda_1\cdot\tau}+\frac{B_1}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\cdot \mathrm{e}^{-\lambda_2\cdot\tau}\right\} \quad (15)$$

$$C_{2,\min,ss}=\frac{D\cdot k_{12}}{V_2}\cdot\left\{\frac{A_2}{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}\cdot \mathrm{e}^{-\lambda_1\cdot\tau}+\frac{B_2}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\cdot \mathrm{e}^{-\lambda_2\cdot\tau}\right\} \quad (16)$$

AUC formulas

The areas under the curve per dosing interval were obtained by integration of the drug concentration from $(n-1)\cdot\tau$ to $n\cdot\tau$.

$$\mathrm{AUC}_{1,n,\tau}=\frac{D}{V_1}\cdot\left[A_1\cdot\frac{\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}{\lambda_1}+B_1\cdot\frac{\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)}{\lambda_2}\right] \tag{17}$$

$$\mathrm{AUC}_{2,n,\tau}=\frac{D\cdot k_{12}}{V_2}\cdot\left[A_2\cdot\frac{\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}{\lambda_1}+B_2\cdot\frac{\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)}{\lambda_2}\right] \tag{18}$$

$$\mathrm{AUC}_{1,\tau,ss}=\frac{D}{V_1}\cdot\left[\frac{A_1}{\lambda_1}+\frac{B_1}{\lambda_2}\right] \tag{19}$$

$$\mathrm{AUC}_{2,\tau,ss}=\frac{D\cdot k_{12}}{V_2}\cdot\left[\frac{A_2}{\lambda_1}+\frac{B_2}{\lambda_2}\right] \tag{20}$$

The maximum drug concentration in the central compartment can be determined from Equation (9) as a function of bolus dose at $t=(n-1)\cdot\tau$.

$$C_{1,n,\max}=\frac{D}{V_1}\cdot\left\{A_1\cdot\frac{\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}+B_1\cdot\frac{\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\right\} \tag{21}$$

$$C_{1,ss,\max}=\frac{D}{V_1}\cdot\left[\frac{A_1}{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}+\frac{B_1}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\right] \tag{22}$$

In order to obtain the maximum drug concentration in the peripheral compartment upon multiple IV boluses we first need to determine the peripheral compartment peak time as a function of intravenous bolus dose ($t_{2,n,\max}$) from Equation (4) (**Appendix**).

$$t_{2,n,\max}=(n-1)\cdot\tau+\frac{\ln\left(\frac{\lambda_2\cdot\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)\cdot\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}{\lambda_1\cdot\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)\cdot\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}\right)}{\left(\lambda_2-\lambda_1\right)} \tag{23}$$

$$\begin{aligned}C_{2,n,\max}=\frac{D\cdot k_{12}}{V_2}\cdot\Bigg\{&A_2\cdot\frac{\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}\cdot\mathrm{e}^{-\lambda_1\cdot\left(t_{2,\max,n}-(n-1)\cdot\tau\right)}\\&+B_2\cdot\frac{\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\cdot\mathrm{e}^{-\lambda_2\cdot\left(t_{2,\max,n}-(n-1)\cdot\tau\right)}\Bigg\}\end{aligned} \tag{24}$$

$$t_{2,n,\max,ss}=(n-1)\cdot\tau+\frac{\ln\left(\frac{\lambda_2\cdot\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}{\lambda_1\cdot\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\right)}{\left(\lambda_2-\lambda_1\right)} \tag{25}$$

$$t^*_{2,\max,ss}=\frac{\ln\left(\frac{\lambda_2\cdot\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}{\lambda_1\cdot\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\right)}{\left(\lambda_2-\lambda_1\right)} \tag{26}$$

where $t^*_{2,\max,ss}$ is the steady state time within a dosing interval $0\le t^*_{2,\max,ss}\le\tau$.

$$C_{2,n,\max,ss} = \frac{D \cdot k_{12}}{V_2} \cdot \left\{ \frac{A_2}{\left(1 - e^{-\lambda_1 \cdot \tau}\right)} \cdot e^{-\lambda_1 \cdot \left(t_{2,n,\max} - (n-1) \cdot \tau\right)} + \frac{B_2}{\left(1 - e^{-\lambda_2 \cdot \tau}\right)} \cdot e^{-\lambda_2 \cdot \left(t_{2,n,\max} - (n-1) \cdot \tau\right)} \right\} \quad (27)$$

$$C_{2,\max,ss} = \frac{D \cdot k_{12}}{V_2} \cdot \left(\frac{A_2}{\left(1 - e^{-\lambda_1 \cdot \tau}\right)} \cdot e^{-\lambda_1 \cdot t^*_{2,\max,ss}} + \frac{B_2}{\left(1 - e^{-\lambda_2 \cdot \tau}\right)} \cdot e^{-\lambda_2 \cdot t^*_{2,\max,ss}} \right) \quad (27a)$$

At the peripheral compartment peak time there is an equal rate of exchange of drug molecules from the central to peripheral compartment and vice versa. Hence, the time of momentary distribution equilibrium, $t_{eq,n}$ where the apparent volume of distribution of the drug with respect to the central phase ($V_{d,1}$) can be determined, is the same as $t_{2,n,\max}$. Therefore,

$$t_{2,n,\max} = t_{eq,n} \quad (28)$$

The time of momentary distribution equilibrium during the first dosing interval ($n = 1$) is:

$$t_{eq,1} = \frac{\ln\left(\frac{\lambda_2}{\lambda_1}\right)}{\left(\lambda_2 - \lambda_1\right)} \quad (23a)$$

The peak time of concentration in the peripheral compartment under steady-state conditions is,

$$t_{eq,ss} = t^*_{2,\max,ss} = \frac{\ln\left(\frac{\lambda_2}{\lambda_1} \cdot \frac{\left(1 - e^{-\lambda_1 \cdot \tau}\right)}{\left(1 - e^{-\lambda_2 \cdot \tau}\right)}\right)}{\left(\lambda_2 - \lambda_1\right)} \quad (26a)$$

The non-steady state drug concentration in the central compartment at momentary distribution equilibrium as a function of IV dose number is shown with Equation (29) whereas the steady state drug concentration in the central compartment at times of momentary distribution equilibrium is expressed by Equation (30).

$$C_{1,eq,n,t} = \frac{D}{V_1} \cdot \left\{ A_1 \cdot \frac{\left(1 - e^{-\lambda_1 \cdot n \cdot \tau}\right)}{\left(1 - e^{-\lambda_1 \cdot \tau}\right)} \cdot e^{-\lambda_1 \cdot \left(t_{2,\max,n} - (n-1) \cdot \tau\right)} + B_1 \cdot \frac{\left(1 - e^{-\lambda_2 \cdot n \cdot \tau}\right)}{\left(1 - e^{-\lambda_2 \cdot \tau}\right)} \cdot e^{-\lambda_2 \cdot \left(t_{2,\max,n} - (n-1) \cdot \tau\right)} \right\} \quad (29)$$

$$C_{1,eq,n,ss} = \frac{D}{V_1} \cdot \left\{ \frac{A_1}{\left(1 - e^{-\lambda_1 \cdot \tau}\right)} \cdot e^{-\lambda_1 \cdot t^*_{2,\max,ss}} + \frac{B_1}{\left(1 - e^{-\lambda_2 \cdot \tau}\right)} \cdot e^{-\lambda_2 \cdot t^*_{2,\max,ss}} \right\} \quad (30)$$

2.2.2. Multiple Oral Administration in a Two-Compartment Mammillary Model

Differential equations for inputs and outputs:

Input: First-order drug absorption into the central compartment.

Output: First-order drug elimination from the central compartment.

$$\dot{x}_1 = -\left(k_{10} + k_{12}\right) \cdot x_1 + k_{21} \cdot x_2 + k_a \cdot x_3; \quad x_1\left(0\right) = 0 \tag{31}$$

$$\dot{x}_2 = k_{12} \cdot x_1 - k_{21} \cdot x_2; \quad x_2\left(0\right) = 0 \tag{32}$$

$$\dot{x}_3 = -k_a \cdot x_3; \quad x_3\left(0\right) = D \tag{33}$$

where D is the drug dose and k_a is the first-order absorption rate constant. Work related to the analytical solutions of Equations (31)-(33) is included in the **Appendix**. Only the final equations are shown in this section.

Analytical solutions to drug concentration after single oral doses

$$x_1\left(t\right) = D \cdot k_a \cdot \left(A_3 \cdot \mathrm{e}^{-\lambda_1 \cdot t} + B_3 \cdot \mathrm{e}^{-\lambda_2 \cdot t} + E_3 \cdot \mathrm{e}^{-k_a \cdot t}\right) \tag{34}$$

$$A_3 = \frac{\left(k_{21} - \lambda_1\right)}{\left(k_a - \lambda_1\right) \cdot \left(\lambda_2 - \lambda_1\right)}; \quad B_3 = \frac{\left(k_{21} - \lambda_2\right)}{\left(k_a - \lambda_2\right) \cdot \left(\lambda_1 - \lambda_2\right)}; \quad E_3 = \frac{\left(k_{21} - k_a\right)}{\left(k_a - \lambda_1\right) \cdot \left(k_a - \lambda_2\right)}$$

$$C_1\left(t\right) = \frac{x_1\left(t\right)}{V_1} \tag{34a}$$

$$x_2\left(t\right) = D \cdot k_a \cdot k_{12} \cdot \left(A_4 \cdot \mathrm{e}^{-\lambda_1 \cdot t} + B_4 \cdot \mathrm{e}^{-\lambda_2 \cdot t} + E_4 \cdot \mathrm{e}^{-k_a \cdot t}\right) \tag{35}$$

$$A_4 = \frac{1}{\left(k_a - \lambda_1\right) \cdot \left(\lambda_2 - \lambda_1\right)}; \quad B_4 = \frac{1}{\left(k_a - \lambda_2\right) \cdot \left(\lambda_1 - \lambda_2\right)};$$

$$E_4 = \frac{1}{\left(k_a - \lambda_1\right) \cdot \left(k_a - \lambda_2\right)}$$

$$C_2\left(t\right) = \frac{x_2\left(t\right)}{V_2} \tag{35a}$$

$$x_3\left(t\right) = D \cdot \mathrm{e}^{-k_a \cdot t} \tag{36}$$

$$C_3\left(t\right) = \frac{x_3\left(t\right)}{V_3} \tag{36a}$$

Partial sums and formulas of the mathematical Series for repetitive oral doses

$$C_{1,n,t} = \frac{D \cdot k_a}{V_1} \cdot \left\{ A_3 \cdot \frac{\left(1 - \mathrm{e}^{-\lambda_1 \cdot n \cdot \tau}\right)}{\left(1 - \mathrm{e}^{-\lambda_1 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_1 \cdot \left(t - (n-1) \cdot \tau\right)} + B_3 \cdot \frac{\left(1 - \mathrm{e}^{-\lambda_2 \cdot n \cdot \tau}\right)}{\left(1 - \mathrm{e}^{-\lambda_2 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_2 \cdot \left(t - (n-1) \cdot \tau\right)} + E_3 \cdot \frac{\left(1 - \mathrm{e}^{-k_a \cdot n \cdot \tau}\right)}{\left(1 - \mathrm{e}^{-k_a \cdot \tau}\right)} \cdot \mathrm{e}^{-k_a \cdot \left(t - (n-1) \cdot \tau\right)} \right\} \quad n, t \in \left[0, \infty\right) \tag{37}$$

$$C_{2,n,t} = \frac{D \cdot k_a \cdot k_{12}}{V_2} \cdot \left\{ A_4 \cdot \frac{\left(1 - \mathrm{e}^{-\lambda_1 \cdot n \cdot \tau}\right)}{\left(1 - \mathrm{e}^{-\lambda_1 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_1 \cdot \left(t - (n-1) \cdot \tau\right)} + B_4 \cdot \frac{\left(1 - \mathrm{e}^{-\lambda_2 \cdot n \cdot \tau}\right)}{\left(1 - \mathrm{e}^{-\lambda_2 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_2 \cdot \left(t - (n-1) \cdot \tau\right)} + E_4 \cdot \frac{\left(1 - \mathrm{e}^{-k_a \cdot n \cdot \tau}\right)}{\left(1 - \mathrm{e}^{-k_a \cdot \tau}\right)} \cdot \mathrm{e}^{-k_a \cdot \left(t - (n-1) \cdot \tau\right)} \right\} \quad n, t \in \left[0, \infty\right) \tag{38}$$

The corresponding steady state concentrations of the drug in the two compartments are,

$$C_{1,n,ss,t} = \frac{D \cdot k_a}{V_1} \cdot \left\{ \frac{A_3}{\left(1-\mathrm{e}^{-\lambda_1 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_1 \cdot \left(t-(n-1)\cdot\tau\right)} + \frac{B_3}{\left(1-\mathrm{e}^{-\lambda_2 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_2 \cdot \left(t-(n-1)\cdot\tau\right)} + \frac{E_3}{\left(1-\mathrm{e}^{-k_a \cdot \tau}\right)} \cdot \mathrm{e}^{-k_a \cdot \left(t-(n-1)\cdot\tau\right)} \right\} \tag{39}$$

$$C_{2,n,ss,t} = \frac{D \cdot k_a \cdot k_{12}}{V_2} \cdot \left\{ \frac{A_4}{\left(1-\mathrm{e}^{-\lambda_1 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_1 \cdot \left(t-(n-1)\cdot\tau\right)} + \frac{B_4}{\left(1-\mathrm{e}^{-\lambda_2 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_2 \cdot \left(t-(n-1)\cdot\tau\right)} + \frac{E_4}{\left(1-\mathrm{e}^{-k_a \cdot \tau}\right)} \cdot \mathrm{e}^{-k_a \cdot \left(t-(n-1)\cdot\tau\right)} \right\} \tag{40}$$

Trough concentrations can be obtained from the general equations above at $t = n \cdot \tau$.

$$C_{1,n,\min} = \frac{D \cdot k_a}{V_1} \cdot \left\{ A_3 \cdot \frac{\left(1-\mathrm{e}^{-\lambda_1 \cdot n \cdot \tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_1 \cdot \tau} + B_3 \cdot \frac{\left(1-\mathrm{e}^{-\lambda_2 \cdot n \cdot \tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_2 \cdot \tau} + E_3 \cdot \frac{\left(1-\mathrm{e}^{-k_a \cdot n \cdot \tau}\right)}{\left(1-\mathrm{e}^{-k_a \cdot \tau}\right)} \cdot \mathrm{e}^{-k_a \cdot \tau} \right\} \quad n \in [0, \infty) \tag{41}$$

$$C_{2,n,\min} = \frac{D \cdot k_a \cdot k_{12}}{V_2} \cdot \left\{ A_4 \cdot \frac{\left(1-\mathrm{e}^{-\lambda_1 \cdot n \cdot \tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_1 \cdot \tau} + B_4 \cdot \frac{\left(1-\mathrm{e}^{-\lambda_2 \cdot n \cdot \tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_2 \cdot \tau} + E_4 \cdot \frac{\left(1-\mathrm{e}^{-k_a \cdot n \cdot \tau}\right)}{\left(1-\mathrm{e}^{-k_a \cdot \tau}\right)} \cdot \mathrm{e}^{-k_a \cdot \tau} \right\} \tag{42}$$

$$C_{1,\min,ss} = \frac{D \cdot k_a}{V_1} \cdot \left\{ \frac{A_3}{\left(1-\mathrm{e}^{-\lambda_1 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_1 \cdot \tau} + \frac{B_3}{\left(1-\mathrm{e}^{-\lambda_2 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_2 \cdot \tau} + \frac{E_3}{\left(1-\mathrm{e}^{-k_a \cdot \tau}\right)} \cdot \mathrm{e}^{-k_a \cdot \tau} \right\} \tag{43}$$

$$C_{2,\min,ss} = \frac{D \cdot k_a \cdot k_{12}}{V_2} \cdot \left\{ \frac{A_4}{\left(1-\mathrm{e}^{-\lambda_1 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_1 \cdot \tau} + \frac{B_4}{\left(1-\mathrm{e}^{-\lambda_2 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_2 \cdot \tau} + \frac{E_4}{\left(1-\mathrm{e}^{-k_a \cdot \tau}\right)} \cdot \mathrm{e}^{-k_a \cdot \tau} \right\} \tag{44}$$

AUC formulas

$$\mathrm{AUC}_{1,n,\tau} = \frac{D \cdot k_a}{V_1} \cdot \left[A_3 \cdot \frac{\left(1-\mathrm{e}^{-\lambda_1 \cdot n \cdot \tau}\right)}{\lambda_1} + B_3 \cdot \frac{\left(1-\mathrm{e}^{-\lambda_2 \cdot n \cdot \tau}\right)}{\lambda_2} + E_3 \cdot \frac{\left(1-\mathrm{e}^{-k_a \cdot n \cdot \tau}\right)}{k_a} \right] \tag{45}$$

$$\mathrm{AUC}_{2,n,\tau} = \frac{D \cdot k_a \cdot k_{12}}{V_2} \cdot \left[A_4 \cdot \frac{\left(1-\mathrm{e}^{-\lambda_1 \cdot n \cdot \tau}\right)}{\lambda_1} + B_4 \cdot \frac{\left(1-\mathrm{e}^{-\lambda_2 \cdot n \cdot \tau}\right)}{\lambda_2} + E_4 \cdot \frac{\left(1-\mathrm{e}^{-k_a \cdot n \cdot \tau}\right)}{k_a} \right] \tag{46}$$

$$\mathrm{AUC}_{1,\tau,ss} = \frac{D \cdot k_a}{V_1} \cdot \left[\frac{A_3}{\lambda_1} + \frac{B_3}{\lambda_2} + \frac{E_3}{k_a} \right] \tag{47}$$

$$\mathrm{AUC}_{2,\tau,ss} = \frac{D \cdot k_a \cdot k_{12}}{V_2} \cdot \left[\frac{A_4}{\lambda_1} + \frac{B_4}{\lambda_2} + \frac{E_4}{k_a} \right] \tag{48}$$

The peak drug concentration in the central compartment can be obtained as a function of oral dose number after we obtain the time to reach maximum central compartment concentration by setting the derivatives in Equation (31) equal to zero.

The time to reach maximum drug concentration $t_{1,n,\max}$, in the central compartment can be determined from Equation (49) by iteration.

$$\frac{\mathrm{d}x_{1,n,t}}{\mathrm{d}t}=0$$

$$\left\{-\lambda_1\cdot A_3\cdot\frac{\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}\cdot\mathrm{e}^{-\lambda_1\cdot\left(t_{1,n,\max}-(n-1)\cdot\tau\right)}-\lambda_2\cdot B_3\cdot\frac{\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\cdot\mathrm{e}^{-\lambda_2\cdot\left(t_{1,n,\max}-(n-1)\cdot\tau\right)}\right.$$
$$\left.-k_a\cdot E_3\cdot\frac{\left(1-\mathrm{e}^{-k_a\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-k_a\cdot\tau}\right)}\cdot\mathrm{e}^{-k_a\cdot\left(t_{1,n,\max}-(n-1)\cdot\tau\right)}\right\}=0 \tag{49}$$

A ballpark figure can be obtained if drug distribution is faster than drug absorption which is in turn much faster than drug elimination. Thus, if $\lambda_1 \gg k_a$, $\mathrm{e}^{-\lambda_1\cdot\left(t_{1,n,\max}-(n-1)\cdot\tau\right)}\to 0$

$$\mathrm{e}^{\left(k_a-\lambda_2\right)\cdot\left(t_{1,n,\max}-(n-1)\cdot\tau\right)}=-\frac{k_a}{\lambda_2}\cdot\frac{E_3}{B_3}\cdot\frac{\left(1-\mathrm{e}^{-k_a\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-k_a\cdot\tau}\right)}\cdot\frac{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)}$$

$$\Rightarrow$$

$$t_{1,n,\max}=(n-1)\cdot\tau+\frac{\ln\left(\frac{k_a\cdot\left(k_{21}-k_a\right)\cdot\left(\lambda_2-\lambda_1\right)\cdot\left(1-\mathrm{e}^{-k_a\cdot n\cdot\tau}\right)\cdot\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}{\lambda_2\cdot\left(k_a-\lambda_1\right)\cdot\left(k_{21}-\lambda_2\right)\cdot\left(1-\mathrm{e}^{-k_a\cdot\tau}\right)\cdot\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)}\right)}{\left(k_a-\lambda_2\right)} \tag{50}$$

$$t_{1,1,\max}=\frac{\ln\left(\frac{k_a\cdot\left(k_{21}-k_a\right)\cdot\left(\lambda_2-\lambda_1\right)}{\lambda_2\cdot\left(k_a-\lambda_1\right)\cdot\left(k_{21}-\lambda_2\right)}\right)}{\left(k_a-\lambda_2\right)} \tag{50a}$$

$$t^*_{1,\max,ss}=\frac{\ln\left(\frac{k_a\cdot\left(k_{21}-k_a\right)\cdot\left(\lambda_2-\lambda_1\right)\cdot\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}{\lambda_2\cdot\left(k_a-\lambda_1\right)\cdot\left(k_{21}-\lambda_2\right)\cdot\left(1-\mathrm{e}^{-k_a\cdot\tau}\right)}\right)}{\left(k_a-\lambda_2\right)} \tag{51}$$

$$t^*_{1,\max,ss}=t_{1,\max,1}+\frac{\ln\left(\frac{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}{\left(1-\mathrm{e}^{-k_a\cdot\tau}\right)}\right)}{\left(k_a-\lambda_2\right)} \tag{51a}$$

$$C_{1,n,\max}=\frac{D\cdot k_a}{V_1}\cdot\left\{A_3\cdot\frac{\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}\cdot\mathrm{e}^{-\lambda_1\cdot\left(t_{1,n,\max}-(n-1)\cdot\tau\right)}\right.$$
$$+B_3\cdot\frac{\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\cdot\mathrm{e}^{-\lambda_2\cdot\left(t_{1,n,\max}-(n-1)\cdot\tau\right)} \tag{52}$$
$$\left.+E_3\cdot\frac{\left(1-\mathrm{e}^{-k_a\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-k_a\cdot\tau}\right)}\cdot\mathrm{e}^{-k_a\cdot\left(t_{1,,n,\max}-(n-1)\cdot\tau\right)}\right\}$$

$$C_{1,\max,ss} = \frac{D \cdot k_a}{V_1} \cdot \left\{ A_3 \cdot \frac{e^{-\lambda_1 \cdot t^*_{1,\max,ss}}}{\left(1-e^{-\lambda_1 \cdot \tau}\right)} + B_3 \cdot \frac{e^{-\lambda_2 \cdot t^*_{1,\max,ss}}}{\left(1-e^{-\lambda_2 \cdot \tau}\right)} + E_3 \cdot \frac{e^{-k_a \cdot t^*_{1,\max,ss}}}{\left(1-e^{-k_a \cdot \tau}\right)} \right\} \quad (53)$$

The time to reach peak concentration $t_{2,\max,n}$, in the peripheral compartment can be determined by iteration from Equation (54), as shown below:

$$k_{12} \cdot x_1 - k_{21} \cdot x_2 = 0$$

$$\left\{ A_4 \cdot \frac{\left(1-e^{-\lambda_1 \cdot n \cdot \tau}\right)}{\left(1-e^{-\lambda_1 \cdot \tau}\right)} \cdot e^{-\lambda_1 \cdot \left(t-(n-1)\cdot\tau\right)} + B_4 \cdot \frac{\left(1-e^{-\lambda_2 \cdot n \cdot \tau}\right)}{\left(1-e^{-\lambda_2 \cdot \tau}\right)} \cdot e^{-\lambda_2 \cdot \left(t-(n-1)\cdot\tau\right)} + E_4 \cdot \frac{\left(1-e^{-k_a \cdot n \cdot \tau}\right)}{\left(1-e^{-k_a \cdot \tau}\right)} \cdot e^{-k_a \cdot \left(t-(n-1)\cdot\tau\right)} \right\} = 0 \quad (54)$$

We can obtain a ballpark estimate of $t_{2,n,\max}$ if $\lambda_1 \gg k_a$.

$$\left\{ \frac{\left(k_{21}-\lambda_2\right)}{\left(k_a-\lambda_2\right)\cdot\left(\lambda_1-\lambda_2\right)} \cdot \frac{\left(1-e^{-\lambda_2 \cdot n \cdot \tau}\right)}{\left(1-e^{-\lambda_2 \cdot \tau}\right)} \cdot e^{-\lambda_2 \cdot \left(t-(n-1)\cdot\tau\right)} + \frac{\left(k_{21}-k_a\right)}{\left(k_a-\lambda_1\right)\cdot\left(k_a-\lambda_2\right)} \cdot \frac{\left(1-e^{-k_a \cdot n \cdot \tau}\right)}{\left(1-e^{-k_a \cdot \tau}\right)} \cdot e^{-k_a \cdot \left(t-(n-1)\cdot\tau\right)} \right\} = 0$$

$$t_{2,n,\max} = (n-1)\cdot\tau + \frac{\ln\left(\frac{k_a \cdot \left(1-e^{-k_a \cdot n \cdot \tau}\right)\cdot\left(\lambda_2-\lambda_1\right)\cdot\left(1-e^{-\lambda_2 \cdot \tau}\right)}{\lambda_2 \cdot \left(1-e^{-\lambda_2 \cdot n \cdot \tau}\right)\cdot\left(k_a-\lambda_1\right)\cdot\left(1-e^{-k_a \cdot \tau}\right)} \right)}{\left(k_a-\lambda_2\right)} \quad (55)$$

$$t^*_{2,\max,ss} = \frac{\ln\left(\frac{k_a \cdot \left(\lambda_2-\lambda_1\right)\cdot\left(1-e^{-\lambda_2 \cdot \tau}\right)}{\lambda_2 \cdot \left(k_a-\lambda_1\right)\cdot\left(1-e^{-k_a \cdot \tau}\right)} \right)}{\left(k_a-\lambda_2\right)} \quad (56)$$

Since at the time of peak peripheral concentration the intercompartmental solute exchange rates are equal, $t_{2,n,\max} = t_{eq,n}$, where $t_{eq,n}$ is the time of momentary distribution equilibrium as a function of dose number (n). The time of momentary distribution equilibrium during the first dosing interval ($n=1$) is,

$$t_{eq,1} = t_{2,1,\max} = \frac{\ln\left[\frac{k_a \cdot \left(\lambda_2-\lambda_1\right)}{\lambda_2 \cdot \left(k_a-\lambda_1\right)} \right]}{\left(k_a-\lambda_2\right)} \quad (55a)$$

The non-steady state and steady state peak peripheral drug concentration and central compartment drug concentration are expressed with Equations (57)-(60).

$$C_{2,n,\max} = \frac{D \cdot k_a \cdot k_{12}}{V_2} \cdot \left\{ A_4 \cdot \frac{\left(1-e^{-\lambda_1 \cdot n \cdot \tau}\right)}{\left(1-e^{-\lambda_1 \cdot \tau}\right)} \cdot e^{-\lambda_1 \cdot \left(t_{2,n,\max}-(n-1)\cdot\tau\right)} + B_4 \cdot \frac{\left(1-e^{-\lambda_2 \cdot n \cdot \tau}\right)}{\left(1-e^{-\lambda_2 \cdot \tau}\right)} \cdot e^{-\lambda_2 \cdot \left(t_{2,n,\max}-(n-1)\cdot\tau\right)} + E_4 \cdot \frac{\left(1-e^{-k_a \cdot n \cdot \tau}\right)}{\left(1-e^{-k_a \cdot \tau}\right)} \cdot e^{-k_a \cdot \left(t_{2,n,\max}-(n-1)\cdot\tau\right)} \right\} \quad (57)$$

$$C_{2,\max,ss} = \frac{D \cdot k_a \cdot k_{12}}{V_2} \cdot \left\{ A_4 \cdot \frac{e^{-\lambda_1 \cdot t^*_{2,\max,ss}}}{\left(1 - e^{-\lambda_1 \cdot \tau}\right)} + B_4 \cdot \frac{e^{-\lambda_2 \cdot t^*_{2,\max,ss}}}{\left(1 - e^{-\lambda_2 \cdot \tau}\right)} + E_4 \cdot \frac{e^{-k_a \cdot t^*_{2,\max,ss}}}{\left(1 - e^{-k_a \cdot \tau}\right)} \right\} \quad (58)$$

$$\begin{aligned} C_{1,eq,n} = \frac{D \cdot k_a}{V_1} \cdot \Bigg\{ & A_3 \cdot \frac{\left(1 - e^{-\lambda_1 \cdot n \cdot \tau}\right)}{\left(1 - e^{-\lambda_1 \cdot \tau}\right)} \cdot e^{-\lambda_1 \cdot \left(t_{2,n,\max} - (n-1) \cdot \tau\right)} \\ & + B_3 \cdot \frac{\left(1 - e^{-\lambda_2 \cdot n \cdot \tau}\right)}{\left(1 - e^{-\lambda_2 \cdot \tau}\right)} \cdot e^{-\lambda_2 \cdot \left(t_{2,n,\max} - (n-1) \cdot \tau\right)} \\ & + E_3 \cdot \frac{\left(1 - e^{-k_a \cdot n \cdot \tau}\right)}{\left(1 - e^{-k_a \cdot \tau}\right)} \cdot e^{-k_a \cdot \left(t_{2,n,\max} - (n-1) \cdot \tau\right)} \Bigg\} \end{aligned} \quad (59)$$

$$\begin{aligned} C_{1,eq,ss} = \frac{D \cdot k_a}{V_1} \cdot \Bigg\{ & A_3 \cdot \frac{1}{\left(1 - e^{-\lambda_1 \cdot \tau}\right)} \cdot e^{-\lambda_1 \cdot t^*_{2,\max,ss}} + B_3 \cdot \frac{1}{\left(1 - e^{-\lambda_2 \cdot \tau}\right)} \cdot e^{-\lambda_2 \cdot t^*_{2,\max,ss}} \\ & + E_3 \cdot \frac{1}{\left(1 - e^{-k_a \cdot \tau}\right)} \cdot e^{-k_a \cdot t^*_{2,\max,ss}} \Bigg\} \end{aligned} \quad (60)$$

2.3. Pharmacokinetic Analysis

Prazosin plasma drug concentration-time values were extracted from **Figure 1** of the published work of Bateman and coworkers (single short intravenous infusion and single oral dose) and the work of Grahnen *et al.*, using the online graph reader tool (graphreader.com). The correctness of the extracted C-t values was also verified by manually drawn values on scaled log y-axis. All pharmacokinetic parameters were determined using linear and nonlinear regression analysis of plasma drug concentration-time data.

2.4. Computer Simulations

Simulations of drug concentration and AUC as a function of time were carried out with Microsoft Excel Spreadsheet Software [3] [14] [15].

3. Results

3.1. Single IV Bolus

Simple linear regression analysis was carried out on published plasma drug concentration as a function of time on four patients using the least squares method [6]. In accord with the two-compartment open model, the plasma is part of the central compartment. Initial estimates of model parameters were obtained by the method of residuals where the coefficient $\left(\frac{D}{V_1} \cdot B_1\right)$ and eigenvector λ_2 were determined from the intercept and slope of the regressed best-fit logarithmic equation of measured plasma drug concentration as a function of terminal time data points where drug distribution reached steady-state, respectively. These two fitted parameters were then used to calculate the drug concentration that was removed from the plasma purely due to drug elimination (C_1'). The residual was

calculated from the difference between the measured plasma drug concentration (C_1) and C_1'. A plot of the logarithmic concentration difference ($C_1 - C_1'$) with time at early data points was linear. The slope and intercept of the best-fit equation were used to determine the eigenvector λ_1 and coefficient $\left(\frac{D}{V_1}\cdot A_1\right)$, respectively. The number of data points that were used to assess the four parameters was decided from the correlation coefficient of each line and the contribution of the two eigenvectors on each phase. In general, the contribution of the distribution phase as assessed from the exponential ratio of the two eigenvectors $e^{-(\lambda_1+\lambda_2)\cdot t}$ to the terminal time data points was between 5.66×10^{-10}% and 0.16%. In agreement with these results of the eigenvector exponential ratio, the contribution of the distribution process to the plasma drug concentration calculated using the first-order formula $\left(\frac{1}{2}\right)^{\left(\frac{t}{t_{1/2,\alpha}}\right)}$ was also found to be zero for the terminal data.

The average estimates out of four patients of the aforementioned parameters were utilized to obtain an initial estimate of the volume of the central compartment. The volume of the central compartment was determined from the initial concentration of the drug in the central compartment after the first intravenous dose $C_{1,1,0}$ using Equation (9a). Initial estimates of the unitless coefficients A_1 and B_1 were calculated from the administered dose and the V_1. Further optimization was carried out using the Excel GRG Nonlinear method of iteration by varying simultaneously all five parameters V_1, A_1, B_1, λ_1 and λ_2. The average value of V_1 was calculated to be 11.25 L. Finally, the values of the micro-rate intercompartmental constants, k_{21}, k_{10} and k_{12} were calculated using Equations (61)-(63) (Table 1).

$$k_{21} = \frac{A_1 \cdot \lambda_2 + B_1 \cdot \lambda_1}{A_1 + B_1} \tag{61}$$

$$k_{10} = \frac{\lambda_1 \cdot \lambda_2}{k_{21}} \tag{62}$$

$$k_{12} = \lambda_1 + \lambda_2 - k_{10} - k_{21} \tag{63}$$

Since the volume of the central compartment is less than the extracellular body fluid we can reasonably assume that the central compartment is a monophase and use Riggs equation (Equation (64)) to determine the apparent volume of distribution of the drug with respect to the central phase [16].

$$V_{d,1} = V_1 \cdot \left(1 + \frac{k_{12}}{k_{21}}\right) \tag{64}$$

The average value of $V_{d,1}$ was found to be equal to 32.87 L. Since this value is not greater than the total body fluid of a 70-kg healthy human subject, and the drug is not known to be involved with any influx transport system we can reasonably assume that $V_{d,1}$ is not the apparent but it is the actual volume of distribution of the drug in the body. The volume of peripheral compartment can be

Table 1. Pharmacokinetic parameters of Prazosin after a single 0.5 mg intravenous bolus dose in a two-compartment open model.

	Patient				
parameter	**B. G.**	**E. R.**	**H. A.**	**M. F.**	**Average ± St Dev**
W (kg)	85	65	110	76	84 ± 19.2
* α (h^{-1})	4.0073	4.8501	3.5422	7.8375	5.0593 ± 1.9296
* β (h^{-1})	0.2613	0.3327	0.1968	0.2911	0.2705 ± 0.0572
k_{12} (h^{-1})	2.1958	2.6317	1.7450	5.1062	2.9197 ± 1.5020
k_{21} (h^{-1})	1.2003	1.1591	1.5420	1.4663	1.3419 ± 0.1906
k_{10} (h^{-1})	0.8725	1.3919	0.4520	1.5561	1.0681 ± 0.5036
V_1 (L)	9.00	8.84	18.96	8.18	11.25 ± 5.16
V_2 (L)	16.46	20.07	21.46	28.50	21.62 ± 5.04
$V_{d,1}$ (L)	25.46	28.91	40.42	36.68	32.87 ± 6.88
AUC_{ss} (ng·h/mL)	63.68	40.63	58.33	39.26	50.48 ± 12.37
CL (L/h)	7.85	12.31	8.57	12.73	10.37 ± 2.51
A_1	0.7493	0.8170	0.5979	0.8443	0.7521 ± 0.1103
B_1	0.2507	0.1830	0.4021	0.1557	0.2479 ± 0.1103
A_2 (h^{-1})	−0.2670	−0.2214	−0.2989	−0.1325	−0.2299 ± 0.0723
B_2 (h^{-1})	0.2670	0.2214	0.2989	0.1325	0.2299 ± 0.0723

* $\alpha = \lambda_1$ and $\beta = \lambda_2$.

determined from the difference of the two volumes. Its value is close to intracellular body fluid volume.

$$V_2 = V_{d,1} - V_1 = 21.62 \text{ L}$$

3.2. Single Intermittent Intravenous Infusion

One of the most comprehensive pharmacokinetic studies of prazosin was conducted by Bateman and coworkers. Although the drug was administered by a slow intravenous 10-minute infusion the two-compartment model average pharmacokinetic parameters were calculated with an IV bolus model using a mid-point rule technique, that is, they have timed sampling not from zero time but from the mid-point of the infusion. This was necessary as the intermittent IV infusion analytical solutions to drug concentration, especially during the infusion phase of the drug, were not available or because nonlinear regression analysis was difficult at the time. We have recently produced the explicit solutions to drug concentration in the one- and two-compartment models after multiple constant rate intermittent intravenous infusions for both ascending and descending phases [3] [14]. First, we time-shifted their sampling times by 5 minutes, that is, the time 10 and 20 minutes became the actual time of 15 and 25 minutes, respectively, and so on and so forth. Second, the plasma drug concentration-time data points after administration of the first dose were fitted using non-linear least squares analysis by the intermittent infusion elimination phase

equations (Equations (65)-(67)) in a two-compartment model [3]. The plot in Figure 2 shows the actual data points extracted from Bateman *et al.*, and our model's fitted line. Notice that with our method we can also recover the peak drug concentration at the end of the infusion period. All calculated average pharmacokinetic parameters of Prazosin are listed in Table 2.

$$C_{e,1,1}(t) = \frac{(k_{21}-\lambda_1)\cdot C_1(T)+k_{21}\cdot C_2(T)}{(\lambda_2-\lambda_1)}\cdot e^{-\lambda_1\cdot(t-T)} + \frac{(k_{21}-\lambda_2)\cdot C_1(T)+k_{21}\cdot C_2(T)}{(\lambda_1-\lambda_2)}\cdot e^{-\lambda_2\cdot(t-T)} \tag{65}$$

where,

$$C_1(T) = \frac{k_0}{V_1}\cdot\left(\frac{k_{21}}{\lambda_1\cdot\lambda_2}+\frac{k_{21}-\lambda_1}{\lambda_1\cdot(\lambda_1-\lambda_2)}\cdot e^{-\lambda_1\cdot T}+\frac{k_{21}-\lambda_2}{\lambda_2\cdot(\lambda_2-\lambda_1)}\cdot e^{-\lambda_2\cdot T}\right) \tag{66}$$

$$C_2(T) = \frac{k_0\cdot k_{12}}{V_2}\cdot\left(\frac{1}{\lambda_1\cdot\lambda_2}+\frac{1}{\lambda_1\cdot(\lambda_1-\lambda_2)}\cdot e^{-\lambda_1\cdot T}+\frac{1}{\lambda_2\cdot(\lambda_2-\lambda_1)}\cdot e^{-\lambda_2\cdot T}\right) \tag{67}$$

3.3. Single 1 mg Prazosin Oral Tablet Administration

The average pharmacokinetic parameters of Prazosin in a two-compartment model were determined from measured plasma drug concentration in six patients (Bateman and coworkers) after administration of a single 1 mg Prazosin tablet (Table 3). The C-t pairs were regressed in the two-compartment model using Equation (34) by minimizing the sum of the squares of the residuals. Regression analysis of the data points was also carried out in the one-compartment model using Equation (68). Neither the two-compartment model nor the one-compartment model fitted the average plasma drug concentrations of the absorption phase very well (Figure 3).

$$C = \frac{F\cdot D\cdot k_a}{V_d\cdot(k_a-k)}\cdot\left(e^{-k\cdot t}-e^{-k_a\cdot t}\right) \tag{68}$$

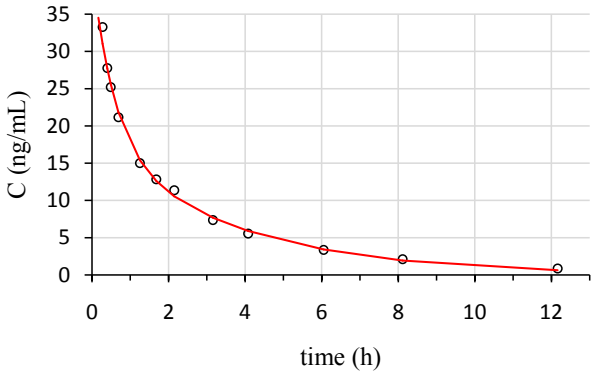

Figure 2. (empty circles, ○) Measured plasma Prazosin concentration (data extracted from the published work of Bateman *et al.*,) after a single 10-minute constant rate infusion of Prazosin 1 mg. (solid line) Model's fitted line using Equation (65).

Table 2. Average pharmacokinetic parameters after administration of a single intermittent intravenous infusion of 1 mg Prazosin at a rate of 0.1 mg/min. Plasma prazosin concentration-time points were extracted from the article of Bateman and coworkers.

λ_1 (h^{-1})	λ_2 (h^{-1})	k_{12} (h^{-1})	k_{21} (h^{-1})	k_{10} (h^{-1})	V_1 (L)	V_2 (L)	$V_{d,1}$ (L)
1.76	0.28	0.5813	0.9373	0.5179	26.5	14.2	42.9

Table 3. Average pharmacokinetic parameters after administration of a single 1 mg Prazosin oral tablet. Plasma prazosin concentration-time data points were extracted from the published article of Bateman and coworkers.

Parameter	One-Compartment	Two-Compartment
λ_1 (h^{-1})	---	3.1761
* λ_2 (h^{-1})	0.3171	0.3171
k_{12} (h^{-1})	---	1.1451
k_{21} (h^{-1})	---	1.7834
k_{10} (h^{-1})	---	0.5645
k_a (h^{-1})	0.6957	0.5335
F	0.547	0.614
V_1 (L)	---	26.5
V_2 (L)	---	17.0
$V_{d,1}$ (L)	43.5	43.5

* $\lambda_2 = k$ (for the one-compartment model).

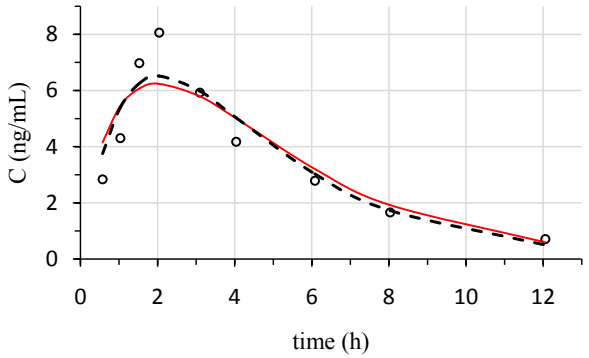

Figure 3. The average plasma Prazosin concentration (measured concentrations were extracted from Bateman *et al.*, empty symbols) was simulated as a function of time by a one-compartment model (dashed-line) and a two-compartment model (solid line).

4. Discussion

4.1. Single IV Bolus

The estimated pharmacokinetic parameters of Prazosin in Table 1 are very similar to those published by Grahnen and coworkers. Using these parameters that were extracted from a single IV bolus we were able to simulate the Prazosin concentration in the central and peripheral compartment after repetitive intravenous boluses at constant dosing frequency as a function of total time using

Equation (9) and Equation (10), respectively. As shown in Figure 4, the plasma drug concentration in the central compartment fluctuates from about 53 ng/mL to 9 ng/mL. The time to reach peak peripheral drug concentration, calculated with Equation (23) and Equation (26) at non-steady state and steady state conditions, respectively, varied with the IV bolus dose number (n) from 36.7 minutes to 29.3 minutes (Table 4).

The apparent volume of distribution of a drug in a two-compartment model was calculated using Equation (64). If our assumption is correct about the central monophase compartment, we should be able to get a similar value for the apparent volume of distribution of Prazosin associated with the central compartment $V_{d,1}$, using Equation (69) [2]. As we have discussed extensively elsewhere, the apparent volume of distribution is a system equilibrium property and

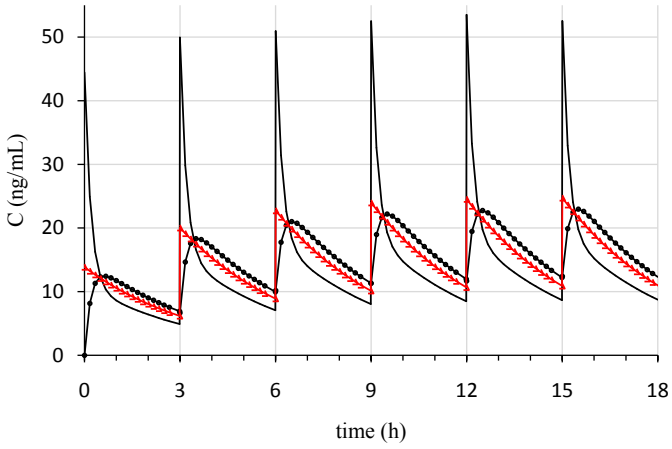

Figure 4. Simulated Prazosin concentration in the central compartment or plasma (solid line) and in the peripheral compartment (empty circles joined by solid line) as a function of time based on a two-compartment pharmacokinetic model. For comparison the simulated plasma drug concentration from a one-compartment model is also drawn (empty triangles joined with solid line). The dosing interval in all simulations was kept constant ($\tau = 3$ h).

Table 4. AUC (ng/mL·h) after repetitive 0.5 mg Prazosin intravenous boluses at the end of each dosing interval ($\tau = 3$ h) in the one- and two-compartment models, and time to reach peak peripheral drug concentration ($t^*_{2,\max,n}$), in units of minutes, as a function of dose number.

n	$\mathrm{AUC}_{\mathrm{one\_comp}}$	$\mathrm{AUC}_{1,\max}$	$\mathrm{AUC}_{2,\max}$	$t^*_{2,\max,n}$
1	28.5	29.3	28.8	36.7
2	41.2	39.3	43.0	32.1
3	46.8	43.8	49.3	30.5
4	49.3	45.8	52.1	29.8
5	50.4	46.6	53.3	29.6
6	50.9	47.0	53.9	29.4
Steady state	51.3	47.3	54.3	29.3

can be determined at times of momentary distribution equilibrium, *i.e.*, when the rates of distribution of Prazosin molecules from central to peripheral compartment and vice versa are equal [3]. The value of $V_{d,1}$ as calculated from the slope of the line in **Figure 5** was 36.06 L which is within the average range of the $V_{d,1}$ calculated with Equation (64).

$$V_{d,1} = \frac{x_{1,eq,n} + x_{2,eq,n}}{C_{1,eq,n}} = \frac{x_{s,eq,n}}{C_{1,eq,n}} \tag{69}$$

$$C_{\text{one-comp},n,t} = \frac{D}{V_{d,1}} \cdot \frac{\left(1 - e^{-k \cdot n \cdot \tau}\right)}{\left(1 - e^{-k \cdot \tau}\right)} \cdot e^{-k \cdot \left(t - (n-1) \cdot \tau\right)} \tag{70}$$

$$C_{\text{one-comp},ss} = \frac{D}{V_{d,1}} \cdot \frac{1}{\left(1 - e^{-k \cdot \tau}\right)} \cdot e^{-k \cdot \left(t - (n-1) \cdot \tau\right)} \tag{71}$$

$$\text{AUC}_{\text{one-comp},\tau,n} = \frac{D}{k \cdot V_{d,1}} \cdot \left(1 - e^{-k \cdot n \cdot \tau}\right) \tag{72}$$

$$\text{AUC}_{1,\tau,ss} = \frac{D}{k \cdot V_{d,1}} \tag{73}$$

Obtaining the value of $V_{d,1}$ is extremely important because it is the only way to carry out simulations of drug concentration with time and calculate the AUC after repetitive IV boluses in the one-compartment model. Equations (70)-(73) simulate non-steady state and steady state drug concentrations and AUC in the one-compartment model. As shown in **Figure 4**, the peak drug concentration after the first IV bolus using the same dose in the one-compartment model is around 14 ng/mL which is about one third of the value calculated from a two-compartment model (~44.5 ng/mL). Although the concentration falls very

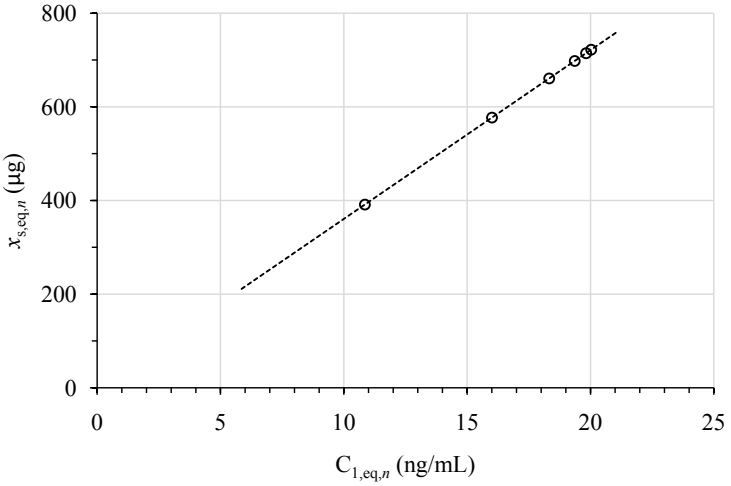

Figure 5. The amount of drug in the body $x_{s,eq,n}$ after repetitive intravenous boluses, was plotted against the drug concentration in the central compartment at momentary distribution equilibrium $C_{1,eq,n}$ as a function of dose number. The Prazosin apparent volume of distribution ($V_{d,1}$) was calculated from the slope of the line using Equation (69) to be equal to 36.06 L.

rapidly due to the very short distribution half-life, this could be significant if the drug concentration in the central compartment is as important as the drug concentration in the peripheral compartment for pharmacological activity. Prazosin is known to be a selective postsynaptic α_1-adrenoceptor blocker. Its blood pressure (BP) lowering effect is exerted after binding and inhibiting α_1-adrenoceptors in the vascular smooth muscle of mainly arteries and arterioles which from the pharmacokinetic viewpoint these tissues are in the central compartment [17] [18]. Furthermore, the inhibitory effect of Prazosin must be related to its binding affinity on these receptors, which is in turn concentration dependent [4]. It is therefore highly possible that the peak plasma concentration of Prazosin is the one that drives a higher receptor occupancy with a more pronounced antihypertensive effect. The concentration of Prazosin in the peripheral compartment is important in maintaining but not initiating its pharmacological effect. If this is the case then although the drug has a distribution half-life of only about 10 minutes as compared to an elimination half-life of about 2.4 h, the one-compartment model will not be able to approximate dosing calculations in the clinic. In support of this conclusion, Bateman *et al.*, recorded highest drop in standing blood pressure during the first one half hour after an IV bolus administration of Prazosin. The one-compartment model simulated steady state peak prazosin plasma concentration is about one half of the corresponding two-compartment model estimate (**Figure 4**). It is not known if the reduction in blood pressure occurs immediately after Prazosin injection as the earliest sample was taken 30 minutes after IV Prazosin administration [5] [6]. Furthermore, the maximum reduction in BP found after 30 minutes coincides with the time to reach maximum peripheral concentration, $t^*_{2,\max,n}$ after an IV bolus administration (**Table 4**). The time to reach maximum peripheral drug concentration after an intermittent infusion was about 1 hour. Thus, it is not possible to resolve from these studies the role of each compartment on the timings of the pharmacological activity of the drug. Similarly, the drop in standing blood pressure is correlated with the peak Prazosin plasma concentration, that is, during the first 2 - 4 hours after an oral drug administration [5] [10] [13] [19] [20]. According to these studies, the minimum effective plasma concentration is about 6 ng/mL while a marginal reduction of mean arterial pressure was reported by Horowitz and coworkers at peak concentration of 4.1 ± 1.4 ng/mL.

The body's exposure to the drug was assessed from the AUC that was calculated in the one- and two-compartment models at non-steady state and steady state conditions using Equation (72) and Equations (17)-(18), and Equation (73) and Equations (19)-(20), respectively (**Table 4**). Grahnen and coworkers have reported an AUC after a 0.5 mg single prazosin IV dose of 49.4 ± 12 as calculated by the trapezoidal method plus the extrapolated area beyond the last sampling point which was always less than 15% of the total area. The AUCs in **Table 4** are calculated for a 3-h dosing interval. Changing our dosing interval to 12 h results in a central compartment area $\mathrm{AUC}_{1,\tau=12\,\mathrm{h}}$ of 45.8 ng/mL·h, which is almost identical to their reported experimentally measured average value.

In his excellent work, Gibaldi has concluded that after intravenous bolus injection the drug distribution ratio in the two compartments in the β-phase is constant (Equation (74)) [21]. Using Equation (74), the prazosin tissue to central compartment drug mass ratio is equal to 2.72.

$$\left(\frac{x_2}{x_1}\right)_{\beta} = \frac{k_{12}}{k_{21} - \beta} \tag{74}$$

We can assess the drug ratio in the two compartments using the non steady-state and the steady-state Equations (9)-(12).

$$\left(\frac{x_{2,ss,t^*}}{x_{1,,ss,t^*}}\right) = \frac{-k_{12}\cdot\left(\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)\cdot\mathrm{e}^{-\lambda_1\cdot t^*} - \left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)\cdot\mathrm{e}^{-\lambda_2\cdot t^*}\right)}{\left(\left(\lambda_1-k_{21}\right)\cdot\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)\cdot\mathrm{e}^{-\lambda_1\cdot t^*} + \left(k_{21}-\lambda_2\right)\cdot\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)\cdot\mathrm{e}^{-\lambda_2\cdot t^*}\right)} \tag{75}$$

The necessary condition for Equation (75) to be approximated by Equation (74) is for $\lambda_1 \gg \lambda_2$ but Equation (75) can tell us much more about the time within a dosing interval that the drug distribution ratio will reach the constant value as dictated by Equation (74). Riegelman *et al.*, have calculated the values 0.08483, 01233, 02670 and 0.04930 for k_{12}, k_{21}, λ_1 and λ_2, respectively, for acetylsalicylic acid [22]. It turns out that for a dosing frequency $\tau = 6$ h the drug distribution ratio will never reach a constant value within the dosing interval. At the end of the dosing interval the drug ratio is only 76% of the final value and it takes about 9 hours from the time of administration for the drug distribution ratio to reach the value of Equation (74) within the β-elimination phase.

4.2. Single Intermittent Intravenous Infusion

The average pharmacokinetic parameters in **Table 2** differ significantly from the ones reported by Bateman *et al.*, with the exception of the elimination rate constant β or λ_2. The trend in the two published IV bolus and intermittent infusion studies (and in our study) regarding the values of macro rate constants is similar, *i.e.* $\lambda_1 > \lambda_2$ but not of the micro rate constants k_{12}, k_{21} and k_{10}. The differences in our parameter estimation were due to first, we have used a two-compartment intermittent infusion model as opposed to the IV bolus model that they have used and second, we have fitted all data points to our model (**Figure 2**). It is possible that Bateman and coworkers have used only the first one or two data points to assess the value of the λ_1 hybrid rate constant for drug distribution and the last four data points for the λ_2 hybrid rate constant for drug elimination. As a result, the measured drug plasma concentrations after 1, 1.5 and 2 hours are not very close to the fitted line in Bateman's work. What is more interesting from our analysis is that although the apparent volume of distribution of Prazosin $V_{d,1}$ is almost equal to total body water in both IV bolus and intermittent infusion studies, the trend in the volumes of the central and peripheral compartment is reversed. In particular, from the IV bolus study, V_1 and V_2 are 11.3 L and 21.6 L, respectively, whereas the two volumes V_1 and V_2 that we have assessed from the intermittent drug infusion study are 26.5 L and 14.2 L, respectively. Bateman and coworkers have also estimated a larger

central than peripheral compartment volume. Thus, slower drug infusion resulted in a larger volume of the central compartment at the expense of the volume of the peripheral compartment. It is possible that the kinetics of drug administration controls the volumes of the two compartments. And it could be that drug disposition after administering the drug at a very slow infusion rate be described by a one-compartment model. As we have cautioned in our recent publication, the kinetics of drug disposition after the first dose may not be identical after the second or third drug doses [14]. Incidentally, Grahnen *et al.* have not determined the apparent volume of distribution of Prazosin. They have instead determined the terminal (non-equilibrium) volume of distribution, V_β (47.9 L), most probably using the AUC of the central compartment. Using their assessed pharmacokinetic parameters, we have calculated a $V_{d,1}$ using Equation (64) of 31.3 L, which is very close to our value. These results are in agreement with the notion that the apparent volume of distribution is always smaller than the V_β which is calculated during intercompartmental pseudo-equilibrium steady-state conditions [21].

The particular solutions and real-time series equations to drug concentration after multiple intermittent constant rate constant dosing frequency infusions that we have recently developed have allowed us to construct the infusion and elimination phases of plasma or central compartment prazosin concentration as a function of infusion dose number and total time using Equation (76) and Equation (77), respectively, in an open two-compartment model. Similarly, Equations (78)-(79) were used to simulate the peripheral compartment prazosin concentration as a function of total time (**Figure 6**) [3].

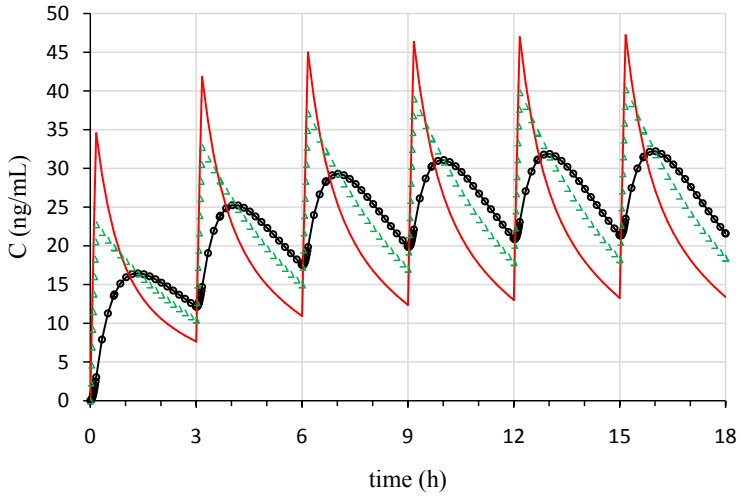

Figure 6. Plasma Prazosin concentration in the central compartment (solid lines), in the peripheral compartment (empty circles joined with solid line) in the two-compartment model and plasma drug concentration in the one-compartment model (empty triangles) after multiple administration of 10-minute intermittent infusions with a dosing interval of 3 hours. The ascending part of the drug infusion curves was constructed using the pharmacokinetic parameters assessed from the elimination phase of the drug.

$$C_{a,1,n}(t)=\sum_{n=1}^{\infty}\frac{(k_{21}-\lambda_1)\cdot C_1((n-1)\cdot\tau)+k_{21}\cdot C_2((n-1)\cdot\tau)}{(\lambda_2-\lambda_1)}\cdot e^{-\lambda_1\cdot(t-(n-1)\cdot\tau)}+\frac{(k_{21}-\lambda_2)\cdot C_1((n-1)\cdot\tau)+k_{21}\cdot C_2((n-1)\cdot\tau)}{(\lambda_1-\lambda_2)}\cdot e^{-\lambda_2\cdot(t-(n-1)\cdot\tau)}+\frac{k_0}{V_1}\cdot\left(\frac{k_{21}}{\lambda_1\cdot\lambda_2}+\frac{k_{21}-\lambda_1}{\lambda_1\cdot(\lambda_1-\lambda_2)}\cdot e^{-\lambda_1\cdot(t-(n-1)\cdot\tau)}+\frac{k_{21}-\lambda_2}{\lambda_2\cdot(\lambda_2-\lambda_1)}\cdot e^{-\lambda_2\cdot(t-(n-1)\cdot\tau)}\right) \tag{76}$$

$$C_{e,1,n}(t)=\sum_{n=1}^{\infty}\frac{(k_{21}-\lambda_1)\cdot C_1((n-1)\cdot\tau+T)+k_{21}\cdot C_2((n-1)\cdot\tau+T)}{(\lambda_2-\lambda_1)}\cdot e^{-\lambda_1\cdot(t-(n-1)\cdot\tau-T)}+\frac{(k_{21}-\lambda_2)\cdot C_1((n-1)\cdot\tau+T)+k_{21}\cdot C_2((n-1)\cdot\tau+T)}{(\lambda_1-\lambda_2)}\cdot e^{-\lambda_2\cdot(t-(n-1)\cdot\tau-T)} \tag{77}$$

$$C_{a,2,n}(t)=\sum_{n=1}^{\infty}\frac{(\lambda_2-k_{21})\cdot C_2((n-1)\cdot\tau)+k_{12}\cdot C_1((n-1)\cdot\tau)}{(\lambda_2-\lambda_1)}\cdot e^{-\lambda_1\cdot(t-(n-1)\cdot\tau)}+\frac{(\lambda_1-k_{21})\cdot C_2((n-1)\cdot\tau)+k_{12}\cdot C_1((n-1)\cdot\tau)}{(\lambda_1-\lambda_2)}\cdot e^{-\lambda_2\cdot(t-(n-1)\cdot\tau)}+\frac{k_0\cdot k_{12}}{V_2}\cdot\left(\frac{1}{\lambda_1\cdot\lambda_2}+\frac{1}{\lambda_1\cdot(\lambda_1-\lambda_2)}\cdot e^{-\lambda_1\cdot(t-(n-1)\cdot\tau)}+\frac{1}{\lambda_2\cdot(\lambda_2-\lambda_1)}\cdot e^{-\lambda_2\cdot(t-(n-1)\cdot\tau)}\right) \tag{78}$$

$$C_{e,2,n}(t)=\sum_{n=1}^{\infty}\frac{(\lambda_2-k_{21})\cdot C_2((n-1)\cdot\tau+T)+k_{12}\cdot C_1((n-1)\cdot\tau+T)}{(\lambda_2-\lambda_1)}\cdot e^{-\lambda_1\cdot(t-(n-1)\cdot\tau-T)}+\frac{(\lambda_1-k_{21})\cdot C_2((n-1)\cdot\tau+T)+k_{12}\cdot C_1((n-1)\cdot\tau+T)}{(\lambda_1-\lambda_2)}\cdot e^{-\lambda_2\cdot(t-(n-1)\cdot\tau-T)} \tag{79}$$

Having assessed the value of the drug apparent volume of distribution, $V_{d,1}$, from the two-compartment model, we were able to use our recently developed explicit solutions to drug concentration and run comparison simulations after multiple intermittent infusions in the one-compartment model [14]. As shown in **Figure 6**, the one-compartment model simulations resulted in peak and trough concentrations that are lower and higher than the corresponding peak and trough central compartment concentration. The one-compartment model multiple intermittent infusion simulations were carried out using Equations (80)-(81) for the ascending and descending curves, respectively [14]. The fluctuation factor difference between the two models is not as pronounced as what we have seen with the IV bolus administration. Coincidentally, the 10-minute constant rate of drug infusion that was used in the study is about the same as the distribution half-life $t_{1/2,\alpha}$ of the drug. Thus, the plasma drug maximum concentration is much lower than that observed after an IV bolus dose considering that the IV dose (0.5 mg) was only half the dose that was administered by intermittent infusion.

The body exposure to the drug was determined for the one- and the two-compartment model after intermittent intravenous infusions with Equations (82)-(84). In agreement with Gibaldi's work the AUC after IV bolus administration was comparable to that after intermittent infusion (double dose (**Table 5**)

[3] [14] [16]. The similarity in the results of the two pharmacokinetic models suggests that Prazosin intermittent infusion dosage calculations can be safely carried out in the clinic with the much simpler one-compartment model equations.

$$C_{a,n,t} = \frac{k_0}{k \cdot V_{d,1}} \cdot \left(1 - \mathrm{e}^{-k \cdot T}\right) \cdot \frac{\left(1 - \mathrm{e}^{-k \cdot (n-1) \cdot \tau}\right)}{\left(1 - \mathrm{e}^{-k \cdot \tau}\right)} \cdot \mathrm{e}^{-k \cdot \left(t - (n-2) \cdot \tau - T\right)} + \frac{k_0}{CL} \cdot \left(1 - \mathrm{e}^{-k \cdot \left(t - (n-1) \cdot \tau\right)}\right) \tag{80}$$

$$C_{e,n,t} = \frac{k_0}{k \cdot V_{d,1}} \cdot \left(1 - \mathrm{e}^{-k \cdot T}\right) \cdot \frac{\left(1 - \mathrm{e}^{-n \cdot k \cdot \tau}\right)}{\left(1 - \mathrm{e}^{-k \cdot \tau}\right)} \cdot \mathrm{e}^{-k \cdot \left(t - (n-1) \cdot \tau - T\right)} \tag{81}$$

$$\mathrm{AUC}_{\text{one-comp},n} = T \cdot \frac{k_0}{CL} - \frac{k_0}{k \cdot CL} \cdot \left(1 - \mathrm{e}^{-k \cdot T}\right) \cdot \mathrm{e}^{-k \cdot (n \cdot \tau - T)} \tag{82}$$

$$\begin{aligned}\mathrm{AUC}_{1,\tau,n} = {} & \frac{\left(k_{21} - \lambda_1\right) \cdot C_{e,1}\left((n-1) \cdot \tau\right) + k_{21} \cdot C_{e,2}\left((n-1) \cdot \tau\right)}{\lambda_1 \cdot \left(\lambda_2 - \lambda_1\right)} \cdot \left(1 - \mathrm{e}^{-\lambda_1 \cdot T}\right) \\ & + \frac{\left(k_{21} - \lambda_2\right) \cdot C_{e,1}\left((n-1) \cdot \tau\right) + k_{21} \cdot C_{e,2}\left((n-1) \cdot \tau\right)}{\lambda_2 \cdot \left(\lambda_1 - \lambda_2\right)} \cdot \left(1 - \mathrm{e}^{-\lambda_2 \cdot T}\right) \\ & + \frac{k_0}{V_1} \cdot \left(\frac{k_{21}}{\lambda_1 \cdot \lambda_2} \cdot T + \frac{k_{21} - \lambda_1}{\lambda_1^2 \cdot \left(\lambda_1 - \lambda_2\right)} \cdot \left(1 - \mathrm{e}^{-\lambda_1 \cdot T}\right) + \frac{k_{21} - \lambda_2}{\lambda_2^2 \cdot \left(\lambda_2 - \lambda_1\right)} \cdot \left(1 - \mathrm{e}^{-\lambda_2 \cdot T}\right) \right) \\ & + \frac{\left(k_{21} - \lambda_1\right) \cdot C_{a,1}\left((n-1) \cdot \tau + T\right) + k_{21} \cdot C_{a,2}\left((n-1) \cdot \tau + T\right)}{\lambda_1 \cdot \left(\lambda_2 - \lambda_1\right)} \cdot \left(1 - \mathrm{e}^{-\lambda_1 \cdot (\tau - T)}\right) \\ & + \frac{\left(k_{21} - \lambda_2\right) \cdot C_{a,1}\left((n-1) \cdot \tau + T\right) + k_{21} \cdot C_{a,2}\left((n-1) \cdot \tau + T\right)}{\lambda_2 \cdot \left(\lambda_1 - \lambda_2\right)} \cdot \left(1 - \mathrm{e}^{-\lambda_2 \cdot (\tau - T)}\right)\end{aligned} \tag{83}$$

$$\begin{aligned}\mathrm{AUC}_{2,\tau,n} = {} & \frac{\left(k_{10} + k_{12} - \lambda_1\right) \cdot C_{e,2}\left((n-1) \cdot \tau\right) + k_{12} \cdot C_{e,1}\left((n-1) \cdot \tau\right)}{\lambda_1 \cdot \left(\lambda_2 - \lambda_1\right)} \cdot \left(1 - \mathrm{e}^{-\lambda_1 \cdot T}\right) \\ & + \frac{\left(k_{10} + k_{12} - \lambda_2\right) \cdot C_{e,2}\left((n-1) \cdot \tau\right) + k_{12} \cdot C_{e,1}\left((n-1) \cdot \tau\right)}{\lambda_2 \cdot \left(\lambda_1 - \lambda_2\right)} \cdot \left(1 - \mathrm{e}^{-\lambda_2 \cdot T}\right) \\ & + \frac{k_0 \cdot k_{12}}{V_2} \cdot \left(\frac{1}{\lambda_1 \cdot \lambda_2} \cdot T + \frac{1}{\lambda_1^2 \cdot \left(\lambda_1 - \lambda_2\right)} \cdot \left(1 - \mathrm{e}^{-\lambda_1 \cdot T}\right) + \frac{1}{\lambda_2^2 \cdot \left(\lambda_2 - \lambda_1\right)} \cdot \left(1 - \mathrm{e}^{-\lambda_2 \cdot T}\right) \right) \\ & + \frac{\left(k_{10} + k_{12} - \lambda_1\right) \cdot C_{a,2}\left((n-1) \cdot \tau + T\right) + k_{12} \cdot C_{a,1}\left((n-1) \cdot \tau + T\right)}{\lambda_1 \cdot \left(\lambda_2 - \lambda_1\right)} \cdot \left(1 - \mathrm{e}^{-\lambda_1 \cdot (\tau - T)}\right) \\ & + \frac{\left(k_{10} + k_{12} - \lambda_2\right) \cdot C_{a,2}\left((n-1) \cdot \tau + T\right) + k_{12} \cdot C_{a,1}\left((n-1) \cdot \tau + T\right)}{\lambda_2 \cdot \left(\lambda_1 - \lambda_2\right)} \cdot \left(1 - \mathrm{e}^{-\lambda_2 \cdot (\tau - T)}\right)\end{aligned} \tag{84}$$

4.3. Single 1 mg Oral Prazosin Tablet Administration

As pointed out in the results section (**Figure 3**), the simulated rate of absorption was lower than that indicated by the experimental data points. Prazosin is known to be a substrate of efflux transporters but not of influx transporters in the GI [23]. The scarcity of the samples taken during the absorption phase of the drug has made our analysis difficult. Among the twenty or so published clinical

Table 5. AUC (ng/mL·h) after repetitive 1 mg Prazosin intermittent intravenous infusions at the end of each dosing interval ($\tau = 3$ h) in the one- and the two-compartment model, as a function of infusion number (n).

n	AUC_{one_comp}	$AUC_{1,\tau,n}$	$AUC_{2,\tau,n}$
1	46.7	46.7	48.2
2	67.9	67.0	66.3
3	77.2	75.9	74.2
4	81.3	79.8	77.7
5	83.1	81.4	79.2
6	83.9	82.2	79.8
12	84.5	82.8	80.4

studies after oral administration of Prazosin the most comprehensive one was that of Bateman and coworkers. Still three concentration-time points are not enough to accurately fit the absorption phase into a pharmacokinetic compartment model. An additional problem is that we are using the average results. Although the standard error of those averages appears to be relatively small the standard error is always smaller than the standard deviation by the square root of the total number of samples, that is, by 2.45 for 6 patients. Contrary to the absorption phase, the elimination phase of the drug after oral administration is simulated relatively accurately by both models.

The concentration-time profile after repetitive oral administration of 1 mg Prazosin tablet is simulated in the two-compartment model using Equation (37) and Equation (38), for the central and peripheral plasma drug concentration, respectively (**Figure 7**). The simulated drug concentration with time in the two compartments after repetitive oral administration of prazosin is very different from the profile in **Figure 4** and **Figure 6**. Both plasma drug concentration and drug concentration in the peripheral compartment are much lower than those achieved after multiple IV boluses or multiple intermittent infusions mainly because of reduced absorption. The regressed bioavailability of the oral administration was only 61.4% which was very close to the one calculated experimentally by Bateman. Also, due to a lower rate of drug absorption as compared to the rate of intermittent drug infusion ($k_a = 0.5335\ \text{h}^{-1}$, $t_{1/2,\text{absorption}} = 1.3$ h) and a slightly higher elimination rate constant λ_2, the levels of drug concentration achieved in both compartments was similar.

Momentary distribution equilibrium (t_{eq}) or $t_{2,n,\max}$ was calculated as a function of time and dose number to be equal to 2.43 h, 1.57 h, 1.38 h and 1.37 h after administration of the 1st, 3rd, 6th dose and at steady-state plasma drug concentration, respectively (**Figure 7**). Simulation of drug concentration with time upon repetitive oral doses in the one-compartment model were carried out with our recently developed Equation (85) [15]. The drug concentration profile in the one-compartment model was very similar to the central compartment concentration but not identical. In particular, the non-steady state central compartment

peak concentration is slightly lower than the one simulated by the one-compartment model. As steady state conditions are approached with successive oral dosing, central compartment drug concentration reaches higher levels while the fluctuation factor is identical in both models (Figure 7). Steady state concentration in the central compartment and in the one-compartment model were simulated using Equation (39) and Equation (86), respectively.

The drug exposure of the body after repetitive oral administration was assessed by the AUC, and it was much lower than that calculated after multiple IV boluses and multiple intermittent infusions. The AUC per dosing interval was calculated with Equations (45)-(48) for the non-steady state and steady state of central and peripheral compartments, respectively, whereas the AUC in the one-compartment model was calculated using Equations (87)-(88) (Table 6).

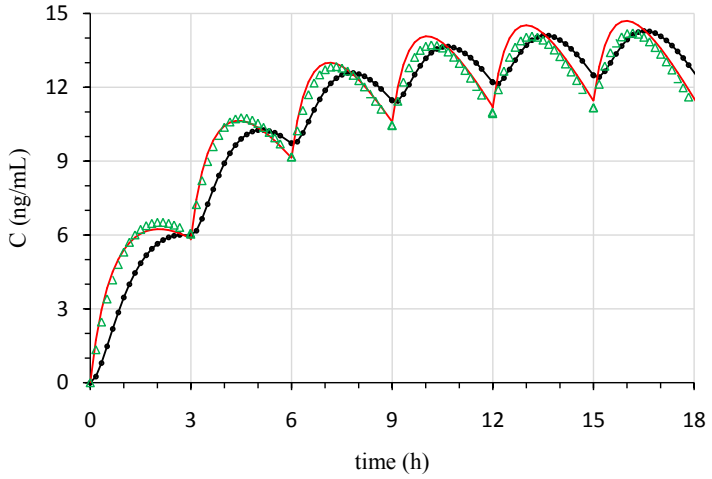

Figure 7. Plasma drug concentration in the central compartment (solid lines), in the peripheral compartment (empty circles joined with solid line) in a two-compartment model and plasma drug concentration in a one-compartment model (empty triangles) after repetitive 1 mg oral tablet administration of Prazosin at a 3-h dosing interval.

Table 6. Calculated non-steady state and steady state AUC (ng/mL·h) per dosing interval ($\tau = 3$ h) after repetitive 1 mg Prazosin oral tablet the one- and two-compartment models, as a function of dose number.

n	AUC_{one_comp}	$AUC_{1,\tau}$	$AUC_{2,\tau}$
1	15.6	15.6	7.4
2	29.3	29.3	16.5
3	35.5	36.1	21.4
4	38.1	39.1	23.5
5	39.1	40.3	24.4
6	39.4	40.7	24.7
Steady state	39.7	41.0	24.9

$$C_{n,t} = \frac{F \cdot D \cdot k_a}{V_d \cdot (k_a - k)} \cdot \left\{ e^{-k \cdot (t-(n-1)\cdot\tau)} \cdot \frac{\left(1 - e^{-k \cdot n \cdot \tau}\right)}{\left(1 - e^{-k \cdot \tau}\right)} - e^{-k_a \cdot (t-(n-1)\cdot\tau)} \cdot \frac{\left(1 - e^{-k_a \cdot n \cdot \tau}\right)}{\left(1 - e^{-k_a \cdot \tau}\right)} \right\} \quad (85)$$

$$C_{ss,n,t} = \frac{F \cdot D \cdot k_a}{V_d \cdot (k_a - k)} \cdot \left\{ \frac{e^{-k \cdot (t-(n-1)\cdot\tau)}}{\left(1 - e^{-k \cdot \tau}\right)} - \frac{e^{-k_a \cdot (t-(n-1)\cdot\tau)}}{\left(1 - e^{-k_a \cdot \tau}\right)} \right\} \quad (86)$$

$$\mathrm{AUC}_{\text{one-comp},\tau,n} = \frac{F \cdot D \cdot k_a}{V_d \cdot (k_a - k)} \cdot \left[\frac{\left(1 - e^{-k \cdot n \cdot \tau}\right)}{k} - \frac{\left(1 - e^{-k_a \cdot n \cdot \tau}\right)}{k_a} \right] \quad (87)$$

$$\mathrm{AUC}_{\text{one-comp},\tau,ss} = \frac{F \cdot D \cdot k_a}{V_d \cdot (k_a - k)} \cdot \left[\frac{1}{k} - \frac{1}{k_a} \right] \quad (88)$$

5. Conclusions

The pharmacokinetic parameters of the drug Prazosin were determined from published clinical data after intravenous bolus injection, intermittent infusion and oral administration using a two-compartment model [5] [6]. It is the first time that steady-state drug concentration equations were derived for all routes of administration in a two-compartment mammillary pharmacokinetic model. With regard to the IV bolus study, our results were similar to those published by Grahnen *et al.*, and we have obtained many additional pharmacokinetic parameters. In particular, we have determined the peak time and peak peripheral drug concentration, the AUC and most importantly the apparent volume of distribution of Prazosin from an open two-compartment model. As far as the single intermittent intravenous infusion study is concerned, the data were fitted with nonlinear regression analysis using the particular solutions of the elimination phase of the drug. The extracted pharmacokinetic parameters were subsequently used to construct the ascending phase during the infusion time period of Prazosin [3]. As for the clinical study of the oral route of administration, several time-dependent pharmacokinetic parameters such as peak time and peak concentration in both the central and peripheral compartments were determined using real-time analytical solutions to drug concentration as a function of oral dose number [15].

The current explicit series solutions in an open two-compartment pharmacokinetic model described herein have allowed non-steady state and steady state simulations of repetitive drug doses at constant dosing frequency for all three routes of administration. In an original way, the value of the apparent volume of distribution of Prazosin was determined from a two-compartment pharmacokinetic model. Its significance is two-fold: first, with a value being close to that of total body water it is suggested that Prazosin is distributed both extracellularly and intracellularly, in all tissues, and second, the apparent volume of distribution allowed simulations in the one-compartment model. It was shown that dosage calculations of Prazosin intermittent infusions can be safely managed using the much simpler one-compartment model.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Savva, M. (2021) On the Origin of the Apparent Volume of Distribution and Its Significance in Solvent Extraction Methods. *Journal of Organic Chemistry and Chemical Sciences*, **1**, 101. https://doi.org/10.17303/jocs.2021.1.101

[2] Savva, M. (2022) On the Origin of the Apparent Volume of Distribution and Its Significance in Pharmacokinetics. *Journal of Biosciences and Medicines*. (In Press)

[3] Savva, M. (2021) Real-Time Analytical Solutions as Series Formulas and Heaviside off/on Switch Functions for Multiple Intermittent Intravenous Infusions. *Journal of Biosciences and Medicines*. (In Press)

[4] Langer, S.Z., Cavero, I. and Massingham, R. (1980) Recent Developments in Noradrenergic Neurotransmission and Its Relevance to the Mechanism of Action of Certain Antihypertensive Agents. *Hypertension*, **2**, 372-382. https://doi.org/10.1161/01.HYP.2.4.372

[5] Bateman, D.N., Hobbs, D.C., Twomey, T.M., Stevens, E.A. and Rawlins, M.D. (1979) Prazosin, Pharmacokinetics and Concentration Effect. *European Journal of Clinical Pharmacology*, **16**, 177-181. https://doi.org/10.1007/BF00562058

[6] Grahnen, A., Seideman, P., Lindstrom, B., Haglund, K. and von Bahr, C. (1981) Prazosin Kinetics in Hypertension. *Clinical Pharmacology & Therapeutics*, **30**, 439-446. https://doi.org/10.1038/clpt.1981.186

[7] Hobbs, D.C., Twomey, T.M. and Palmer, R.F. (1978) Pharmacokinetics of Prazosin in Man. *The Journal of Clinical Pharmacology*, **18**, 402-406. https://doi.org/10.1002/j.1552-4604.1978.tb02456.x

[8] Baughman, R.A., Arnold, S., Benet, L.Z., Lin, E.T., Chatterjee, K. and Williams, R.L. (1980) Altered Prazosin Pharmacokinetics in Congestive Heart Failure. *European Journal of Clinical Pharmacology*, **17**, 425-428. https://doi.org/10.1007/BF00570159

[9] Chau, N.P., Flouvat, B.L., Roux, E.L. and Safar, M.E. (1980) Prazosin Kinetics in Essential Hypertension. *Clinical Pharmacology & Therapeutics*, **28**, 6-11. https://doi.org/10.1038/clpt.1980.123

[10] Dynon, M.K., Jarrott, B., Drummer, O. and Louis, W.J. (1980) Pharmacokinetics of Prazosin in Normotensive Subjects after Low Oral Doses. *Clinical Pharmacology & Therapeutics*, **5**, 583-590. https://doi.org/10.2165/00003088-198005060-00007

[11] Guelen, P.J.M., Janssen, T.J., Lam, M.H., Vree, T.B. and Exler, P.S. (1990) Comparative Bioavailability of Two Brands of Prazosin-Containing Tablets in Healthy Volunteers. *Pharmaceutisch Weekblad Scientific*, **12**, 184-187. https://doi.org/10.1007/BF01980043

[12] Dynon, M.K., Jarrott, B. and Louis, W.J. (1983) Tissue Distribution and Hypotensive Effect of Prazosin in the Conscious Rat. *Journal of Cardiovascular Pharmacology and Therapeutics*, **5**, 235-239. https://doi.org/10.1097/00005344-198303000-00012

[13] Graham, R.M., Thornell, J.R., Gain, J.M., Bagnoli, C., Oates, H.F. and Stokes, G.S. (1976) Prazosin: The First Dose Phenomenon. *British Medical Journal*, **2**, 1293-1294. https://doi.org/10.1136/bmj.2.6047.1293

[14] Savva, M. (2021) A Mathematical Treatment of Multiple Intermittent Intravenous

Infusions in a One-Compartment Model. *Computer Methods and Programs in Biomedicine*, **205**, Article ID: 106103. https://doi.org/10.1016/j.cmpb.2021.106103

[15] Savva, M. (2021) A Method to Custom-Build Equations of Drug Concentration as a Function of Real Time in the One-Compartment Open Model and Their Application in Multiple Intravenous Bolus and Multiple Oral Doses. *Pharmaceutical and Biosciences Journal*, **9**, 12-29. https://pharmabiosciencejournal.com/index.php/pbj/article/view/2284

[16] Riggs, D.S. (1963) Transfer of Substances between Biological Compartments. General Kinetics. In: *The Mathematical Approach to Physiological Problems*, Williams and Wilkins, Baltimore, 193-217.

[17] Grimm Jr., R.H. (1989) α_1-Antagonists in the Treatment of Hypertension. *Hypertension*, **13**, I131-I136. https://doi.org/10.1161/01.HYP.13.5_Suppl.I131

[18] Akinaga, J., Garcia-Sainz, J.A. and Pupo, A.S. (2019) Updates in the Function and Regulation of α_1-Adrenoceptors. *British Journal of Pharmacology*, **176**, 2343-2357. https://doi.org/10.1111/bph.14617

[19] Lameire, N. and Gordts, J. (1986) A Pharmacokinetic Study of Prazosin with Varying Degrees of Chronic Renal Failure. *European Journal of Clinical Pharmacology*, **31**, 333-327. https://doi.org/10.1007/BF00981133

[20] Horowitz, J.D., Dynon, M.K., Jarrott, B., Brennan, J.B., Oliver, L.E., Goble, A.J. and Louis, W.J. (1984) Haemodynamic Effects of a Single Low Dose of Prazosin with Chronic Congestive Cardiac Failure Correlations with Pharmacokinetics. *Clinical and Experimental Pharmacology and Physiology*, **11**, 7-15. https://doi.org/10.1111/j.1440-1681.1984.tb00234.x

[21] Gibaldi, M. (1969) Effect of Mode of Administration on Drug Distribution in a Two-Compartment Open System. *Journal of Pharmaceutical Sciences*, **58**, 327-331. https://doi.org/10.1002/jps.2600580308

[22] Riegelman, S., Loo, J. and Rowland, M. (1968) Concept of a Volume of Distribution and Possible Errors in Evaluation of This Parameter. *Journal of Pharmaceutical Sciences*, **57**, 128-133. https://doi.org/10.1002/jps.2600570125

[23] Speer, J.E., Gunasekara, D.B., Wang, Y., Fallon, J.K., Attayek, P.J., Smith, P.C., Sims, C.E. and Allbritton, N.L. (2019) Molecular Transport through Primary Human Small Intestinal Monolayers by Culture on a Collagen Scaffold with a Gradient of Chemical Cross-Linking. *Journal of Biological Engineering*, **13**, 36. https://doi.org/10.1186/s13036-019-0165-4

Appendix

Time to reach peak concentration in the peripheral compartment as a function of IV bolus dose number (*n*).

$$k_{12}\cdot x_1 - k_{21}\cdot x_2 = 0$$

$$k_{12}\cdot D\cdot\left\{A_1\cdot\left(\frac{\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}\cdot\mathrm{e}^{-\lambda_1\cdot\left(t-(n-1)\cdot\tau\right)}\right)+B_1\cdot\left(\frac{\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\cdot\mathrm{e}^{-\lambda_2\cdot\left(t-(n-1)\cdot\tau\right)}\right)\right\}$$

$$=k_{21}\cdot D\cdot k_{12}\cdot\left\{A_2\cdot\frac{\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}\cdot\mathrm{e}^{-\lambda_1\cdot\left(t-(n-1)\cdot\tau\right)}+B_2\cdot\frac{\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\cdot\mathrm{e}^{-\lambda_2\cdot\left(t-(n-1)\cdot\tau\right)}\right\}$$

$$\left[A_1\cdot\frac{\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}-k_{21}\cdot A_2\cdot\frac{\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}\right]\cdot\mathrm{e}^{-\lambda_1\cdot\left(t-(n-1)\cdot\tau\right)}$$

$$=\left[k_{21}\cdot B_2\cdot\frac{\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}-B_1\cdot\frac{\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\right]\cdot\mathrm{e}^{-\lambda_2\cdot\left(t-(n-1)\cdot\tau\right)}$$

$$\left[A_1-k_{21}\cdot A_2\right]\cdot\frac{\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}\cdot\mathrm{e}^{-\lambda_1\cdot\left(t-(n-1)\cdot\tau\right)}$$

$$=\left[k_{21}\cdot B_2-B_1\right]\cdot\frac{\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\cdot\mathrm{e}^{-\lambda_2\cdot\left(t-(n-1)\cdot\tau\right)}$$

$$\left[\frac{\lambda_1-k_{21}}{\left(\lambda_1-\lambda_2\right)}-\frac{k_{21}}{\left(\lambda_2-\lambda_1\right)}\right]\cdot\frac{\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}\cdot\mathrm{e}^{-\lambda_1\cdot\left(t-(n-1)\cdot\tau\right)}$$

$$=\left[\frac{k_{21}}{\left(\lambda_1-\lambda_2\right)}-\frac{k_{21}-\lambda_2}{\left(\lambda_1-\lambda_2\right)}\right]\cdot\frac{\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\cdot\mathrm{e}^{-\lambda_2\cdot\left(t-(n-1)\cdot\tau\right)}$$

$$\frac{\lambda_1\cdot\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}{\left(\lambda_1-\lambda_2\right)\cdot\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}\cdot\mathrm{e}^{-\lambda_1\cdot\left(t-(n-1)\cdot\tau\right)}=\frac{\lambda_2\cdot\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)}{\left(\lambda_1-\lambda_2\right)\cdot\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\cdot\mathrm{e}^{-\lambda_2\cdot\left(t-(n-1)\cdot\tau\right)}$$

$$\mathrm{e}^{\left(\lambda_2-\lambda_1\right)\cdot\left(t-(n-1)\cdot\tau\right)}=\frac{\lambda_2}{\lambda_1}\cdot\frac{\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)}\cdot\frac{\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}$$

$$t_{2,n,\max}=\left(n-1\right)\cdot\tau+\frac{\ln\left(\frac{\lambda_2\cdot\left(1-\mathrm{e}^{-\lambda_2\cdot n\cdot\tau}\right)\cdot\left(1-\mathrm{e}^{-\lambda_1\cdot\tau}\right)}{\lambda_1\cdot\left(1-\mathrm{e}^{-\lambda_2\cdot\tau}\right)\cdot\left(1-\mathrm{e}^{-\lambda_1\cdot n\cdot\tau}\right)}\right)}{\left(\lambda_2-\lambda_1\right)}\tag{23}$$

Multiple Oral administration in a two-compartment mammillary model

Differential equations for inputs and outputs:

Input: First-order drug absorption into the central compartment.

Output: First-order drug elimination from the central compartment.

$$\dot{x}_1=-\left(k_{10}+k_{12}\right)\cdot x_1+k_{21}\cdot x_2+k_a\cdot x_3;\quad x_1\left(0\right)=0\tag{31}$$

$$\dot{x}_2=k_{12}\cdot x_1-k_{21}\cdot x_2;\quad x_2\left(0\right)=0\tag{32}$$

$$\dot{x}_3 = -k_a \cdot x_3; \quad x_3(0) = D \tag{33}$$

where D is the drug dose and k_a is the first-order absorption rate constant.

Analytical solutions and sequence terms for multiple oral doses

Equations (31)-(33) can be written in matrix form $\vec{x}' = M \cdot \vec{x}$:

$$\vec{x}' = \begin{pmatrix} -(k_{10}+k_{12}) & k_{21} & k_a \\ k_{12} & -k_{21} & 0 \\ 0 & 0 & -k_a \end{pmatrix} \cdot \vec{x}; \quad \vec{x}(0) = \begin{pmatrix} 0 \\ 0 \\ D \end{pmatrix}$$

Applying the Laplace transform,

$$\begin{pmatrix} (s+k_{10}+k_{12}) & -k_{21} & -k_a \\ -k_{12} & (s+k_{21}) & 0 \\ 0 & 0 & (s+k_a) \end{pmatrix} \cdot \vec{X}(s) = \begin{pmatrix} 0 \\ 0 \\ D \end{pmatrix};$$

Using the Cramer's rule,

$$X_1(s) = \frac{\det(M_1)}{\det(M)}; \quad X_2(s) = \frac{\det(M_2)}{\det(M)}; \quad X_3(s) = \frac{\det(M_3)}{\det(M)}$$

$$M = \begin{pmatrix} (s+k_{10}+k_{12}) & -k_{21} & -k_a \\ -k_{12} & (s+k_{21}) & 0 \\ 0 & 0 & (s+k_a) \end{pmatrix}$$

$$M_1 = \begin{pmatrix} 0 & -k_{21} & -k_a \\ 0 & (s+k_{21}) & 0 \\ D & 0 & (s+k_a) \end{pmatrix}$$

$$M_2 = \begin{pmatrix} (s+k_{10}+k_{12}) & 0 & -k_a \\ -k_{12} & 0 & 0 \\ 0 & D & (s+k_a) \end{pmatrix}$$

$$M_3 = \begin{pmatrix} (s+k_{10}+k_{12}) & -k_{21} & 0 \\ -k_{12} & (s+k_{21}) & 0 \\ 0 & 0 & D \end{pmatrix}$$

$$\det(M) = (s+k_a) \cdot \left(s^2 + (k_{10}+k_{12}+k_{21}) \cdot s + k_{10} \cdot k_{12}\right)$$

Let $\lambda_1 + \lambda_2 = k_{10} + k_{12} + k_{21}$ and $\lambda_1 \cdot \lambda_2 = k_{10} \cdot k_{12}$

$$\det(M) = (s+k_a) \cdot (s+\lambda_1) \cdot (s+\lambda_2)$$

$$\det(M_1) = D \cdot k_a \cdot (s+k_{21})$$

$$\det(M_2) = D \cdot k_a \cdot k_{12}$$

$$\det(M_3) = (s+k_{10}+k_{12})$$

$$X_1(s) = \frac{D \cdot k_a \cdot (s+k_{21})}{(s+k_a) \cdot (s+\lambda_1) \cdot (s+\lambda_2)}; \quad X_2(s) = \frac{D \cdot k_a \cdot k_{12}}{(s+k_a) \cdot (s+\lambda_1) \cdot (s+\lambda_2)};$$

$$X_3(s) = \frac{(s+k_{10}+k_{12})}{(s+k_a) \cdot (s+\lambda_1) \cdot (s+\lambda_2)}$$

Using partial fraction decomposition,

$$X_1(s) = D \cdot k_a \cdot \left[\frac{(k_{21} - \lambda_1)}{(s+\lambda_1)\cdot(k_a - \lambda_1)\cdot(\lambda_2 - \lambda_1)} + \frac{(k_{21} - \lambda_2)}{(s+\lambda_2)\cdot(k_a - \lambda_2)\cdot(\lambda_1 - \lambda_2)} + \frac{(k_{21} - k_a)}{(s+k_a)\cdot(k_a - \lambda_1)\cdot(k_a - \lambda_2)} \right]$$

$$X_2(s) = D \cdot k_a \cdot k_{12} \cdot \left[\frac{1}{(s+\lambda_1)\cdot(k_a - \lambda_1)\cdot(\lambda_2 - \lambda_1)} + \frac{1}{(s+\lambda_2)\cdot(k_a - \lambda_2)\cdot(\lambda_1 - \lambda_2)} + \frac{1}{(s+k_a)\cdot(k_a - \lambda_1)\cdot(k_a - \lambda_2)} \right]$$

$$X_3(s) = \frac{D}{(s+k_a)}$$

Taking the inverse transforms,

$$x_1(t) = D \cdot k_a \cdot \left(A_3 \cdot \mathrm{e}^{-\lambda_1 \cdot t} + B_3 \cdot \mathrm{e}^{-\lambda_2 \cdot t} + E_3 \cdot \mathrm{e}^{-k_a \cdot t} \right) \tag{34}$$

$$A_3 = \frac{(k_{21} - \lambda_1)}{(k_a - \lambda_1)\cdot(\lambda_2 - \lambda_1)}; \quad B_3 = \frac{(k_{21} - \lambda_2)}{(k_a - \lambda_2)\cdot(\lambda_1 - \lambda_2)}; \quad E_3 = \frac{(k_{21} - k_a)}{(k_a - \lambda_1)\cdot(k_a - \lambda_2)}$$

$$C_1(t) = \frac{x_1(t)}{V_1} \tag{34a}$$

$$x_2(t) = D \cdot k_a \cdot k_{12} \cdot \left(A_4 \cdot \mathrm{e}^{-\lambda_1 \cdot t} + B_4 \cdot \mathrm{e}^{-\lambda_2 \cdot t} + E_4 \cdot \mathrm{e}^{-k_a \cdot t} \right) \tag{35}$$

$$A_4 = \frac{1}{(k_a - \lambda_1)\cdot(\lambda_2 - \lambda_1)}; \quad B_4 = \frac{1}{(k_a - \lambda_2)\cdot(\lambda_1 - \lambda_2)}; \quad E_4 = \frac{1}{(k_a - \lambda_1)\cdot(k_a - \lambda_2)}$$

$$C_2(t) = \frac{x_2(t)}{V_2} \tag{35a}$$

$$x_3(t) = D \cdot \mathrm{e}^{-k_a \cdot t} \tag{36}$$

$$C_3(t) = \frac{x_3(t)}{V_3} \tag{36a}$$

Terms of the mathematical sequence for multiple doses administered with a dosing interval τ.

$$\{C_{1,n}\} = \left\{ \frac{D \cdot k_a}{V_1} \cdot \left(A_3 \cdot \mathrm{e}^{-\lambda_1 \cdot t} + B_3 \cdot \mathrm{e}^{-\lambda_2 \cdot t} + E_3 \cdot \mathrm{e}^{-k_a \cdot t} \right), \frac{D \cdot k_a}{V_1} \cdot \left(A_3 \cdot \mathrm{e}^{-\lambda_1 \cdot t} + B_3 \cdot \mathrm{e}^{-\lambda_2 \cdot t} + E_3 \cdot \mathrm{e}^{-k_a \cdot t} \right) + \frac{D \cdot k_a}{V_1} \cdot \left(A_3 \cdot \mathrm{e}^{-\lambda_1 \cdot (t-\tau)} + B_3 \cdot \mathrm{e}^{-\lambda_2 \cdot (t-\tau)} + E_3 \cdot \mathrm{e}^{-k_a \cdot (t-\tau)} \right), \cdots \right\}$$

Pattern of Sequence

$$\{C_{1,n}\} = \left\{ \frac{F \cdot D \cdot k_a}{V_1} \cdot \left(A_3 \cdot \mathrm{e}^{-\lambda_1 \cdot (t-(n-1)\cdot\tau)} + B_3 \cdot \mathrm{e}^{-\lambda_2 \cdot (t-(n-1)\cdot\tau)} + E_3 \cdot \mathrm{e}^{-k_a \cdot (t-(n-1)\cdot\tau)} \right) \right\}$$

where, t is the total time.

Partial sums and formula of the mathematical Series for repetitive oral doses

$$C_{1,n} = \sum_{n=1}^{\infty} \frac{D \cdot k_a}{V_1} \cdot \left(A_3 \cdot \mathrm{e}^{-\lambda_1 \cdot (t-(n-1)\cdot\tau)} + B_3 \cdot \mathrm{e}^{-\lambda_2 \cdot (t-(n-1)\cdot\tau)} + E_3 \cdot \mathrm{e}^{-k_a \cdot (t-(n-1)\cdot\tau)} \right)$$

Dividing and multiplying corresponding terms by $\left(1-\mathrm{e}^{-\lambda_1 \cdot \tau}\right)$, $\left(1-\mathrm{e}^{-\lambda_2 \cdot \tau}\right)$ and by $\left(1-\mathrm{e}^{-k_a \cdot \tau}\right)$, yields the partial sums of the series shown below:

$$\begin{aligned}
C_{1,n} &= \sum_{n=1}^{\infty} \frac{D \cdot k_a}{V_1} \cdot \left(A_3 \cdot \mathrm{e}^{-\lambda_1 \cdot (t-(n-1)\cdot\tau)} + B_3 \cdot \mathrm{e}^{-\lambda_2 \cdot (t-(n-1)\cdot\tau)} + E_3 \cdot \mathrm{e}^{-k_a \cdot (t-(n-1)\cdot\tau)} \right) \\
&= \frac{D \cdot k_a}{V_1} \cdot \left\{ A_3 \cdot \left(\frac{\mathrm{e}^{-\lambda_1 \cdot t} + \mathrm{e}^{-\lambda_1 \cdot (t-\tau)} + \mathrm{e}^{-\lambda_1 \cdot (t-2\cdot\tau)} + \cdots + \mathrm{e}^{-\lambda_1 \cdot (t-(n-1)\cdot\tau)} - \mathrm{e}^{-\lambda_1 \cdot (t+\tau)} - \mathrm{e}^{-\lambda_1 \cdot t} - \mathrm{e}^{-\lambda_1 \cdot (t-\tau)} - \mathrm{e}^{-\lambda_1 \cdot (t-2\cdot\tau)} - \cdots - \mathrm{e}^{-\lambda_1 \cdot (t-(n-2)\cdot\tau)}}{\left(1-\mathrm{e}^{-\lambda_1 \cdot \tau}\right)} \right) \right. \\
&\quad + B_3 \cdot \left(\frac{\mathrm{e}^{-\lambda_2 \cdot t} + \mathrm{e}^{-\lambda_2 \cdot (t-\tau)} + \cdots + \mathrm{e}^{-\lambda_2 \cdot (t-(n-1)\cdot\tau)} - \mathrm{e}^{-\lambda_2 \cdot (t+\tau)} - \mathrm{e}^{-\lambda_2 \cdot t} - \mathrm{e}^{-\lambda_2 \cdot (t-\tau)} - \cdots - \mathrm{e}^{-\lambda_2 \cdot (t-(n-2)\cdot\tau)}}{\left(1-\mathrm{e}^{-\lambda_2 \cdot \tau}\right)} \right) \\
&\quad \left. + E_3 \cdot \left(\frac{\mathrm{e}^{-k_a \cdot t} + \mathrm{e}^{-k_a \cdot (t-\tau)} + \cdots + \mathrm{e}^{-k_a \cdot (t-(n-1)\cdot\tau)} - e^{-k_a \cdot (t+\tau)} - \mathrm{e}^{-k_a \cdot t} - \mathrm{e}^{-k_a \cdot (t-\tau)} - \cdots - \mathrm{e}^{-k_a \cdot (t-(n-2)\cdot\tau)}}{\left(1-\mathrm{e}^{-k_a \cdot \tau}\right)} \right) \right\} \\
&= \frac{D \cdot k_a}{V_1} \cdot \left\{ A_3 \cdot \left(\frac{\mathrm{e}^{-\lambda_1 \cdot (t-(n-1)\cdot\tau)} - \mathrm{e}^{-\lambda_1 \cdot (t+\tau)}}{\left(1-\mathrm{e}^{-\lambda_1 \cdot \tau}\right)} \right) + B_3 \cdot \left(\frac{\mathrm{e}^{-\lambda_2 \cdot (t-(n-1)\cdot\tau)} - \mathrm{e}^{-\lambda_2 \cdot (t+\tau)}}{\left(1-\mathrm{e}^{-\lambda_2 \cdot \tau}\right)} \right) + E_3 \cdot \left(\frac{\mathrm{e}^{-k_a \cdot (t-(n-1)\cdot\tau)} - \mathrm{e}^{-k_a \cdot (t+\tau)}}{\left(1-\mathrm{e}^{-k_a \cdot \tau}\right)} \right) \right\}
\end{aligned}$$

$$\begin{aligned}
C_{1,n,t} = \frac{D \cdot k_a}{V_1} \cdot \left\{ A_3 \cdot \frac{\left(1-\mathrm{e}^{-\lambda_1 \cdot n \cdot \tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_1 \cdot (t-(n-1)\cdot\tau)} \right. \\
\left. + B_3 \cdot \frac{\left(1-\mathrm{e}^{-\lambda_2 \cdot n \cdot \tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_2 \cdot (t-(n-1)\cdot\tau)} + E_3 \cdot \frac{\left(1-\mathrm{e}^{-k_a \cdot n \cdot \tau}\right)}{\left(1-\mathrm{e}^{-k_a \cdot \tau}\right)} \cdot \mathrm{e}^{-k_a \cdot (t-(n-1)\cdot\tau)} \right\} \quad n,t \in [0,\infty) \quad (37)
\end{aligned}$$

Similarly,

$$\begin{aligned}
C_{2,n,t} = \frac{D \cdot k_a \cdot k_{12}}{V_2} \cdot \left\{ A_4 \cdot \frac{\left(1-\mathrm{e}^{-\lambda_1 \cdot n \cdot \tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_1 \cdot (t-(n-1)\cdot\tau)} \right. \\
\left. + B_4 \cdot \frac{\left(1-\mathrm{e}^{-\lambda_2 \cdot n \cdot \tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_2 \cdot (t-(n-1)\cdot\tau)} + E_4 \cdot \frac{\left(1-\mathrm{e}^{-k_a \cdot n \cdot \tau}\right)}{\left(1-\mathrm{e}^{-k_a \cdot \tau}\right)} \cdot \mathrm{e}^{-k_a \cdot (t-(n-1)\cdot\tau)} \right\} \quad n,t \in [0,\infty) \quad (38)
\end{aligned}$$

$$C_{3,n,t} = \frac{D}{V_3} \cdot \frac{\left(1-\mathrm{e}^{-k_a \cdot n \cdot \tau}\right)}{\left(1-\mathrm{e}^{-k_a \cdot \tau}\right)} \cdot \mathrm{e}^{-k_a \cdot (t-(n-1)\cdot\tau)} \quad n,t \in [0,\infty) \quad (A1)$$

AUC formulas

$$\begin{aligned}
\mathrm{AUC}_{1,\max,n} = \int_{(n-1)\cdot\tau}^{n\cdot\tau} \frac{D \cdot k_a}{V_1} \cdot \left\{ A_3 \cdot \frac{\left(1-\mathrm{e}^{-\lambda_1 \cdot n \cdot \tau}\right)}{\left(1-\mathrm{e}^{-\lambda_1 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_1 \cdot (t-(n-1)\cdot\tau)} \right. \\
\left. + B_3 \cdot \frac{\left(1-\mathrm{e}^{-\lambda_2 \cdot n \cdot \tau}\right)}{\left(1-\mathrm{e}^{-\lambda_2 \cdot \tau}\right)} \cdot \mathrm{e}^{-\lambda_2 \cdot (t-(n-1)\cdot\tau)} + E_3 \cdot \frac{\left(1-\mathrm{e}^{-k_a \cdot n \cdot \tau}\right)}{\left(1-\mathrm{e}^{-k_a \cdot \tau}\right)} \cdot \mathrm{e}^{-k_a \cdot (t-(n-1)\cdot\tau)} \right\} \mathrm{d}t \quad (A2)
\end{aligned}$$