Biomathematics:
A course on some applications of dynamical systems

Empirical pharmacokinetics

Anders Källén
MatematikCentrum
LTH
anderskallen@gmail.com
Introduction

In this chapter we will discuss how an externally given drug is handled by the body. We will start with a simple model which is much used in real life, after which we will discuss versions of more complicated models. We will end the discussion with a short alternative which builds on a probabilistic approach.

Concepts in modern pharmacokinetics

Consider the body to be a container into which drug is entered and from which it is eliminated. There are three fundamental functions we address:

\[ M(t) \]: The amount of drug in the body (can be measured in mole or as weight).

\[ a(t) \]: The rate with which drug is given to the body. The unit is amount per unit time, like mmol/h.

\[ e(t) \]: The rate with which drug is eliminated. The same unit as for \( a(t) \).

The fundamental mass balance equation is now

\[ M'(t) = a(t) - e(t). \]

The problem with this equation is that nothing in it can be directly measured. What we normally can measure is

\[ C(t) \]: The concentration of drug in the blood, or some of the blood components plasma or serum. In order to simplify the discussion we assume we measure in plasma.

\[ D \] The amount of drug given to the individual. In general that is not the same as the amount that actually enters the blood stream.

**Remark** There are exceptions: som drugs are measured in urine as well and some can be measured in the cerebrospinal fluid.

When the drug enters the body it first appear in the blood, from which it is distributed to other parts and eliminated from. There are two main elimination routes: either (1) the drug is metabolised in the liver to something else, or (2) it is excreted with the urine. Both of these can happen to a drug, and there are other ways out, but we ignore them.

The distribution and elimination processes are often simple in that what happens to a particular drug molecule is independent of other drug molecules. It does not have to be so – both can be involved in some capacity limited processes. A typical example is a drug that is broken down in the liver by a special enzyme, and this enzyme is relatively scarce. At best only a fixed amount of drug can then be metabolised per unit time, which means that the fate of a particular molecule is dependent on how many others are around.

We will focus our discussion around drugs that are of this type. They are said to follow a linear kinetic which is mathematically translated into a time homogenous, linear system.
Clearance

Our first assumption is that the elimination rate is proportional to the plasma concentration:

\[ e(t) = CL \cdot C(t). \]

The proportionality constant \( CL \) is called clearance and measure the rate with which plasma is cleared from the drug. Its unit is therefore volume per time unit, so clearance is a flow. The fundamental equation can now be written

\[ M'(t) = a(t) - CLC(t), \quad M(0) = 0. \]

If we integrate it, we see that (since \( M(\infty) = 0 \))

\[ CL = \frac{\int_{0}^{\infty} a(t) \, dt}{\int_{0}^{\infty} C(t) \, dt}. \]

The numerator is the total amount of drug that entered the body. When we take a tablet of a drug, not everything that is in the tablet will be absorbed by the body. We therefore introduce

\[ F = \text{fraction of dose that enters the body}, \]

so that

\[ CL = \frac{FD}{\int_{0}^{\infty} C(t) \, dt}. \]

where \( D \) is the dose given. The fraction \( F \) is of independent interest when we want to describe how the drug enters the body.

About giving a bolus dose

In order to know \( F \) we need to give the drug intravenously (which means \( F = 1 \)). That can only be done by a more or less slow infusion into the blood, but it is convenient to first discuss the theoretical case when

\[ M'(t) = -CL \cdot C(t), \quad M(0) = D. \]

The assumption here is that all drug is given instantaneously and also equilibrates in the blood in no time (in reality it would take a few circulations around the blood system for this to happen).

In this theoretical case the drug is in the blood from the start, distributed in a region of volume \( V_c \) (called the central volume and contains blood) – it is the volym that is in rapid diffusive equilibrium with the blood. With this assumption we have

\[ C(0) = \frac{D}{V_c}. \]

In real life it is impossible to measure \( V_c \), but from plasma concentration data we can have a guess about what \( C(0) \) was and use it to compute \( V_c \).

If we integrate the equation above we get (assuming \( M(\infty) = 0 \)) that

\[ M(t) = CL \int_{t}^{\infty} C(t) \, dt. \]
Remark We cannot assume that $M(t) = V_c C(t)$ for $t > 0$ because of distribution processes, as will be discussed soon.

MRT and terminal half life

As the drug circulates the body, it is also eliminated from it. Under normal circumstances the plasma concentration $C(t)$ more and more resemble an exponential function $C_0 e^{-\lambda_{el} t}$ after some time. We can see this in our data by plotting $\log C(t)$ versus $t$; for large $t$ the curve should approach a straight line. The number

$$t_{1/2} = \frac{\ln 2}{\lambda_{el}}$$

is called the terminal half life (and $\lambda_{el}$ the terminal elimination rate). If $t_{1/2}$ is large it might be a sign that the drug has problems returning to the blood from other parts of the body, a question we will return to.

But the terminal half life says nothing about how long we expect a drug molecule to remain in the body. To describe this we introduce a stochastic variable $T$ which is the time a single drug molecule spends in the body. Then we have

$$P(T > t) = \frac{M(t)}{D}$$

and the mean value of $T$ is given by

$$\int_0^\infty t \left(\frac{-M'(t)}{D}\right) dt = \frac{CL}{D} \int_0^\infty t C(t) dt.$$  

This number is called the Mean Residence Time for the drug, abbreviated MRT. If we use the formula for clearance above we find that

$$\text{MRT} = \frac{\int_0^\infty t C(t) dt}{\int_0^\infty C(t) dt}.$$

Remark The interpretation of MRT assumes a bolus dose. However, we can compute the number from any plasma concentration curve, which is also done. We will soon see why.

Volumes

In order to describe how a drug is distributed in the body it is customary nowadays to use various volume concepts. For this we introduce a function $V(t)$ by the relation

$$M(t) = V(t) C(t).$$

The notation is somewhat misleading. If $C(t)$ is the concentration everywhere in the body this would be a well-defined volume. But $C(t)$ is the concentration i plasma, which need
PK-parameter notation formula

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Notation</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal half life</td>
<td>$t_{1/2}$</td>
<td>$\ln(2)/\lambda_{el}$</td>
</tr>
<tr>
<td>Clearance</td>
<td>$CL$</td>
<td>$D/\int_0^\infty C(t) , dt$</td>
</tr>
<tr>
<td>Mean Residence Time</td>
<td>MRT</td>
<td>$\int_0^\infty tC(t) , dt/\int_0^\infty C(t) , dt$</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>$V_d$</td>
<td>$CL/\lambda_{el}$</td>
</tr>
<tr>
<td>Steady state volume</td>
<td>$V_{ss}$</td>
<td>$CL\cdot MRT$</td>
</tr>
</tbody>
</table>

Table 1: Basic PK-parametrar describing distribution and elimination

not be the concentration anywhere else in the body. So even though $V(t)$ is measured in volume units, it is nothing more than a proportionality factor.

For a bolus dose we now have that

$$V(t) = \frac{CL \int_t^\infty C(s) \, ds}{C(t)},$$

which in particular means that

$$V(0) = \frac{D}{C(0)} = V_c.$$

For large $t$, where we can approximate $C(t)$ with $C_0 e^{-\lambda_{el} t}$, we get

$$V(t) \approx \frac{CLC_0 e^{-\lambda_{el} t} / \lambda_{el}}{C_0 e^{-\lambda_{el} t}} = \frac{CL}{\lambda_{el}}.$$

This volume is called the volume of distribution of the drug and denoted $V_d$.

There is also another volume, much used in practice. It assumes a constant infusion, i.e. $a(t) = R$, which gives us the differential equation

$$M'(t) = R - CL \cdot C(t).$$

Its equilibrium, $C(t) = C_{ss}$, satisfies $R = CL \cdot C_{ss}$. The amount of drug in the body is then $M_{ss} = R \cdot MRT$, and the corresponding volume should be

$$V_{ss} = \frac{M_{ss}}{C_{ss}} = CL \cdot MRT.$$

This volume is called the steady state volume of the drug.

**Polyexponentials**

The plasma concentration for a drug with linear kinetics is usually well approximated by polyexponential function:

$$C(t) = \sum_{k=1}^c A_k e^{-\lambda_k t}.$$

However, all constant here, including the number of terms, $c$, are unknown. What is done practically is to choose the smallest $c$ for which we can get a reasonable fit to our
data. The exact values of the parameters are not important, only the fit to data. This is because our PK-parameters are all computed from only three entities:

\[ \lambda_e, \quad \int_0^\infty C(t) \, dt, \quad \int_0^\infty tC(t) \, dt. \]

In the case of a polyexponential function we have that

\[ \int_0^\infty C(t) \, dt = \sum_{k=1}^c \frac{A_k}{\lambda_k}, \quad \int_0^\infty tC(t) \, dt = \sum_{k=1}^c \frac{A_k}{\lambda_k^2}. \]

**Example 1** The bolus dose \( D = 10 \text{ mg} \) of a drug was given to a patient and plasma concentrations measured. It turned out that the following function

\[ C(t) = 0.38e^{-1.64t} + 0.18e^{-0.182t} \]

fit the data well. The concentration unit is \( \text{mg/ℓ} \) and time unit is hours, \( h \). From this information we will now computed the basic PK-parameters.

First we note that \( C(0) = 0.38 + 0.18 = 0.56 \), which means that \( V_c = D/C(0) = 17.9 \ell \). The terminal elimination rate is seen to be 0.182, so the terminal half life is \( \ln(2)/0.182 = 3.8 \, h \). Next we compute

\[ \int_0^\infty C(t) \, dt = 1.22, \quad \int_0^\infty tC(t) \, dt = 5.57, \]

from which we see that \( CL = 10/1.22 = 8.20 \ell/h \) and \( MRT = 5.57/1.22 = 4.6 \, h \). From that we finally get \( V_{ss} = 8.20 \cdot 4.57 = 37.5 \ell \) and \( V_d = 8.20/0.182 = 45.1 \ell \).

The plot above shows the graph of \( V(t) \). It starts at \( V_c = 17.9 \) and grows asymptotically to \( V_d \).

**Remark** It is not necessary to fit a polyexponential to concentration data in order to obtain the PK parameters. Instead one can use some simple numerical integration method to estimate the two integrals.
Absorption

Consider a drug for which the kinetics is linear and let

\[ G(t) = \text{plasma concentration after a unit bolus dose of the drug.} \]

If we give dose \( D \) as a bolus, the plasma concentration is \( DG(t) \). If we give dose \( D \) at time \( s \) the plasma concentration at time \( t > s \) equals \( DG(t - s) \).

During a small time interval \([s, s + \Delta s]\) the model assumes that approximately \( a(s)\Delta s \) drug enter the body, and these molecules contribute the amount \( a(s)\Delta sG(t - s) \) to the plasma concentration at time \( t > s \). We get the total plasma concentration at time \( t \) by taking the sum of such contributions:

\[ C(t) = \int_0^t G(t - s)a(s)\, ds. \]

Convolution

Let us introduce the (temporary) notations:

\[ I(f) = \int_0^\infty f(t)\, dt, \quad E(f) = \int_0^\infty tf(t)\, dt. \]

We always assume that \( f \geq 0 \) and that all integrals converge. In the field of pharmacokinetics the number \( I(f) \) is called the area under the curve and usually denoted AUC, whereas \( E(f) \) is called the area under the moment curve and denoted AUMC.

If \( f, g \) are two functions, defined for \( t \geq 0 \), we call the expression

\[ (f \ast g)(t) = \int_0^t f(t - s)g(s)\, ds \]

the convolution of \( f \) and \( g \). It is commutative and associative, i.e. we have that

\[ (f \ast g)(t) = (g \ast f)(t), \quad ((f \ast g) \ast h)(t) = (f \ast (g \ast h))(t). \]

**Example 2** The convolution of two exponential functions is useful in our context:

\[ e^{-at} \ast e^{-bt} = e^{-at} \int_0^t e^{(a-b)s}\, ds = \frac{1}{a - b}(e^{-bt} - e^{-at}) \]

if \( a \neq b \), whereas

\[ e^{-at} \ast e^{-at} = te^{-at}. \]

Two important observations for the convolution are that

\[ I(f \ast g) = I(f)I(g), \quad E(f \ast g) = I(f)E(g) + E(f)I(g). \]
To proofs are a matter of switching order of integration in a double integral. Let us only do the first:

\[
I(f \ast g) = \int_0^\infty \int_0^t f(t-s)g(s)dsdt = \int_0^\infty (\int_0^\infty f(t-s)dt)g(s)ds = \\
(\int_0^\infty f(t)dt)(\int_0^\infty g(s)ds) = I(f)I(g).
\]

The other is left as an exercise. As a consequence we have that

\[
\frac{E(f \ast g)}{I(f \ast g)} = \frac{E(f)}{I(f)} + \frac{E(g)}{I(g)}.
\]

**Mean Absorption Time (MAT)**

To summarize, we have that

\[
C(t) = (a \ast G)(t)
\]

and that \(I(C) = I(a)I(G)\), i.e.

\[
FD = \frac{\int_0^\infty C(t) dt}{\int_0^\infty G(t) dt}
\]

Moreover, we have that

\[
\frac{E(C)}{I(C)} = \frac{E(G)}{I(G)} + \frac{E(a)}{I(a)}
\]

Here

\[
\frac{E(C)}{I(C)} = MRT_{niv}, \quad \frac{E(G)}{I(G)} = MRT_{iv}
\]

where the first identity refers to MRT computed with the plasma concentrations at hand, and the second the MRT we obtain after a bolus dose. The remaining entity,

\[
MAT = \frac{\int_0^\infty ta(t) dt}{\int_0^\infty a(t) dt}
\]

can be interpreted as the average time it takes for a drug molecule to be taken up by the body.

We will now have a closer look at two important cases.

**Intravascular infusion**

This is a situation in which we know \(a(t)\) completely (i.e. \(F = 1\)). We give an infusion of the drug with a constant rate \(R\) mg/h and do this for \(\tau\) hours. This means that

\[
a(t) = \begin{cases} R & t \leq \tau \\ 0 & t > \tau. \end{cases}
\]
As a consequence (unsurprisingly)

\[
\text{MAT} = \frac{\int_0^\tau tR \, dt}{\int_0^\tau R \, dt} = \frac{\tau}{2}.
\]

From the corresponding plasma concentration we can in principle reconstruct \(G(t)\). We do not discuss this further, only note the important consequence

\[
\text{MRT}_{iv} = \text{MRT}_{inf} - \frac{\tau}{2}.
\]

**Extravascular administration**

Extravascular administration refers to all ways of giving a drug in such a way that it does not enter the blood directly. It can refer to tablets that should be swallowed, an aerosol to be inhaled or a suppository with anal administration. The primary problem in these cases is that we do not know the amount of drug that actually enters the blood. The process can be rather complex, in which case one can try to reconstruct it by first determining \(C(t)\) and \(G(t)\) and solve for \(a(t)\) from the convolution equation.

In many cases we might not have the data (or even the ambition) to derive \(a(t)\) exactly, but a simple model might be sufficient. Consider a tablet which is in the intestine and let \(D(t)\) be the amount of drug still not absorbed at time \(t\). A simple model is that

\[
D'(t) = -k_a D(t), \quad D(0) = D.
\]

If \(F\) is the fraction that is taken up (of total dose) by the body, this means that we assume

\[
a(t) = -FD'(t) = FDk_a e^{-k_at}.
\]

A short computation shows that in this case we have that

\[
\text{MAT} = \frac{1}{k_a}.
\]

**Modeling the distribution process**

So far we have described how a drug is distributed in the body in terms of volumes. Much because these can be computed directly from measured plasma concentrations. But there is a more physiological alternative that we now will have a closer look into.

The basis for it is that we divide the body into two spaces, the definition of which depends on the physiological properties of the drug.

**The central space:** This space is the space defined earlier with volume \(V_c\), which is at least 5 liter (the volume of the blood). But it can be much larger. Let the amount of drug in the central space be denoted \(M_c(t) = V_c C(t)\).

**The periferal space** This is the rest of those parts of the body the drug can access. This space may be very heterogeneous and in general we cannot speak of a concentration in this space. The amount drug in this space is denoted \(M_p(t)\).
We note that $M(t) = M_c(t) + M_p(t)$.

Mass balance now shows that after a bolus dose we have that

$$
\begin{align*}
M'_c(t) &= k_{pc}(t) - k_{cp}(t) - CL \cdot C(t), \quad M_c(0) = D, \\
M'_p(t) &= k_{cp}(t) - k_{pc}(t), \quad M_p(0) = 0.
\end{align*}
$$

Here $k_{xy}(t)$ denote the transit rate from $x$ to $y$ and we have made one additional assumption, namely that the drug is eliminated from the central space. Note that $M'_c(t) = V_cC'(t)$, but that we do not have a similar expression for $M'_p(t)$.

Our next, general, assumption is that $k_{cp}(t) = CL_d \cdot C(t)$, where $CL_d$ is a constant with the same unit as clearance. This leaves us with

$$
\begin{align*}
V_cC'(t) &= k_{pc}(t) - (CL_d + CL)C(t), \quad C(0) = D/V_c \\
M'_p(t) &= CL_dC(t) - k_{pc}(t), \quad M_p(0) = 0.
\end{align*}
$$

We will now discuss how we can proceed from here.

Two compartment models

With this model we assume that the peripheral space is a compartment in which the drug is well mixed. Its volume we denote $V_p$ and its concentration $C_p(t)$, so that $M_p(t) = V_pC_p(t)$. We also assume that $k_{pc}(t) = B \cdot C_p(t)$ for some constant $B$. This gives us a new system of equations, which is often expressed in terms of $M_c(t)$ and $M_p(t)$, instead of the corresponding concentrations:

$$
\begin{align*}
M'_c(t) &= k_{pc}M_p(t) - (k_{cp} + k_{ce})M_c(t), \quad M_c(0) = D \\
M'_p(t) &= k_{cp}M_c(t) - k_{pc}M_p(t), \quad M_p(0) = 0,
\end{align*}
$$

where

$$
k_{cp} = \frac{CL_d}{V_c}, \quad k_{pc} = \frac{B}{V_p}, \quad k_{ce} = \frac{CL}{V_c},$$

all are rate constants (unit 1/time). A graphical illustration is shown in Figure 1.

In a coming chapter we will see that such a model lead to a biexponential plasma concentration profile.

From this we get that the volume function is

$$
V(t) = \frac{M_c(t) + M_p(t)}{C(t)} = V_c + \frac{C_p(t)}{C(t)} V_p.
$$

The true volume is $V_c + V_p$, whereas $V(t)$ tells us is what the volume should be if the concentration in the whole body is $C(t)$.

Later we will investigate the relation between the so-called macro constants in the expression

$$
C(t) = A_1e^{-\lambda_1 t} + A_2e^{-\lambda_2 t}
$$

and the rate constants $k_{pc}$, $k_{cp}$ och $k_{ce}$, which are called micro constants. We illustrate with an example.
Example 3 In our previous example it can (and will) be shown that
\[ k_{pc} = 0.65, \quad k_{cp} = 0.72, \quad k_{ce} = 0.46. \]

From this we can compute our two clearance terms
\[ CL_d = k_{cp}V_c = 0.72 \cdot 17.9 = 12.8, \quad CL_c = k_{ce}V_c = 0.46 \cdot 17.9 = 8.2. \]

Another observation is this: We found earlier that the terminal elimination rate is 0.182 per hour, but the “true” elimination rate is 0.46 per hour. This illustrates that the terminal elimination rate observed from the plasma profile is a net effect of elimination and influx from peripheral parts.

A convolution-differential equation

Let us return to the two compartment model. The second equation in it has the solution
\[ M_p(t) = k_{cp} \int_0^t e^{-k_{pc}(t-s)} M_c(s) ds. \]

If we therefore introduce the function
\[ h(t) = k_{cp}k_{pc}e^{-k_{pc}t} \]
we have that
\[ k_{pc}M_p(t) = (h \ast M_c)(t), \]
from which we get the single equation
\[ M'_c(t) = (h \ast M_c)(t) - (k_{cp} + k_{ce})M_c(t), \quad M_c(0) = D. \]

Finally, with \( M_c(t) = V_cC(t) \) this can be rewritten as
\[ V_cC'(t) = CL_d(h \ast C)(t) - (CL_d + CL_c)C(t), \quad C(0) = D/V_c, \]
where
\[ h(t) = k_{pc}e^{-k_{pc}t} \]
is the probability density for an exponential distribution with expected value $1/k_{pc}$.

This gives us a clue to how we can generalise to more general situations. We simply assume that Equation 1 is valid for some function $h(t)$, the interpretation of which is as a probability density for the stochastic variable that describes the time a molecule which has left the blood stream (but is not eliminated) to return to it. The problem with the model is that it is in general difficult to decide $h(t)$, but on theoretical grounds it should (for drugs with linear kinetics) be a polyexponential function. We will not discuss this any further.

**Exercises**

**Exercise 1** Phenytoin sodium (300 mg) was administered as an intravenous bolus dose to a patient with epilepsy. The plasma concentration of phenytoin was then monitored to determine the pharmacokinetic behaviour of the drug and to help establish an optimal oral dosage regimen for this patient. The results obtained were as follows:

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C$ (µg/mL)</td>
<td>4.7</td>
<td>3.65</td>
<td>3.05</td>
<td>2.40</td>
<td>1.45</td>
<td>0.93</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Compute the pharmacokinetic parameters for phenytoin for this patient.

**Exercise 2** The same dose of phenytoin was subsequently given to the same patient, but now as an oral dose (tablet). Compute the pharmacokinetic parameters from the following plasma concentrations recorded.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>1</th>
<th>2</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C$ (µg/mL)</td>
<td>0.65</td>
<td>2.00</td>
<td>3.55</td>
<td>4.05</td>
<td>3.60</td>
<td>3.20</td>
<td>2.00</td>
<td>1.20</td>
<td>0.75</td>
</tr>
</tbody>
</table>

**Exercise 3** A patient was given an intravenous injection of 50 mg of pethidine for post-operative pain. The kinetics of this drug are obviously of importance since pain relief is closely related to plasma concentration. The following data were obtained.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>2.5</th>
<th>3</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C$ (µg/mL)</td>
<td>0.42</td>
<td>0.29</td>
<td>0.22</td>
<td>0.18</td>
<td>0.15</td>
<td>0.125</td>
<td>0.096</td>
<td>0.06</td>
<td>0.038</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Determine an appropriate compartment model for pethidine in this patient and use it to determine the corresponding pharmacokinetic parameters.
Answers to exercises

Exercise 1 A log concentration vs. time plot shows that the data follow a straight line, and a linear regression estimates it to \( \ln C = 1.774 - 0.0458t \). We therefore compute the PK-parameters for \( C(t) = 5.89 e^{-0.0458t} \). We get \( t_{1/2} = 15.2 \) h, \( CL = 2.33 \) L/h, \( V_c = V_d = V_{ss} = 50.9 \) L, MRT = 21.9 h.

Exercise 2 We assume that \( a(t) = FDk_a e^{-k_a t} \). It follows that \( C(t) = A(e^{-k_a t} - e^{-k_{cl} t}) \) for some constant \( A \). A nonlinear least squares estimation gives \( A = 9.45, k_{cl} = 0.0515 \) and \( k_a = 0.177 \) (note there is a small difference in \( k_{cl} \) compared to the previous exercise.) The AUC is now 131.5, whereas it was 128.8 in the previous exercise. From that we get an estimate of \( F \) to 1.02. One might alternatively want to fit the model with \( k_{cl} \) from the previous exercise.

Exercise 3 A plot of the data indicates a two compartment model with a bolus dose, so we fit \( C(t) = A e^{-at} + B e^{-bt} \) to the data and get the estimates \( A = 0.412, B = 0.251, a = 1.476, b = 0.238 \). For the basic PK parameters we find that \( k_{cl} = 0.238 \) h\(^{-1}\), so \( t_{1/2} = 2.9 \) h. Furthermore, \( CL = 37.6 \) L/h, MRT = 3.46 h, \( V_c = 75.4, V_d = 157.6, V_{ss} = 129.9 \) L.