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ORIGINAL PAPER

Constant infusion case of one compartment pharmacokinetic model with simultaneous first-order and Michaelis–Menten elimination: analytical solution and drug exposure formula

Xiaotian Wu[1] · Min Chen[1] · Jun Li[2,3]

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Abstract

The main objective of this article is to propose the closed-form solution of one-compartment pharmacokinetic model with simultaneous first-order and Michaelis–Menten elimination for the case of constant infusion. For the case of bolus administration, we have previously established a closed-form solution of the model through introducing a transcendent X function. In the same vein, we found here a closed-form solution of constant infusion could be realized through introducing another transcendent Y function. For the general case of constant infusion of limited duration, the closed-form solution is then fully expressed using both X and Y functions. As direct results, several important pharmacokinetic surrogates, such as peak concentration C_{max} and total drug exposure $AUC_{0-\infty}$, are found the closed-form expressions and ready to be analyzed. The new pharmacokinetic knowledge we have gained on these parameters, which largely exhibits in a nonlinear feature, is in clear contrast to that of the linear case. Finally, with a pharmacokinetic model adapted from that formerly reported on phenytoin, we numerically analyzed and illustrated the roles of different model parameters and discussed their influence on drug exposure. To conclude, the present findings elucidate the intrinsic quantitative structural properties of such pharmacokinetic model and provide a new avenue for future modelling and rational drug designs.

Keywords Pharmacokinetic model · Closed-form solution · Constant infusion · Simultaneous first-order and Michaelis–Menten elimination · Total drug exposure $AUC_{0-\infty}$

Introduction

Many drugs, mostly biologics, have complex physicochemical characteristics and show specific pharmacokinetics in absorption, distribution, metabolism and excretion (ADME) compared to small molecules [1]. Typical examples are hormones, growth factors, monoclonal antibodies, which often manifest parallel elimination mechanisms [2–7]. Generally, their elimination involves a linear elimination pathway through organs such as kidney, lung, skin, etc., and simultaneously combined with a nonlinear saturate elimination pathway that metabolizes or clears the parent products. To model the pharmacokinetics (PK) of such drugs, compartment models concurrently considering first-order and Michaelis–Menten elimination are widely used [2–10]. While the major effort in modeling application is the parameter estimation from data, many authors have studied the closed-form solutions of compartmental models involving exclusively the Michaelis–Menten elimination pathway through the use of *Lambert W* function [11–13]. Whereas for the models of simultaneous first-order and Michaelis–Menten elimination, we have introduced a new family of transcendent X functions that constitutes the base for expressing the closed-form solutions in the case of intravenous bolus administration [14–16].

The administration route is however an important issue that influences the absorption aspect of a drug. To have better control of drug disposition, there have been

✉ Jun Li
jun.li.2@umontreal.ca

[1] Department of Mathematics, Shanghai Maritime University, Shanghai 201306, People's Republic of China

[2] Faculté de pharmacie, Université de Montréal, Montreal, QC H3C 3J7, Canada

[3] Centre de recherches mathématiques, Université de Montréal, Montreal, QC H3C 3J7, Canada

widespread considerations of various administration routes. For example, the constant infusion of growth factors, MAbs, hormones are studied and reported [17–20]. Unlike the usual case of linear elimination, the principle of convolution for the linear time-invariant system cannot be applied to easily deduce the analytic solution of these nonlinear elimination systems for constant infusion. Though numerical approximations for fitting are feasible, it is still a difficult issue to make good judgment and prediction before the hidden mathematical mechanism is clarified. To our knowledge, this issue has been studied for the single Michaelis–Menten elimination [11], whereas the general case of simultaneous first-order and Michaelis–Menten elimination is always an open problem. Since a simple closed-form solution will be of great help to establish and simplify the application, we will investigate in the current article this plausibility by exploring some specific mathematical functions.

Suppose a drug is administered intravenously by a constant infusion into the system, and from which the elimination takes place simultaneously through two types of pathways, one first-order and one Michaelis–Menten. Using a one-compartment model, the change of drug plasma concentration $C(t)$ at time t can be characterized by the following differential equation

$$\begin{cases} \dfrac{dC(t)}{dt} = \dfrac{R}{V_d} - k_{el}C(t) - \dfrac{V_m C(t)}{K_m + C(t)}, & t > 0 \\ C(0) = 0, & t = 0, \end{cases} \tag{1}$$

where V_d represents the apparent volume of distribution; k_{el} is the elimination rate constant for the linear elimination pathway; V_m and K_m are the maximum rate of the Michaelis–Menten kinetics (in the unit of concentration/time) and the so-called Michaelis–Menten constant, respectively. The latter is known as the concentration value at which the rate of change of Michaelis–Menten kinetics reaches a half of V_m. Moreover, we suppose the drug is constantly infused at the rate of R (in the unit of amount/time), and at time $t = 0$, the drug concentration value is zero. To be realistic for their pharmacokinetic meaning, it has to be reminded that all model parameters are positive.

As we have mentioned, for the intravenous bolus administration, we previously introduced a transcendent X function that allowed us to express the closed-form solution of a one-compartment pharmacokinetic model of simultaneous linear and Michaelis–Menten elimination. With X function, the descending elimination phase of such types of models can be fully characterized [14–16]. However, if we consider the infusion mechanism, it is found that the use of X function is not enough, and another transcendent Y function as we name it in this article should be introduced for the closed-form expression of the ascending phase. For the usual case of the constant infusion of limited duration, we will demonstrate that the application of both X and Y functions will provide a full mathematical characterization of such kind of pharmacokinetic profiles. And this will be the key result of the current article. Moreover, by using this closed-form expression, the pharmacologically important drug exposure surrogates such as $C_{\max}$, total or partial AUC will be naturally obtained and analyzed for their nonlinear properties to the administered doses, which will be found in clear contrast to the known linear situations.

This article is organized as follows. We will first summarize the concept of X function previously introduced based on a one-compartment model of simultaneous linear and Michaelis–Menten elimination in the case of intravenous bolus administration. Then we will introduce the family of Y functions and use it for the expression of the closed-form solution of a one-compartment model of simultaneous linear and Michaelis–Menten elimination in the case of constant infusion. Using this closed-form solution, we will focus on the practical case of constant infusion of a limited duration, and the closed-form solution of drug concentration-time course, as well as the drug exposure surrogates (C_{max} and AUC), will be provided. For an illustrative purpose, we will adapt a real drug example from literature to show the impact of our findings on the current pharmacokinetic knowledge as well as some possible applications. Moreover, several topics will be addressed in the discussion.

Transcendent *X* function

The family of X functions is introduced for expressing the closed-form solution of the pharmacokinetic model of simultaneous first-order and Michaelis–Menten elimination in the case of intravenous bolus administration [14]. In fact, the pharmacokinetics of a one compartment model can be mathematically described as

$$\begin{cases} \dfrac{dC(t)}{dt} = -k_{el}C(t) - \dfrac{V_m C(t)}{K_m + C(t)}, \\ C(0^+) = D/V_d \triangleq C_0, \end{cases} \tag{2}$$

where the model coefficients are the same as described in Model (1), except D here is the bolus dose amount intravenously administered at time $t = 0$.

To facilitate the description of X function, we introduce two concepts below:

(i) $k_{em} = \frac{V_m}{K_m}$: the intrinsic elimination rate constant of the Michaelis–Menten elimination pathway. It indicates the maximum strength of the nonlinear pathway to reduce the drug concentration and can

only be attained for very low drug concentration by letting $C(t) \to 0$. In fact, when drug concentration tends to zero, we have

$$\left.\frac{d}{dC(t)}\left(\frac{V_m C(t)}{K_m + C(t)}\right)\right|_{C(t)=0} = \left.\frac{V_m K_m}{(K_m + C(t))^2}\right|_{C(t)=0} = \frac{V_m}{K_m}.$$

(ii) $k_{e,tot} = k_{el} + k_{em}$: the intrinsic total elimination rate constant. It indicates the maximum strength of the system to drop the drug concentration by simultaneously combining the two elimination pathways.

Using these notations and performing partial fraction decomposition, the differential equation of Model (2) can be changed as

$$\left(\frac{p_1}{C(t)} + \frac{p_2}{C(t) + C_\beta}\right) dC(t) = -k_{el} dt, \tag{3}$$

where p_1, p_2 and C_β are defined as

$$p_1 = \frac{k_{el}}{k_{e,tot}}, \quad p_2 = \frac{k_{em}}{k_{e,tot}}, \quad C_\beta = \frac{k_{e,tot}}{k_{el}} \cdot K_m, \tag{4}$$

respectively. It is noteworthy that p_1 and p_2 are the fractions that share in the intrinsic total elimination rate constant of the linear and Michaelis–Menten elimination pathways, respectively. Thus $p_1 + p_2 = 1$. C_β is a constant of concentration obtained from K_m multiplied by the ratio of the intrinsic total elimination constant to that of the linear pathway. Pharmacokinetically, if we consider the rate of change in drug concentration at K_m for a linear model with the elimination coefficient $k_{e,tot}$, then C_β is the corresponding concentration value of this linear model that gives the same rate of change but with the elimination coefficient replaced by k_{el} (for more details see [14]).

Performing integration from time 0^+ to time $t > 0$, Eq. (3) can be transformed as

$$C(t)^{p_1}(C(t) + C_\beta)^{p_2} = (C_0)^{p_1}(C_0 + C_\beta)^{p_2} e^{-k_{el}t},$$

which is equivalent to

$$\left(\frac{C(t)}{C_\beta}\right)^{p_1}\left(1 + \frac{C(t)}{C_\beta}\right)^{p_2} = \left(\frac{C_0}{C_\beta}\right)^{p_1}\left(1 + \frac{C_0}{C_\beta}\right)^{p_2} e^{-k_{el}t}. \tag{5}$$

Equation (5) is transcendent and the solution cannot be expressed through composition of elementary functions in a conventional way. Motivated by the *Lambert W* function [21], which had been rediscovered its application for the closed-form solution of the pharmacokinetic model with a single Michaelis–Menten elimination, a new family of transcendent X functions in [14] was introduced for the closed-form expression of $C(t)$ of Eq. (5).

Definition 1 [14] Given both p_1 and p_2 positive real numbers, $X(s)$ is defined as the multivalued solution of the following equation:

$$X(s)^{p_1} \cdot (1 + X(s))^{p_2} = s \tag{6}$$

where s is a complex variable. Depending on situations, notation $X(s, p_1, p_2)$ will be used as well as $X(s)$.

It is noteworthy that the value of X function is determined by the choice of parameters p_1, p_2 and the independent variable s. In fact, we have investigated the real branches of X function in the scope of real numbers. As a result, for any positive real number $s \in \mathcal{R}^+$, there is a unique positive $X(s)$ satisfying Eq. (6). For the purpose of applications, we define the real branch of X function occurring in the first quadrant as the principal real branch of X function and denoted it by $X_0(s, p_1, p_1)$ [22]. Based on the above definition, the following result is obtained.

Theorem 1 [14] *For Model (2) with the simultaneous first-order and Michaelis–Menten elimination and an intravenous bolus administration, the concentration time course can have a closed-form solution as*

$$C(t) = C_\beta \cdot X_0\left(\left(\frac{C_0}{C_\beta}\right)^{p_1}\left(1 + \frac{C_0}{C_\beta}\right)^{p_2} e^{-k_{el}t}, p_1, p_2\right), \quad t > 0, \tag{7}$$

where X_0 is the aforementioned principal real branch of X function in the first quadrant.

With an explicit expression of C(t), the qualitative properties of many pharmacological parameters, as we have shown for the elimination half-life and area under the curve, can be revealed and even quantitatively expressed [14–16]. Moreover, Eq. (7) will be further used to solve the closed-form solution of the pharmacokinetic model with a constant infusion of limited duration in this article.

Transcendent *Y* function

If we change the drug administration in Model (2) to an intravenous constant infusion, the already introduced one compartment pharmacokinetic model (Eq. (1)) could be rewritten as

$$\begin{cases} \dfrac{dC(t)}{dt} = r - k_{el}C(t) - \dfrac{V_m C(t)}{K_m + C(t)}, & t > 0 \\ C(0) = 0, \quad t = 0, \end{cases} \tag{8}$$

where $r = R/V_d$ is a constant that represents the rate of constant infusion per volume (in the unit of

concentration/time). All other model parameters are as described in Eq. (1) and positive.

The first equation of Model (8) can be rewritten as

$$\frac{dC(t)}{dt} = -k_{el}\frac{(C(t)-C^{\infty})(C(t)+C_{\beta}^{\infty})}{K_m + C(t)}, \tag{9}$$

where

$$C^{\infty} = \frac{1}{2}\left[\sqrt{\left(C_{\beta}-\frac{r}{k_{el}}\right)^2 + 4\frac{r}{k_{el}}K_m} - \left(C_{\beta}-\frac{r}{k_{el}}\right)\right] > 0 \tag{10}$$

and

$$C_{\beta}^{\infty} = \frac{1}{2}\left[\sqrt{\left(C_{\beta}-\frac{r}{k_{el}}\right)^2 + 4\frac{r}{k_{el}}K_m} + \left(C_{\beta}-\frac{r}{k_{el}}\right)\right] > 0. \tag{11}$$

Clearly, the two quantities of C^{∞} and C_{β}^{∞} play a crucial role to express the closed-form solution of Model (8). Accordingly we summarize their mathematical properties below, and their proof is provided in Appendix 1.

Lemma 1 *For Model (8) that describes the change of drug concentration induced by the constant infusion and simultaneous first-order and Michaelis–Menten elimination, we have*

(i) C^{∞} in Eq. (10) is the unique positive equilibrium. Moreover, $C(t)$ is strictly increasing with respect to $t \geq 0$ and asymptotically converges to C^{∞} as $t \to +\infty$, that is, $C(t) < C^{\infty}$ for all $t \geq 0$.

(ii) C_{β}^{∞} in Eq. (11) is a positive value which is greater than K_m, that is $C_{\beta}^{\infty} > K_m$.

Using a straightforward algebraic manipulation, Eq. (9) can be changed as

$$\left(\frac{q_1}{C(t)-C^{\infty}} + \frac{q_2}{C(t)+C_{\beta}^{\infty}}\right) dC(t) = -k_{el}\,dt \tag{12}$$

where

$$q_1 = \frac{C^{\infty}+K_m}{C^{\infty}+C_{\beta}^{\infty}}, \quad q_2 = \frac{C_{\beta}^{\infty}-K_m}{C^{\infty}+C_{\beta}^{\infty}}, \quad \text{and} \quad q_1+q_2 = 1. \tag{13}$$

Clearly, it follows from Lemma 1 that both q_1 and q_2 are positive numbers between 0 and 1.

We now integrate both sides of Eq. (12) from time 0 to t and apply Lemma 1, and we have

$$q_1\ln(C^{\infty}-C(t)) + q_2\ln(C_{\beta}^{\infty}+C(t)) = q_1\ln C^{\infty} + q_2\ln C_{\beta}^{\infty} - k_{el}t,$$

which is equivalent to

$$\left(\frac{C^{\infty}-C(t)}{C^{\infty}+C_{\beta}^{\infty}}\right)^{q_1}\left(1-\frac{C^{\infty}-C(t)}{C^{\infty}+C_{\beta}^{\infty}}\right)^{q_2} = \left(\frac{C^{\infty}}{C^{\infty}+C_{\beta}^{\infty}}\right)^{q_1}\left(\frac{C_{\beta}^{\infty}}{C^{\infty}+C_{\beta}^{\infty}}\right)^{q_2} e^{-k_{el}t}. \tag{14}$$

Equation (14) is a transcendent equation if $C(t)$ is considered the sole variable. It is noteworthy the form likeness between Eqs. (14) and (5), and the latter had led to the introduction of X functions for the closed-form solution of the case of intravenous bolus. Thus we introduce the following Y functions.

Definition 2 Given both q_1 and q_2 positive real numbers, $Y(s)$ is defined as a multivalued solution of the following equation:

$$Y(s)^{q_1}\cdot(1-Y(s))^{q_2} = s \tag{15}$$

where s is a complex variable. As notations, $Y(s,q_1,q_2)$ will be used as well as $Y(s)$ as the situation requires.

To show the existence of solution to Eq. (14), we need the following properties characterizing the transcendent Y functions.

Lemma 2 *Given real parameters* $q_1 \in (0,1)$, $q_2 \in (0,1)$ *and* $q_1+q_2 = 1$, *there exists a unique* $Y \in (0,q_1) \subset (0,1)$ *for any* $s \in (0, q_1^{q_1}q_2^{q_2}) \subset (0,1)$ *such that Eq. (15) holds.*

Proof Consider the following derivative with respect to x

$$\frac{d}{dx}\left[x^{q_1}(1-x)^{q_2}\right] = x^{q_1}(1-x)^{q_2}\frac{q_1-x}{x(1-x)},$$

which is positive when x belongs to $(0,q_1)$. Accordingly, $x^{q_1}(1-x)^{q_2}$ is increasing in this interval and its range is $(0, q_1^{q_1}q_2^{q_2}) \subset (0,1)$. By the inverse function theorem, Eq. (15) admits a unique real value $Y(s,q_1,q_2) \in (0,q_1)$ corresponding to $s \in (0, q_1^{q_1}q_2^{q_2})\square$.

Similar to aforementioned X_0, we define this positive real solution belonging to the interval $(0, \frac{q_1}{q_1+q_2})$ as a principal real branch of Y functions in the first quadrant, denoted by Y_0. However, a thorough mathematical investigation of Y function is not intended here since it is out of the scope of the current article. To provide readers a direct view of $X_0(s,p_1,p_2)$ and $Y_0(s,q_1,q_2)$, these functions are simulated and plotted for different values of p_1, p_2, q_1 and q_2 using MATLAB (R2015a, MathWorks, Inc.) (see Appendix 2).

Let us go back to Eq. (14), and we can check

$$0 < \frac{C^{\infty}-C(t)}{C^{\infty}+C_{\beta}^{\infty}} < \frac{C^{\infty}+K_m}{C^{\infty}+C_{\beta}^{\infty}} = q_1.$$

And

$$0 < \left(\frac{C^\infty}{C^\infty + C_\beta^\infty}\right)^{q_1} \left(\frac{C_\beta^\infty}{C^\infty + C_\beta^\infty}\right)^{q_2} e^{-k_{el}t} < \left(\frac{C^\infty}{C^\infty + C_\beta^\infty}\right)^{q_1} \left(\frac{C_\beta^\infty}{C^\infty + C_\beta^\infty}\right)^{q_2},$$

which is less than

$$\left(\frac{C^\infty + K_m}{C^\infty + C_\beta^\infty}\right)^{q_1} \left(1 - \frac{C^\infty + K_m}{C^\infty + C_\beta^\infty}\right)^{q_2} = q_1^{q_1} q_2^{q_2}.$$

Therefore, by the definition of the principal real branch of Y functions and Lemma 2, Eq. (14) admits a unique solution $\frac{C^\infty - C(t)}{C^\infty + C_\beta^\infty}$ that can be expressed as

$$\frac{C^\infty - C(t)}{C^\infty + C_\beta^\infty} = Y_0\left(\left(\frac{C^\infty}{C^\infty + C_\beta^\infty}\right)^{q_1} \left(\frac{C_\beta^\infty}{C^\infty + C_\beta^\infty}\right)^{q_2} e^{-k_{el}t}, q_1, q_2\right).$$

Finally, we have the following result.

Theorem 2 *For Model (8) with the simultaneous first-order and Michaelis–Menten elimination and a constant infusion, the closed-form solution of concentration time course is*

$$C(t) = C^\infty - (C^\infty + C_\beta^\infty) \cdot Y_0\left(\left(\frac{C^\infty}{C^\infty + C_\beta^\infty}\right)^{q_1} \left(\frac{C_\beta^\infty}{C^\infty + C_\beta^\infty}\right)^{q_2} e^{-k_{el}t}, q_1, q_2\right), \quad t > 0, \tag{16}$$

where Y_0 is the principal real branch of Y functions in the first quadrant.

Compared to Theorem 1, the closed-formed solution found in Theorem 2 has a more complex form. In fact, in the former, only a decreasing elimination is involved, whereas an accumulation process is integrated into the latter, which interacts with the elimination process. So, Eq. (16) clearly characterizes how $C(t)$ increases from 0 at $t = 0$ to the steady-state C^∞ when t tends to infinity. Depending upon the infusion rate r (or R), C^∞ and C_β^∞ play a crucial role for the closed-form solution of Model (8). To better understand the pharmacokinetics of this model, the relationships between C^∞ and C_β^∞ with the infusion rate and the pharmacokinetic meaning of C_β^∞ are clarified below.

Proposition 1 *For Model (8) with the simultaneous first-order and Michaelis–Menten elimination and a constant infusion, we have*

(i) If $r = 0$, which is same as $R = 0$, then $C^\infty = 0$ and $C_\beta^\infty = C_\beta$.

(ii) If $r \begin{pmatrix} = \\ > \\ < \end{pmatrix} k_{e,tot} K_m$, which is same as $R \begin{pmatrix} = \\ > \\ < \end{pmatrix} V_d k_{e,tot} K_m$, then $C^\infty \begin{pmatrix} = \\ > \\ < \end{pmatrix} C_\beta^\infty$.

(iii) C^∞ is monotonically increasing with respect to r (or R) and eventually tends to infinity; and C_β^∞ is monotonically increasing with respect to r (or R) and eventually tends to K_m, that is

$$\lim_{r\to\infty} C^\infty = +\infty \quad \text{and} \quad \lim_{r\to\infty} C_\beta^\infty = K_m.$$

Proof See Appendix 3. □

Figure 1 illustrates the variations of C^∞ and C_β^∞ with respect to the infusion rate r, respectively, where C^∞ is monotonically increasing towards to infinity, C_β^∞ is monotonically decreasing towards to zero, and they are equal at $r = k_{e,tot} K_m$.

Pharmacokinetic meaning of C_β^∞

It is understandable that C^∞ is the steady state drug concentration that the system will asymptotically attain when the constant infusion is continued to be administered. As shown in Fig. 1, a larger constant infusion induces a higher C^∞.

For the positive value of C_β^∞, a pharmacokinetic interpretation can be similarly attributed as in [15]. Let us

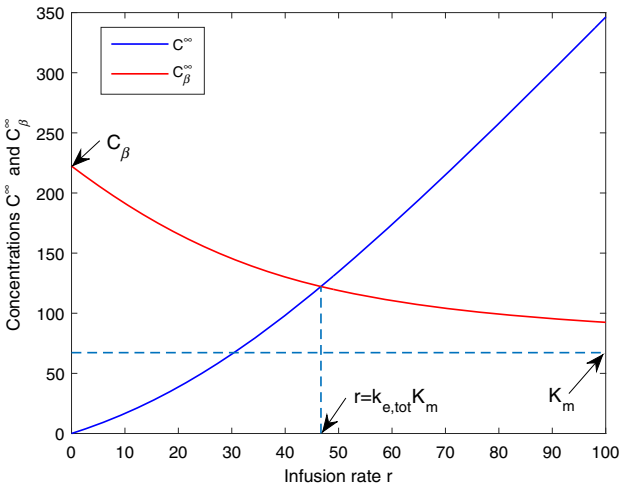

Fig. 1 Illustration of C^∞ and C_β^∞ with respect to infusion rate $r \in [0, 100$ mIU/ml/h]. Here $k_{el} = 0.21\,1/h$, $V_d = 61.18$ ml, $V_m = 32.58$ mIU/ml/h, $K_m = 67.23$ mIU/ml are adapted from [10]

consider two linear pharmacokinetic models with a constant infusion and a first-order elimination:

(a)

$$\frac{dC_1(t)}{dt} = k_{el}C^{\infty} - k_{el}C_1(t),$$

and

(b)

$$\frac{dC_2(t)}{dt} = r - k_{e,tot}C_2(t),$$

then C_{β}^{∞} is the drug concentration level in Model (a) that has the same change rate of concentration or slope as that of Model (b) but at the concentration level K_m, that is

$$\left.\frac{dC_1(t)}{dt}\right|_{C_1(t)=C_{\beta}^{\infty}} = \left.\frac{dC_2(t)}{dt}\right|_{C_2(t)=K_m} = r - k_{e,tot}K_m.$$

In fact this concentration change rate is $r - k_{e,tot}K_m$ (or $k_{el}(C^{\infty} - C_{\beta}^{\infty})$) that may be positive or negative, depending on how C_1 and C_2 converge to their steady states, respectively, whether from above or below. If $C^{\infty} > C_{\beta}^{\infty}$ (samely as $r > k_{e,tot}K_m$), we assume $C_1(t)$ and $C_2(t)$ are initially below their respective steady state levels, then this change rate is positive. If $C^{\infty} < C_{\beta}^{\infty}$ (samely as $r < k_{e,tot}K_m$), we assume $C_1(t)$ and $C_2(t)$ are initially above their respective steady state levels, then this change rate is negative. If $C^{\infty} = C_{\beta}^{\infty}$ (samely as $r = k_{e,tot}K_m$), then the two systems are at their steady state with change rate zero.

Pharmacokinetic model with a constant infusion of limited duration

By introducing a transcendent Y function, we arrive to provide in the last section the closed-form solution for the constant infusion case of the pharmacokinetic model with the simultaneous first-order and Michaelis–Menten elimination. For a more general application in pharmacokinetic practice, we still need to extend its use to pharmacokinetic models of a constant infusion of limited duration. To achieve this objective, we can combine the use of transcendent X and Y functions.

In this case, we assume a dose D is executed as a constant infusion for a time duration T. For the sake of simplicity, we further assume the administration starts from time zero and ends at time T. The one-compartment pharmacokinetic model is

$$\begin{cases} \dfrac{dC(t)}{dt} = f(t) - k_{el}C(t) - \dfrac{V_m \cdot C(t)}{K_m + C(t)}, & t > 0, \\ C(0) = 0, & t = 0, \end{cases} \tag{17}$$

where the drug input function is

$$f(t) = \begin{cases} R/V_d, & t \in [0, T], \\ 0, & t > T \end{cases} \quad \text{and} \quad R = \frac{D}{T}. \tag{18}$$

Closed-form solution of $C(t)$

The time course of drug concentration of Model (17) can be separated into two phases according to drug input (Eq. 18). In the first phase from time zero to T, the drug is intravenously administered at a constant rate $R = \frac{D}{T}$, and drug concentration increases from zero to its maximum value occurring at time T. Hence, during [0, T], the time evolution of drug concentration in Model (17) is the same as that in Model (8). And from time T, there is no more drug input, Model (17) enters the second phase where only simultaneous first-order and Michaelis–Menten elimination exists. This leads to the situation as described in Model (2) but the initial time is changed to T equivalently with a bolus dose $C(T)V_d$ administered. By Theorems 1 and 2, we immediately have the result below.

Theorem 3 *For Model (17) with a limited constant infusion time, the closed-form solution of time course of drug concentration can be expressed as*

$$C(t) = \begin{cases} C^{\infty} - (C^{\infty} + C_{\beta}^{\infty}) \cdot Y_0\left(\left(\frac{C^{\infty}}{C^{\infty} + C_{\beta}^{\infty}}\right)^{q_1}\left(\frac{C_{\beta}^{\infty}}{C^{\infty} + C_{\beta}^{\infty}}\right)^{q_2} e^{-k_{el}t}, q_1, q_2\right), & 0 < t \le T, \\ C_{\beta} \cdot X_0\left(\left(\frac{C(T)}{C_{\beta}}\right)^{p_1}\left(1 + \frac{C(T)}{C_{\beta}}\right)^{p_2} e^{-k_{el}(t-T)}, p_1, p_2\right), & t > T \end{cases} \tag{19}$$

where C^{∞}, C_{β}^{∞}, q_1 and q_2 are given by Eqs. (10)–(11) and Eq. (13) while $r = D/(TV_d)$; p_1, p_2, C_{β} are given in Eq. (4); $C(T)$ is the last concentration of the ascending phase and is also the peak concentration, which is

$$C_{max} = C(T) = C^{\infty} - (C^{\infty} + C_{\beta}^{\infty}) \cdot Y_0\left(\left(\frac{C^{\infty}}{C^{\infty} + C_{\beta}^{\infty}}\right)^{q_1}\left(\frac{C_{\beta}^{\infty}}{C^{\infty} + C_{\beta}^{\infty}}\right)^{q_2} e^{-k_{el}T}, q_1, q_2\right). \tag{20}$$

Total drug exposure

The area under the concentration-time curve (AUC) is a useful parameter that reflects the actual body exposure to an administered drug. The total drug exposure $\mathrm{AUC}_{0-\infty}$ is the integral of drug concentration time curve from the dose administration ($t = 0$) to $t = +\infty$, namely

$$\mathrm{AUC}_{0-\infty} = \int_0^{+\infty} C(t)\, dt.$$

For the pharmacokinetics of linear elimination, the total drug exposure $\mathrm{AUC}_{0-\infty}$ is proportional to the administered

dose. However, this property may change for the simultaneous first order and Michaelis–Menten elimination. In the following, we will give the exact formula for the case of a constant infusion of a limited duration.

Theorem 4 *For Model (17) describing the simultaneous first-order and Michaelis–Menten elimination and a constant infusion with limited duration T, the exact formula of total drug exposure is*

$$\mathrm{AUC}_{0-\infty} = \frac{1}{k_{el}}\left[-q_1 C^{\infty}\ln\left(1-\frac{C(T)}{C^{\infty}}\right) + q_2 C_{\beta}^{\infty}\ln\left(1+\frac{C(T)}{C_{\beta}^{\infty}}\right) - p_2 C_{\beta}\ln\left(1+\frac{C(T)}{C_{\beta}}\right)\right],$$

where C^{∞}, C_{β}^{∞}, q_1 *and* q_2 *are given in Eqs. (10)–(11) and Eq. (13) while* $r = D/(TV_d)$; p_2 *and* C_{β} *are given in Eq. (4).*

Proof Firstly, we calculate the partial area under the curve AUC_{0-T} for the ascending phase of drug infusion.

During the time period $[0, T]$, the drug concentration follows Eq. (12). Multiplying both sides of this equation by $C(t)$ and making a rearrangement yields

$$\left(1 + q_1 C^{\infty}\frac{1}{C(t)-C^{\infty}} - q_2 C_{\beta}^{\infty}\frac{1}{C(t)+C_{\beta}^{\infty}}\right)dC(t) = -k_{el}C(t)\,dt.$$

Thus

$$\int_0^T\left(1 + q_1 C^{\infty}\frac{1}{C(t)-C^{\infty}} - q_2 C_{\beta}^{\infty}\frac{1}{C(t)+C_{\beta}^{\infty}}\right)dC(t) = -k_{el}\int_0^T C(t)\,dt.$$

Using the fact $C(0) = 0$, it yields

$$C(T) + q_1 C^{\infty}\ln\frac{C^{\infty}-C(T)}{C^{\infty}} - q_2 C_{\beta}^{\infty}\ln\frac{C_{\beta}^{\infty}+C(T)}{C_{\beta}^{\infty}} = -k_{el}\mathrm{AUC}_{0-T},$$

which gives rise to

$$\mathrm{AUC}_{0-T} = \frac{1}{k_{el}}\left[-q_1 C^{\infty}\ln\left(1-\frac{C(T)}{C^{\infty}}\right) + q_2 C_{\beta}^{\infty}\ln\left(1+\frac{C(T)}{C_{\beta}^{\infty}}\right) - C(T)\right].$$

Secondly, we calculate the area under the curve $\mathrm{AUC}_{T-\infty}$ for the descending phase of the drug elimination that elapses from time T to $+\infty$. During the time period $[T, +\infty)$, the drug concentration follows Eq. (3). For both sides of Eq. (3), multiplying first by $C(t)$ and then integrating from time T to $+\infty$, we have

$$\int_T^{+\infty}\left(1 - p_2 C_{\beta}\frac{1}{C(t)+C_{\beta}}\right)dC(t) = -k_{el}\int_T^{+\infty} C(t)\,dt.$$

Taking the fact $\lim_{t\to+\infty} C(t) = 0$, it yields

$$-C(T) - p_2 C_{\beta}\ln\frac{C_{\beta}}{C(T)+C_{\beta}} = -k_{el}\mathrm{AUC}_{T-\infty}$$

which is equivalent to

$$\mathrm{AUC}_{T-\infty} = \frac{1}{k_{el}}\left[C(T) - p_2 C_{\beta}\ln\left(1+\frac{C(T)}{C_{\beta}}\right)\right]. \tag{21}$$

Accordingly, the total drug exposure $\mathrm{AUC}_{0-\infty}$ from time zero to infinity is

$$\begin{aligned}\mathrm{AUC}_{0-\infty} &= \mathrm{AUC}_{0-T} + \mathrm{AUC}_{T-\infty}\\ &= \frac{1}{k_{el}}\left[-q_1 C^{\infty}\ln\left(1-\frac{C(T)}{C^{\infty}}\right) + q_2 C_{\beta}^{\infty}\ln\left(1+\frac{C(T)}{C_{\beta}^{\infty}}\right) - p_2 C_{\beta}\ln\left(1+\frac{C(T)}{C_{\beta}}\right)\right].\end{aligned}$$

□

It is noteworthy that, for the pharmacokinetics of linear elimination, we usually use $\frac{C(t_{last})}{k_{el}}$ to estimate $\mathrm{AUC}_{t_{last}-\infty}$. According to Eq. (21), for the current model of simultaneous linear and Michaelis–Menten elimination, it should be replaced by $\frac{1}{k_{el}}C(t_{last}) - \frac{1}{k_{el}}p_2 C_{\beta}\ln\left(1+\frac{C(t_{last})}{C_{\beta}}\right)$ where the first term is the drug exposure left for linear elimination in absence of Michaelis–Menten elimination, the second term clearly shows the reduction to this exposure when the Michaelis–Menten elimination presents.

Illustration with case studies

Phenytoin (diphenylhydantoin, DPH) is an anticonvulsant known for narrow therapeutic window and nonlinear pharmacokinetics [23]. Therapeutic drug monitoring is usually required for its safe and effective use. It is originally reported to follow a one-compartment model structure with nonlinear pharmacokinetics as presented by Model (17) in [23]. For an illustration purpose, we extracted the data from [23] and re-estimated the mean values of our studied model.

From Table 1 in [23], we averaged the weights of five subjects as 76.38 kg, and the mean V_d is 48.58 L using the data of mean volume per weight (0.636 l/kg). The maximum change rate $V_m = V_{\max}/V_d$ and Michaelis–Menten constant K_m were estimated to be 0.334 mg/l/h and 5.28 mg/l using the data of mean $V_{\max}$ (= 5.10 mg/kg/day) and mean Michaelis–Menten constant (= 3.36 mg/kg) of phenytoin, respectively. Moreover, k_{el} was estimated using

CL_R/V_d, where $CL_R = 0.072$ ml/min is the renal clearance of phenytoin in [23]. The total dose amount is based on the mean dose amount per weight (4.6 mg/kg) of phenytoin in [23].

In summary, we obtained the following parameters for the studied one-compartment model:

$$D = 351.30\,mg,\ V_d = 48.58\,l,\ k_{el} = 8.75 \times 10^{-5}\,h^{-1},\\ V_m = 0.334\,mg/l/h,\ K_m = 5.28\,mg/l. \tag{22}$$

From these parameters, we further calculated $k_{em} = 0.0633\,h^{-1}$. The result of $k_{em} \gg k_{el}$ is consistent with what is reported in [23], where the capacity-limited metabolism or protein binding process plays a major role in the systemic disposition of phenytoin.

Consider a constant infusion time $T = 8\,h$, then the ascending infusion phase of phenytoin concentration-time course is characterized by the first formula in Eq. (19), while the second formula gives the descending post-infusion elimination phase. Using Eqs. (10)–(11) and Eq. (13), we can calculate the following parameters as required in the first formula of Eq. (19):

$$C^{\infty} = 6517.10\,mg/l, \quad C_{\beta}^{\infty} = 8.37\,mg/l,\\ q_1 = 0.9995 \quad \text{and} \quad q_2 = 0.0005.$$

It should be pointed out that the values of the above parameters depend on the infusion rate of $R = D/T$.

Thus, for the infusion period $0 < t \le 8\,h$, we have

$$C(t) = 6517.10 - 6525.47 \times \\ Y_0\left(0.9954e^{-0.0000875t}, 0.9995, 0.0005\right). \tag{23}$$

At the end of infusion time $T = 8\,h$, the peak concentration is attained, we can use the above formula to find $C_{max} = 6.29\,mg/l$.

The post infusion phase only consists of elimination. Using formulas in Eq. (4), we can calculate the following parameters as required in the second formula of Eq. (19):

$$C_{\beta} = 3823.20\,mg/l, \quad p_1 = 0.0014 \quad \text{and} \quad p_2 = 0.9986.$$

It has to be reminded these parameters are independent of the infusion rate R.

Hence for $t > 8\,h$, we have

$$C(t) = 3823.20 \times X_0\left(0.9927e^{-0.0000875(t-8)}, 0.0014, 0.9986\right). \tag{24}$$

More cases with different infusion times and doses are simulated, and associated parameters are calculated and listed in Table 1.

As shown in Table 1, we observe that $p_1 \ll p_2$, which is independent of any infusion rate, and the relationships of $q_1 \gg q_2$, $C^{\infty} \gg C_{\beta}^{\infty}$ are true for the high dose infusion rate R. The reason behind this is the principal role of the capacity-limited elimination process in the elimination of phenytoin. In other words, for those high levels of drug concentrations, the capacity-limited elimination pathway largely outpasses the linear elimination pathway. However, if we slow down the input rate by increasing infusion duration or decreasing the dose, it can be observed that q_1 and C^{∞} slowly decrease whereas q_2 and C_{β}^{∞} slowly increase. Whereas, when the infusion rate R reduces to $15.97\,mg/h$, C^{∞} and C_{β}^{∞} as well as q_1 and q_2 are close. Particularly when R continually reduces to $14.05\,mg/h$, the situation is completely inverted to $q_1 \ll q_2$ and $C^{\infty} \ll C_{\beta}^{\infty}$. This is due to the fact that a lower infusion rate of phenytoin leads to a lower drug concentration, thus the importance of the capacity-limited elimination pathway is diminished compared to that of the linear pathway which is

Table 1 Simulated parameters of phenytoin concentration time course during and after infusion (Eq. (19)) for different scaled doses to $D = 351.30\,mg$ and different infusion times T

Dose	$T\,(h)$	$R\,(mg/h)$	$C^{\infty}\,(mg/L)$	$C_{\beta}^{\infty}\,(mg/L)$	q_1	q_2
D	1.0	351.30	98,838.00	5.54	0.999997	0.000003
	2.0	175.65	37,510.00	5.82	0.999986	0.000014
	3.0	117.12	23,735.00	6.13	0.99996	0.00004
$\frac{D}{4}$	1.0	87.83	16847.00	6.48	0.9999	0.0001
	2.0	43.91	6517.10	8.37	0.9995	0.0005
	3.0	29.28	3076.50	11.82	0.9979	0.0021
$\frac{D}{10}$	2.0	17.58	368.72	59.18	0.8740	0.1260
	2.2	15.97	111.60	177.76	0.4039	0.5961
	2.5	14.05	31.81	548.82	0.0639	0.9361
$C_{\beta} = 3823.20\,(mg/L)$, $p_1 = 0.0014$, $p_2 = 0.9986$						

C^{∞}, C_{β}^{∞}, q_1 and q_2 are calculated from Eqs. (10)–(11) and Eq. (13), which are dose-dependent; C_{β}, p_1 and p_2 are calculated from Eqs. (4), which are dose-independent

largely increased, a phenomenon that we have discussed in [14].

The time courses of phenytoin concentration for the cases of $T = 1, 2, 4, 8, 16\,h$ are presented in Fig. 2. Note that the ascending phase of absorption is reproduced with Y function, whereas X function is used for the descending phase of elimination, and the maximum phenytoin concentration occurs at the time when the infusion terminates.

Table 2 lists the corresponding exposure surrogates using the formulas we derived in the current article. With a fixed total dose D, it is observed that, as the infusion time T increases, both the maximum (peak) concentration and the total drug exposure decrease, and it is the same for $\mathrm{AUC}_{T-\infty}$. However AUC_{0-T} increases as well as its share in the total drug exposure.

Discussion and conclusion

The goal of the current study was to find a closed-form mathematical solution for the concentration-time course of a one-compartment pharmacokinetic model with simultaneous first-order and Michaelis–Menten elimination for the case of intravenous constant infusion. In fact, the result of the post-infusion phase is not surprising given our previous works for the bolus administration, for which we introduced a transcendent X function that enlarges the classical description of the negative exponential approach and even generalizes the *Lambert W* function that had been proven suitable for the model with solely Michaelis–Menten elimination [11]. When we considered the constant infusion, we realized that we needed to introduce another transcendent Y function to describe the ascending absorption phase. To our surprise, Y function almost has the same form as that of X function with only a mathematical symbol shift from $+$ to $-$. This almost perfect match of *Y for ascending* and *X for descending* alludes to some intrinsic relationships needed to be further explored for the absorption and elimination processes of such kind of nonlinear pharmacokinetic models, no matter from the viewpoint of pharmacokinetics or simply mathematics.

Model (17) in fact extends two pharmacokinetic models with a single elimination pathway, either the type of linear first-order or that of nonlinear Michaelis–Menten. In Appendix 4, these models, (25) and (27), and their associated closed-form solutions of concentration time courses, using either elementary exponential function (Eqs. (26)) or transcendent *Lambert W* function (Eqs. (28)–(29)), are reported. It is noteworthy that both real branches of *Lambert W* function are equally used for the latter.

In Fig. 3, we display different pharmacokinetic profiles of three models simulated using their corresponding closed-form solutions, under the condition of the same constant infusion rate R. The first is the model of the simultaneous first-order and Michaelis–Menten elimination (Model (17)), the second is the single first-order linear elimination model (Model (25)) by dropping the Michaelis–Menten elimination pathway out of the first, the third is the single Michaelis–Menten elimination model (Model (27)) by dropping the linear elimination pathway out of the first. We may note that the simultaneous elimination model has the lowest concentration-time course compared with the other two models. This is understandable since the elimination capacity of the model includes two possible pathways and it influences the whole pharmacokinetic process. Moreover, it could be observed that the ascending trend during the infusion period fades off more quickly than that of the single-elimination model. However, when the infusion terminates, it also drops faster than the other two. In terms of the two single elimination models, the

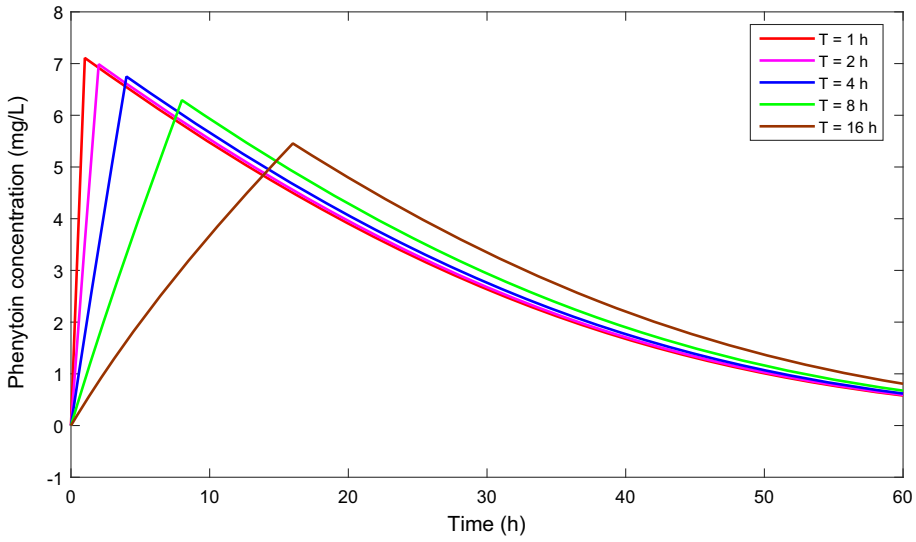

Fig. 2 Simulated time course of phenytoin concentrations using the principal real branches X_0 and Y_0 functions for different intravenous infusion time T=1, 2, 4, 8, 16 h. $D = 351.3\,mg$, $V_d = 48.58\,L, k_{el} = 8.75 \times 10^{-5}\,h^{-1}, V_m = 0.334\,mg/L/h$ and $K_m = 5.28\,mg/L$ are used from (22) which are re-estimated from [23]

Table 2 Calculated exposure surrogates of phenytoin for constant infusion with a fixed dose $D = 351.30\,mg$ and different infusion time period $T = 1, 2, 4, 8, 16\,h$

$T\,(h)$	$R\,(mg/h)$	$C_{max}\,(mg/L)$	$\mathrm{AUC}_{0-T}\,(mg\cdot h/L)$	$\mathrm{AUC}_{T-\infty}\,(mg\cdot h/L)$	$\mathrm{AUC}_{0-\infty}\,(mg\cdot h/L)$
1	351.30	7.1092	3.5695	187.5475	191.1170
2	175.65	6.9877	7.0466	183.0764	190.1230
4	87.83	6.7494	13.7305	174.4398	188.1703
8	43.91	6.2923	26.0621	158.3426	184.4048
16	21.96	5.4555	46.9405	130.4857	177.4261

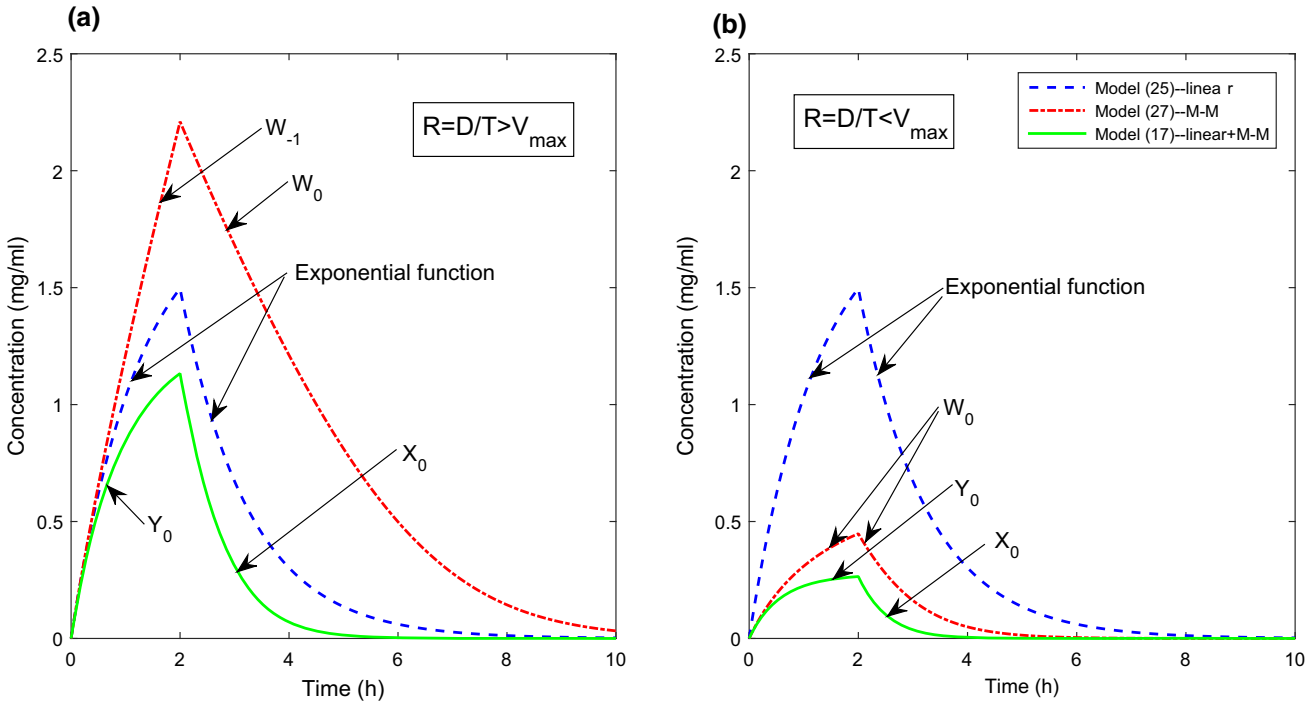

Fig. 3 Drug concentration time courses directly calculated from closed-form solutions. Model (25): dash line, Model (27): dot dash line, Model (17): solid lines. (**a**) $D = 3\,mg$, $T = 2\,h$ and $V_m = 0.8\,mg/ml/h$ where $R = D/T = 1.5 > V_m V_d = 0.8$; (**b**) $D = 1\,mg$, $T = 2\,h$ and $V_m = 1.3\,mg/ml/h$ where $R = D/T = 0.5 < V_m V_d = 1.3$. Other parameters are: $V_d = 1\,ml$; $k_{el} = 0.8\,h^{-1}$; $K_m = 1\,mg/ml$

relation between k_{el} and k_{em} may play a crucial role. In fact, if $k_{el} \geq k_{em}$, which naturally implies $k_{el}C(t) > \frac{V_m}{K_m + C(t)}C(t)$, thus the ascending speed of $C(t)$ for Model (27) is faster than that of Model (25) (Fig. 3a), as for the latter, the drug concentration drops more quickly under the same concentration level. However, if $k_{el} < k_{em}$, it is uncertain to predict the situation. Generally, if the infusion period is not too long, the ascending of $C(t)$ of the linear elimination model should be faster than that of the Michaelis–Menten elimination model and may remain until the end of infusion (Fig. 3b). However, since k_{em} is the intrinsic elimination rate constant of the Michaelis–Menten elimination that only behaves as in the linear case when the drug concentration is low, and when $C(t)$ goes up, the situation may be inverted due to the saturated mechanism of Michaelis–Menten elimination. As a remark to the discussion above, we have to note that the choice of representative real branches of *Lambert W* function used for the pharmacokinetic model with Michaelis–Menten elimination alone depends on the relation between the infusion rate R and the maximum change rate of Michaelis–Menten kinetics $V_m V_d$ in the unit of amount/time. For more detailed information, the reader is referred to Appendix 4.

One advantage of a closed-form solution is it allows easy access to a precise prediction of the values of several pharmacokinetic surrogates, such as peak, trough concentrations as well as total or partial drug exposures. As we have done for phenytoin, these parameters are computed directly from a well defined mathematical function, which avoids unnecessary uncertainty around numerical evaluation processes in solving differential equations. Moreover, for targeted safety and efficacy, estimations of these surrogates are crucial for therapeutic drug monitoring or the design of optimal drug regimens. It is not only the reliability of numerical estimates provided by these formulas

but also the possibility to quantitatively analyze and study their relationship to dosing and administration. For instance, the numerical value of peak concentration can be predicted with Eq. (20) as it is known to occur at the end of constant infusion. For the total drug exposure ($AUC_{0-\infty}$) of the pharmacokinetics of linear elimination, it is common knowledge that it is independent of the infusion time for a fixed-dose, or changes proportionally to varying doses. However, in the case of Model (17), this observation is no more sustainable. In Fig. 4, we simulate the impact on the total drug exposure in terms of infusion time or dose. This dose-dependency of $AUC_{0-\infty}$ is clearly observed. As shown in Fig. 4a, for a fixed total drug amount D, $AUC_{0-\infty}$ decreases remarkably when the infusion time T increases, particularly from bolus ($T = 0$) to infusion ($T > 0$). While, if we continually increase T, it looks like $AUC_{0-\infty}$ tends to a limited value that we guess it will reach the lower bound $D/(V_d k_{e,tot})$. Meanwhile, if we consider a constant infusion time T, the behavior of $AUC_{0-\infty}$ is nonlinear though it always monotonously increases with dose D (see Fig. 4b).

Since the introduction of X functions, the analytical solutions of many pharmacokinetic models involving the simultaneous first-order and Michaelis–Menten elimination have been found. These include single/multiple intravenous bolus administrations with or without the constant endogenous production [14–16]. In fact, all these pharmacokinetic profiles only concern the descending elimination phase. The current work has made significant progress for the nontrivial drug intake: (1) With the introduction of Y functions, we have been able to solve the ascending absorption phase of pharmacokinetic model with simultaneous first-order and Michaelis–Menten elimination. Although the solved case is for the constant infusion, it may help to open a new avenue for other absorption forms, such as the first order oral administration, etc.; (2) With the relatively simple algebraic forms, X and Y functions can be easily programmed and implemented into professional software for the purpose of numerical and symbolic calculations. This will greatly reduce the uncertainty around such kind of models; (3) To meet the current needs in therapeutic drug design, the surrogates such as C_{max} and AUC can be not only directly computed using defined mathematical formulas but also quantitatively studied and analyzed.

Appendix 1: Proof of Lemma 1

Proof *(i)* It is clear that C^∞ is the unique positive equilibrium of Model (8) since $\left.\frac{dC(t)}{dt}\right|_{C(t)=C^\infty} = 0$. Moreover, we have $C'(t) > 0$ as long as $0 \le C(t) < C^\infty$, resulting in $C(t)$ is monotonically increasing as t increases. Hence, C^∞ is an upper bound for $C(t)$ for $t > 0$. As well, when $0 \le C(t) < C^\infty$, the second order derivative

$$\frac{d^2C(t)}{dt^2} = -\left(k_{el} + \frac{V_m K_m}{(K_m + C(t))^2}\right) \cdot \frac{dC(t)}{dt} < 0,$$

implying $C'(t)$ decreases to zero as $t \to \infty$. By the monotone bounded convergence theorem, we can deduce that C^∞ is the upper limit for $C(t)$.

(ii) Denote a function by $f(x) = \sqrt{x^2 + a} + x\,(a > 0)$ for a real variable x. It follows $f'(x) = x/\sqrt{x^2 + a} + 1 > 0$

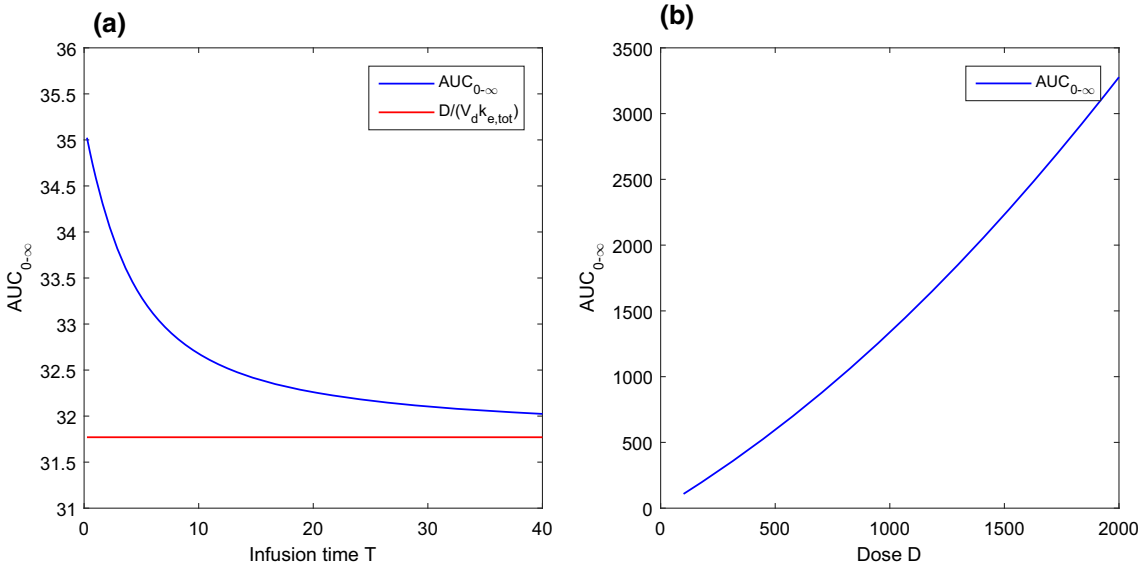

Fig. 4 Impact of infusion time T and dose D on the total drug exposure $AUC_{0-\infty}$, (**a**) D = 1350 mIU; (**b**) T = 1 h. Model parameters (adapted from [10]) for simulation: $k_{el} = 0.21\ h^{-1}$, $V_d = 61.18$ ml, $V_m = 32.58$ mIU/ml/h, $K_m = 67.23$ mIU/ml

that $f(x)$ is strictly increasing with respect to x. Let $a = 4\frac{r}{k_{el}}K_m > 0$, then we obtain

$$C_\beta^\infty = \frac{1}{2}f\left(C_\beta - \frac{r}{k_{el}}\right) > \frac{1}{2}f\left(K_m - \frac{r}{k_{el}}\right) = K_m$$

since $C_\beta > K_m$□.

Appendix 2: Illustration of X_0 and Y_0 for different values of p_1, p_2, q_1 and q_2

In Fig. 5, we plot how parameters p_1, p_2, q_1 and q_2 change the appearance of X and Y functions in the first quadrant, where $p_1 + p_2 = 1$ and $q_1 + q_2 = 1$ are considered. As shown in Fig. 5a, when p_1 varies from a small value of 1/500 to a large value of 1/2, we observe that $X_0(s, p_1, p_2)$ tends to increase faster for a larger value of p_1, and when p_1 is close to unity, $X_0(s, p_1, p_2)$ is close to the identity line as $X_0(s, p_1, p_2) = s$. In Fig. 5b, $Y_0(s, q_1, q_2)$ shows a similar property as a faster increase of $Y_0(s, q_1, q_2)$ can be observed for a larger q_1. Meanwhile, the $Y(s, q_1, q_2)$ is also close to the identity line as $Y_0(s, q_1, q_2) = s$ when q_1 is close to unity. The range of $Y_0(s, q_1, q_2)$ is $(0, q_1/(q_1 + q_2))$ that depends on the choice of q_1 and q_2.

Appendix 3: Proof of Proposition 1

Proof (i) By checking the explicit expressions of C^∞ and C_β^∞, it is easy to see $C^\infty = 0$ and $C_\beta^\infty = C_\beta$ when $r = 0$.

(ii) If $C_\beta = \frac{r}{k_{el}}$, namely $r = k_{el}C_\beta = k_{e,tot}K_m$, then we have $C^\infty = C_\beta^\infty = \sqrt{\frac{k_{e,tot}}{k_{el}}}K_m$. If $C_\beta > \frac{r}{k_{el}}$, namely $r < k_{el}C_\beta$, then we obtain $C_\beta^\infty > C^\infty$. If $C_\beta < \frac{r}{k_{el}}$, we have $r < k_{el}C_\beta$ and $C_\beta^\infty < C^\infty$.

(iii) Consider the derivatives of C^∞ and C_β^∞ with respect to variable r. With straightforward calculations and denote $x = \frac{r}{k_{el}}$, we obtain

$$\frac{dC^\infty(r)}{dr} = \frac{K_m + C^\infty}{\sqrt{(C_\beta - x)^2 + 4K_m x}}\frac{1}{k_{el}} > 0$$

and

$$\frac{dC_\beta^\infty(r)}{dr} = \frac{K_m - C_\beta^\infty}{\sqrt{(C_\beta - x)^2 + 4K_m x}}\frac{1}{k_{el}} < 0$$

due to $K_m < C_\beta^\infty$ by Lemma 1. Therefore with respect to r, C^∞ is an increasing function and C_β^∞ is a decreasing function.

Now we consider the limit of C_β^∞ as r tends to infinity. Multiplying by

$$\sqrt{(C_\beta - \frac{r}{k_{el}})^2 + 4\frac{r}{k_{el}}K_m} - (C_\beta - \frac{r}{k_{el}})$$

at both the numerator and denominator for expression of C_β^∞ if we write C_β^∞ as $C_\beta^\infty/1$, we obtain

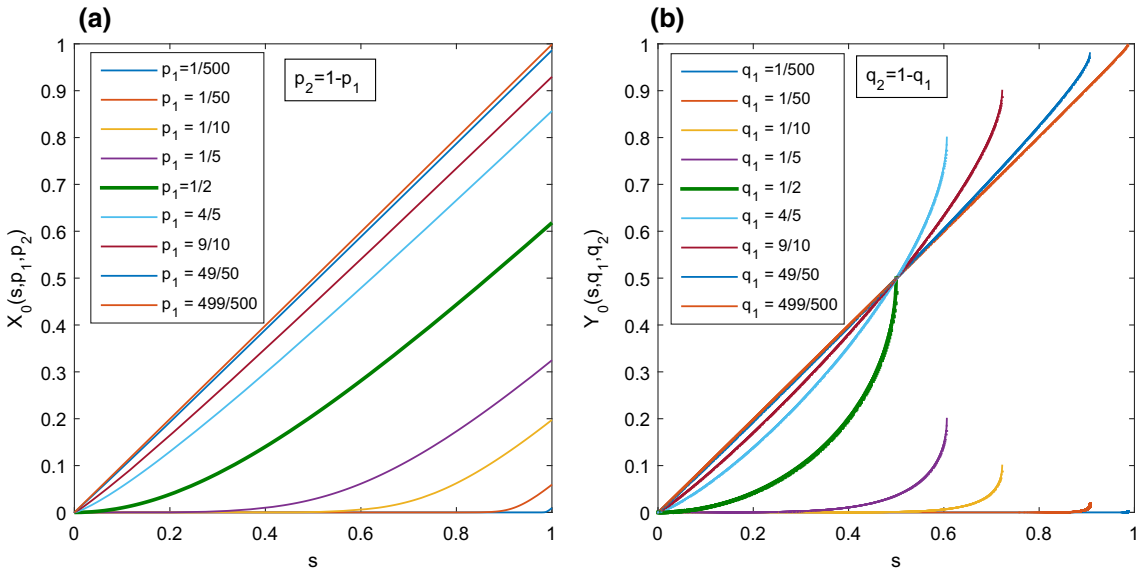

Fig. 5 Illustration of how parameters p_1, p_2, q_1 and q_2 affect the graphs of principal real branches X_0 and Y_0 transcendent functions in the first quadrant, where $p_1 + p_2 = q_1 + q_2 = 1$, $X_0 \in (0, \infty)$ for all $s > 0$ and $Y_0 \in (0, q_1) \subset (0, 1)$ for all $s \in (0, q_1^{q_1} q_2^{q_2}) \subset (0, 1)$

$$\lim_{r\to+\infty} C_\beta^\infty = \lim_{r\to+\infty} \frac{\frac{2}{k_{el}}K_m}{\sqrt{(\frac{C_\beta}{r}-\frac{1}{k_{el}})^2+4\frac{K_m}{k_{el}r}}-(\frac{C_\beta}{r}-\frac{1}{k_{el}})} = K_m.$$

$\lim_{r\to+\infty} C^\infty = +\infty$ is obvious. □

Appendix 4: Explicit solutions of one-compartment models with a single elimination pathway, linear or Michaelis–Menten, in the case of constant infusion

One-compartment pharmacokinetic model with a single linear elimination pathway for a constant infusion:

$$\begin{cases} C'(t) = f(t) - k_{el}C(t), t > 0 \\ C(0) = 0, \end{cases} \tag{25}$$

where $f(t)$ is given by Eq. (18). Its explicit solution is

$$C(t) = \begin{cases} \frac{D}{TV_d k_{el}}\left(1 - e^{-k_{el}t}\right), & 0 \le t \le T, \\ C(T)e^{-k_{el}(t-T)}, & t \ge T. \end{cases} \tag{26}$$

One-compartment pharmacokinetic model with a single Michaelis–Menten elimination pathway for a constant infusion:

$$\begin{cases} C'(t) = f(t) - \frac{V_m \cdot C(t)}{K_m + C(t)}, t > 0 \\ C(0) = 0, \end{cases} \tag{27}$$

where $f(t)$ is given by Eq. (18). Its explicit solution is

(i) If $0 \le t \le T$, we have

$$C(t) = \begin{cases} -K_m + \sqrt{K_m^2 + 2V_m K_m t}, & R = V_m V_d, \\ -\frac{DK_m}{D - TV_m V_d} - \frac{K_m TV_m V_d}{D - TV_m V_d} W\left(-1, -\frac{D}{TV_m V_d}\exp\left(-\frac{DK_m TV_d + (D - TV_m V_d)^2 t}{K_m V_m (TV_d)^2}\right)\right), & R > V_m V_d, \\ -\frac{DK_m}{D - TV_m V_d} - \frac{K_m TV_m V_d}{D - TV_m V_d} W\left(0, -\frac{D}{TV_m V_d}\exp\left(-\frac{DK_m TV_d + (D - TV_m V_d)^2 t}{K_m V_m (TV_d)^2}\right)\right), & R < V_m V_d. \end{cases} \tag{28}$$

(ii) If $t \ge T$, we have

$$C(t) = K_m \cdot W\left(0, \frac{C(T)}{K_m}\exp\left(\frac{C(T) - V_m \cdot (t - T)}{K_m}\right)\right). \tag{29}$$

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