Title

Estimating a drug's elimination rate-constant or half-life from a single blood sample: a practical approach with particular benefits for critically ill/vulnerable patients.

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Abstract

In this paper we present a mathematical solution that allows the elimination rate-constant or half life of a drug to be estimated from a *single* blood drug measurement. This is of great utility in clinical areas involving care of criticallly ill or vulnerable patients, where providing more than one blood sample can involve significant risks. The calculations used in our approach, based solely on a single sample, do not require complex pharmacokinetic software, but instead can be simply performed at the patient's bedside using standard personal computing tools. The proposed method allows a personalised estimate of the drug's half life, which is preferable to using population averages, or using estimates based on proxy markers of lagging organ function, which are both indirect and generally inaccurate for a patient with confounding factors.

Introduction

Pharmacokinetics is the study of how drugs are absorbed, distributed, metabolised, and eliminated from the human body. It is principally a mathematical subject that involves the development of models that describe the way the concentration of a drug in the blood changes with time. When applied clinically, pharmacokinetics allows clinicians to devise dosing regimens that ensure blood (or, more precisely, blood plasma) concentrations of a drug are maintained within the therapeutic window.

A pharmacokinetic parameter of practical utility to clinicians is the elimination rate-constant, k. This is the rate at which a given drug is eliminated from the blood. Closely related to the elimination constant is the drug's half-life, $t_{1/2}$, which is the time it takes for a drug's plasma concentration to fall to half its initial value. The drug's half-life is given by $t_{1/2} = \ln(2)/k$, where $\ln(2) \approx 0.693$ is the natural logarithm of 2. In what follows, we shall refer solely to the elimination elimination rate-constant, k, rather than the half-life, $t_{1/2}$, which contains identical information.

The elimination rate constant, *k*, can be used, for example, to directly determine the time it takes the plasma concentration of a drug to fall from one given value to another value. In the case of a drug overdose for example, *k* can be used to determine when the concentration of a drug will fall out of the toxic range. Knowledge of *k* can also be used to determine how long it will take for the plasma concentration to reach a therapeutic level during initial dosing, thereby

providing information to clinicans and patients about when they may expect to see a beneficial response to a drug. Other clinically useful parameters are related to the elimination rate constant, *k*. For example, a drug's clearance, Cl, is the product of k and the apparent volume of distribution, V. The clearance can be used to calculate maintenance doses and dosage intervals for any drug, but is routinely used to tailor doses for patients taking drugs of the highest level of risk, due to their toxicity profile. These include established drugs such as digoxin, vancomycin, gentamicin and theophylline. However, application to other drug classes such as sedatives, analgesics, anaesthetics and biological therapies is also useful in certain clinical scenarios. It is therefore clear that an accurate knowledge of k (or equivalently $t_{1/2}$) is of clinical importance and, when used in specific cases, can increase the chances of a safe and effective treatment.

Estimates of k can be obtained directly from the literature for a range of drugs. However, these have typically been derived from large population datasets, and an individual's 'true' (or personal) value can deviate substantially from such estimates. For example, in one study involving infusion of digoxin to healthy volunteers, the measured half-life of the drug ranged from 33.2 to 51.6 hours, with a coefficient of variation of 16% [1]. Generally, there is appreciable inter- and intra- patient variability in the many physiological, environmental, pathological and genetic factors that determine the elimination rate constant, *k*. For example, smoking can decrease the half-life of theophylline by a factor of 0.64 [2]. Even meat cooked on charcoal can increase theophylline clearance [3]. Genetic polymorphisms in mixed function oxidases can also lead to high variability in the clearance of warfarin, another high risk drug [4].

Thus for a specific drug, in a particular individual, their personal k can be appreciably different from the value quoted in the literature.

There are a number of ways to obtain the true k for an individual patient, but these typically involve taking multiple plasma samples at accurately recorded times. This is seldom feasible in a clinical setting, where taking blood samples: (i) carry risks to both the patient and practitioner, (ii) are expensive, and (iii) are resource intensive. Importantly, in some vulnerable patient groups, for example premature neonates, it is simply *not possible* to take sufficient (i.e., multiple) quantities of blood for a complete analysis. As a consequence, researchers have developed models which incorporate physiological measurements from an individual patient (e.g. creatinine clearance, ideal body weight) to provide more accurate, individualised estimates of k, without the need of multiple blood samples. However, this approach still carries a potentially significant degree of error in the estimate of k, and can lead to the design of an inappropriate dosage regimen, with concomitant risks. Furthermore, there are few examples of models, that are used routinely in clinical practice, that are able to account for more subtle factors that effect drug elimination, such as drug interactions, or genetic polymorphisms.

A viable approach, which may provide more accurate estimates of k, compared to models built using physiological surrogates alone, is a *personalised* approach based on a *single* plasma drug concentration measurement of an individual patient. Despite only a single measurement, the data it carries provides key information about the pharmacokinetics of the drug in the

particular patient, and may thus improve the accuracy of the estimate. Current pharmacokinetic models however, only allow for the determination of k from a single measurement under two circumstances: (i) when a single plasma concentration is taken at steady state during drug delivery by continuous infusion, or (ii) when a single trough plasma concentration is taken *immediately* prior to the next scheduled dose, for a drug delivered by intermittent dosing that has reached steady state [4]. These pharmacokinetic approaches thus have strong limitations on when a single plasma concentration measurement can be used to estimate k.

In this paper, we set out a mathematical approach which addresses the problem of how a single plasma drug concentration measurement can be used to determine an individual patient's elimination constant, k, with the advantages listed above. With this mathematical approach, we are able to expand the number of scenarios for which data, from a single plasma drug concentration measurement, can be used to predict k in patients. These scenarios include estimating k from a single plasma concentration that is taken:

1. at any time post drug-administration (i.e. during the exponential elimination period), assuming the drug concentration reached steady state during drug administration
2. at any time during the initial drug-administration period (up to, and including steady state)
3. at any time post drug administration, during an exponential decay period, *without* assuming the drug concentration had reached steady state.

We will show how this mathematical approach is compatible with previous estimates of k (based on multiple measurements of plasma concentration) that have been calculated in published studies. We discuss how the proposed approach could be of practical benefit to patients in both a clinical setting, and in clinical trails.

2. Results

2.1 Model derivation

2.1.1 Scenario 1: estimating k from a single plasma sample taken at any time post drug administration, assuming plasma drug concentration had reached steady state

Let us consider a drug, say X, that is administered to a patient by continuous infusion. If the drug follows a first order elimination process after infusion has stopped, then the plasma concentration of X will fall exponentially (see red part of curve, Figure 1).

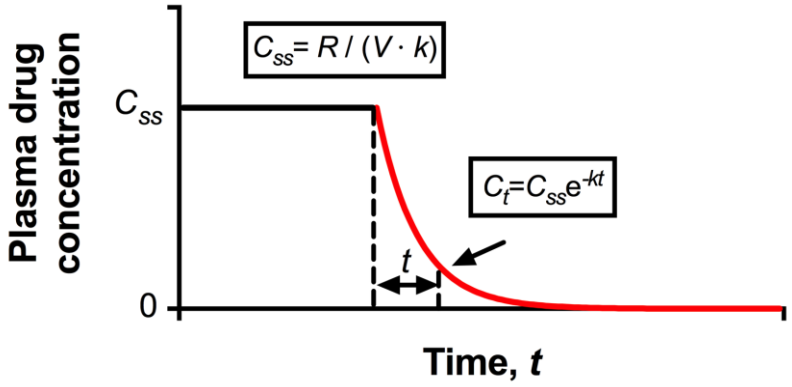


Figure 1

Figure 1 Caption: Relationship between plasma concentration and time during the continuous infusion, steady-state period (black line), and the post drug-administration exponential decay period (red line). A plasma concentration measurement that is taken at any time *t* after drug administration has ceased (red line), written C_t, can be used to predict the elimination rate constant, k, using Eq. (4). In the figure, we have *R* = dose rate, *V* = apparent volume of distribution, *k* = elimination rate constant, *t* = time since administration ceased, and C_{ss} = plasma drug concentration at steady state.

To derive our results, let us first consider the case where there is no drug administration occurring. With the initial plasma concentration at time 0 denoted by C_0, and the plasma concentration at a later time, t, denoted by C_t, the rate at which the plasma concentration falls is determined by k according to the equation

$$C_t = C_0 e^{-kt}. \tag{1}$$

We shall refer to C_0 as the reference or initial value.

To estimate k, knowledge of the plasma concentrations are required at at least two times. Indeed, when only two plasma concentrations are available, say at times 0 and t, taking the natural logarithm of Eq. (1) and rearranging the result allows determination of k, as $k = -\ln(C_t/C_0)/t$. Alternatively, if multiple plasma concentrations are available over the drug

elimination period, then a linear function of *t* can fitted to a $\ln(C_t)$ vs. *t* plot, to obtain an estimate of k.

However, our objective is to estimate k from knowledge of only a *single*, post administration plasma drug concentration value at time t (namely C_t), rather than carrying out any curve fitting or other procedures. Our objective can be achieved under the two conditions: (i) that drug administration occurred for times prior to time 0 and was stopped at time 0, (ii) the plasma concentration of the drug achieved a steady state value of C_{ss} prior to time 0, and hence at time 0, the plasma concentration was the steady state value, C_{ss}. Then the plasma concentration of drug X at any positive time t (written C_t) follows from Eq. (1) when the reference (or initial) value C_0 is replaced by C_{ss}. This leads to

$$C_t = C_{ss}e^{-kt}. \tag{2}$$

Importantly, C_{ss} is not an unknown quantity but is related to the following data: the rate of drug administration (R), the apparent volume of distribution (V), and the elimination rate constant (k). See Table 1 for a list of key **pharmacokinetic parameters we use in this work**. The balance between drug elimination and drug administration in the steady state leads to $R/V = kC_{ss}$ which is an equation that yields a steady state plasma concentration of *X* of

$$C_{ss} = \frac{R}{Vk} \tag{3}$$

Parameter	Description	Units
k	Elimination rate constant	hr^{-1}
V	Apparent volume of distribution	L
R	Dose rate	mg/hr
C_{ss}	Plasma drug concentration at steady state	mg/L
C_t	Plasma drug concentration at time t	mg/L
t	Time since drug administration stopped / started	hr
t_0*	Duration of infusion	hr
t_1*	Time since drug administration stopped	hr

Table 1. Key pharmacokinetic parameters. The starred times (*) are used in Eq. (7).

Equation (3) allows Eq. (2) to be written as $\frac{Rt}{VC_t} = kte^{kt}$, which takes the form $y = xe^x$ and is an equation that does not have an elementary solution for x. However such an equation can be solved in terms of a special function, known as the Lambert W function, whose properties are fully known, with the solution of $y = xe^x$ given by $x = W(y)$ [1]. Using the Lambert W function allows the equation $\frac{Rt}{VC_t} = kte^{kt}$ to be solved for k, with the following result, for the particular scenario considered:

$$k = \frac{1}{t} W\left(\frac{Rt}{VC_t}\right). \quad (4)$$

This[1] is an explicit result for k, for a drug, in an individual patient, in terms of the known parameters V and R, and the single measured value of the plasma concentration of the drug at time t, namely C_t.

While the right-hand-side of Eq. (4) *appears* to be time-dependent, we note that as long as C_t has the exponential form in Eq. (2), the value of *k* predicted by Eq. (4) is a constant, independent of the time, *t*. Results analogous to Eq. (4), that we shall present later, also have the time appearing on the right-hand-side of the equation, but again yield time-independent values of *k*.

[1] There are implementations of the Lambert W function in many numerical software packages, such as Maple, Mathematica, Matlab and *R*. In addition, in Eq. (5.9) in the paper by Corless *et. al.*, a straightforward and rapidly converging iterative method is given to determine the value of the Lambert W function. Using this method in Matlab, we found that starting with the initial value $w_0 = 0$ typically required less than 10 iterations to obtain a result that is accurate to machine precision ($O(10^{-16})$).

2.1.2 Scenario 2: estimating k from a single plasma sample taken during the initial drug administration period

Let us now consider the plasma concentration of drug X in a patient during an infusion of the drug, which started at time 0. During the initial dosing period, the plasma concentration increases from 0, at time 0, towards the steady state concentration C_{ss} (Eq. (3)) according to the equation

$$C_t = C_{ss}(1 - e^{-kt}). \quad (5)$$

This equation allows the plasma concentration at any time t since drug administration commenced, namely C_t, to be predicted from joint knowledge of k and the steady state plasma drug concentration. An illustration of the behaviour of the concentration of drug X with time is given in Figure 2.

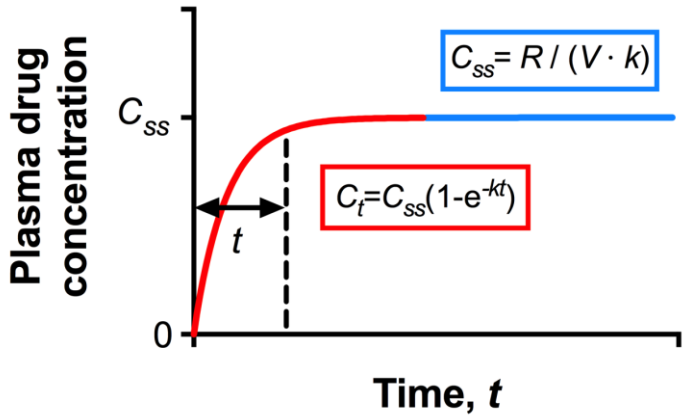


Figure 2

Figure 2 Caption: Relationship between plasma concentration and time during the initial drug-administration period up to steady-state being reached. A plasma concentration, which is taken at any time during drug administration (red line), and written C_t, can be used to predict k using Eq. (6). The blue line shows the steady state concentration. In the figure, we have *R* = dose rate, *V* = apparent volume of distribution, *k* = elimination rate constant, *t* = time since administration ceased, and C_{ss} = plasma drug concentration at steady state.

In Appendix A we show that Eq. (5) allows determination of k from knowledge of only a single plasma concentration at an arbitrary time, t, since drug commencement, namely C_t. The result for k is again expressed in terms of the rate of drug administration, R, the apparent volume of distribution, V, and the Lambert W function:

$$k = \frac{R}{VC_t} + \frac{1}{t} W\left(-\frac{Rt}{VC_t} e^{-\frac{Rt}{VC_t}}\right). \quad (6)$$

2.1.3 Scenario 3: estimating k from a single plasma sample taken at any time post drug administration, *without* assuming plasma drug concentration had reached steady state

In the first scenario (above), we considered a dosing regimen where, after steady-state had been reached, dosing was ceased, and the plasma concentration of drug X subsequently declined exponentially with time. We saw how a plasma sample taken during this period of exponential decay could then be used to estimate k using the Lambert W function, along with the parameters R and V. But what if steady-state had not been reached?

For the purpose of addressing this particular problem, which we term Scenario 3, we will assume that: (i) the infusion of drug X started at time 0 and lasted for a time interval of t_1, at which time drug administration *ceased*; (ii) after a *further* time-interval of t_0, i.e., *post drug administration*, a single plasma sample was taken. Thus the sample was actually taken at time $t_1 + t_0$ after initial drug commencement - see Figure 3.

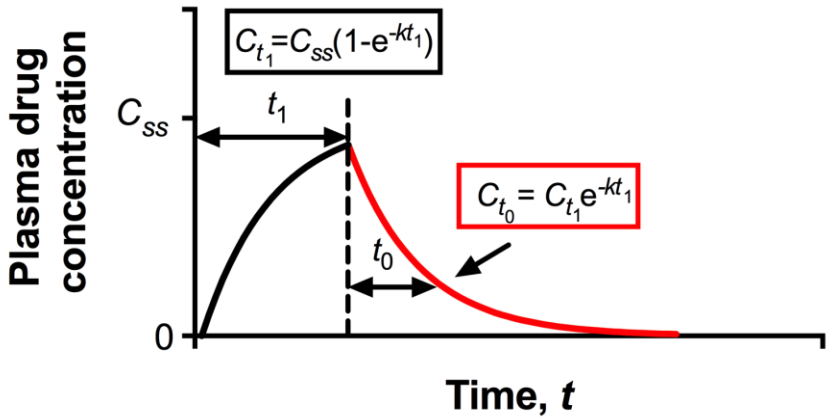


Figure 3

Figure 3 Caption: Estimating k from a post administration plasma drug concentration assuming the plasma concentration has *not* reached steady state. In this scenario, drug infusion took place from time 0 to time t_1 (black line) and steady state was not reached by the time infusion of the drug ceased (time t_1). A concentration measurement was made a time t_0 after cessation of drug infusion (red line), with value C_{t_1}, and this can be used to predict k using Eq. (7). In the figure, *k* = elimination rate constant, t_1 = duration of infusion, t_0 = time since infusion stopped, C_{t_1} = plasma drug concentration at time infusion stopped, C_{t_0} = plasma drug concentration at a time t_0 after infusion stopped.

We write C_{t_0} for the measured plasma concentration of the sample taken after infusion cessation. We can use similar reasoning to that used in the first two scenarios, as explained in Appendix B and illustrated in Figure 3, to determine a formula for k. In particular, in Appendix B we show that k can be expressed in terms of a function of two variables T_0 and T_1, written $K(T_0, T_1)$, according to

$$k = \frac{R}{C_{t_0}V} K\left(\frac{Rt_0}{C_{t_0}V}, \frac{Rt_1}{C_{t_0}V}\right) \tag{7}$$

where $K \equiv K(T_0, T_1)$ obeys the non-linear equation $1 = (1 - e^{-KT_1})e^{-KT_0}/K$.

Unlike the previous scenarios, an exact result for k for Scenario 3 cannot generally be found. However, a *numerical* value for k may be straightforwardly obtained. The numerical method to find k is: (i) first evaluate the quantities $T_0 = \frac{Rt_0}{C_{t_0}V}$ and $T_1 = \frac{Rt_1}{C_{t_0}V}$; (ii) for these values of T_0 and T_1, determine the value of $K(T_0, T_1)$ by numerically solving the equation $1 = (1 - e^{-KT_1})e^{-KT_0}/K$ for K (see Appendix B for a method of solution); (iii) by Eq. (7) the value of k follows as $\frac{R}{C_{t_0}V}$ times the numerical value of K found. In Table 2, we give numerical results for the function $K(T_0, T_1)$, that appears in Eq. (7), for a range of values of T_0 and T_1.

T_0	T_1	$K(T_0, T_1)$
0.2	1.2	0.232
	2.0	0.632
	5.0	0.833
	10.0	0.844
	50.0	0.845
1.0	1.2	0.114
	2.0	0.357
	5.0	0.543
	10.0	0.566
	50.0	0.567
5.0	1.2	0.033
	2.0	0.116
	5.0	0.221
	10.0	0.256
	50.0	0.265
10.0	1.2	0.017
	2.0	0.063
	5.0	0.130
	10.0	0.161
	50.0	0.175
50.0	1.2	0.004
	2.0	0.014
	5.0	0.031
	10.0	0.042
	50.0	0.056

Table 2

Table 2 Caption: Numerical values of the function $K(T_0, T_1)$, which appears in Eq. (7) for the rate constant, under Scenario 3. This table contains numerical values of the function $K(T_0, T_1)$ for a set of different values of T_0 and T_1. The function $K(T_0, T_1)$ is defined for $T_0 \geq 0$ but only for $T_1 > 1$ (see Appendix B for details).

The result of Eq. (7) indicates that from a single plasma measurement under Scenario 3, the elimination rate constant, k, can be numerically determined, and the problem is thus fully solved. To complement the numerical results of Table 2, and give insight into the behaviour of k, we give analytical approximations of $K(T_0, T_1)$ in Appendix B.

2.2 Application of the results derived for k to three cases described in the literature

The results of the three scenarios, derived above, can be used to estimate k from a single plasma drug concentration measurement under different conditions of drug administration. We shall consider three specific cases that were published in the literature involving drugs upon which therapeutic drug monitoring is clinically necessary.

- *Case 1* Theophylline, where a plasma drug measurement was taken post drug administration, assuming steady state was reached. This is an example of Scenario 1.
- *Case 2* Cyclosporin, where a plasma drug measurement was taken during the initial dosing period, prior to achievement of steady state. This is an example of Scenario 2.
- *Case 3* Theophylline, where a plasma drug measurement was taken post drug administration, *without* the steady state having been reached. This is an example of Scenario 3.

We obtain estimates of k, that arise from a single plasma drug concentration measurement, and compare these to estimates generated from the original research, through established experimental methods. Where possible, we also relate our estimates of k to pharmacokinetic models that are clinically used to predict k using population data. We go on to describe how our results may be used both clinically and experimentally in the future.

2.2.1 Case 1: Theophylline - post drug administration, assuming steady state was reached

Theophylline is a therapeutically important drug that continues to play an integral role in the treatment of a range of inflammatory respiratory conditions such as asthma and chronic obstructive pulmonary disease [5]. It is a dimethylated xanthine that is structurally related to compounds such as caffeine and theobromine. Its precise mechanism of action remains unclear but has activity at adenosine receptors, and is an inhibitor of phosphodiesterase.

Despite its therapeutic effects, theophylline also provokes a number of toxic reactions at plasma concentrations that close to those required for its positive bronchodilator effects. Small variations in a patient's ability to eliminate the drug from the plasma can therefore lead to serious adverse effects being observed. As a consequence, it is standard clinical practice to monitor adverse effects and plasma concentrations of theophylline, and to calculate, using pharmacokinetic models, suitable dosing regimens that take into consideration clinical variables that are associated with reduced clearance such as cardiac function, liver dysfunction, ideal body weight and smoking behaviour.

To test the validity of the exact result of Eq. (4), we have utilised data from a publication by Jonkman *et al.* (1991) [6] in which the authors tested the effect of caffeine on the pharmacokinetics of intravenous theophylline. In their study, a group of $n = 8$ patients were administered theophylline for 24 hours by continuous intravenous infusion; this is substantially more time than necessary to reach the steady state, and plasma concentrations recorded in the

study prior to termination of dosing confirmed that the steady state had been reached. Post-dose theophylline concentrations were measured every 2 hours for a period of 36 hours. The trial itself was a cross-over design in which the same *n* = 8 individuals subsequently went on to receive a second intravenous infusion of thophylline, albeit this time whilst co-administered caffeine. The paper compared these two groups to establish if caffeine affected the elimination rate of theophylline. The paper did not provide details of the plasma concentrations of theophylline for each individual patient vs. time, but did give the mean, across all patients, of the theoplylline concentrations at each time. Additionally, the paper gave experimentally determined estimates of *V* and *k* for each individual, along with the mean values for these quantities over the group, which we write as $\bar{V}$ and $\bar{k}$, respectively. A plot of the mean concentration vs. time is shown in Figure 4A.

To compare our results with the experimentally determined mean k (i.e., $\bar{k}$), we adopted the following procedure, which was motivated by Eq. (4).

For each of the 15 times used in [6] we calculated the quantity $\hat{k}$ defined by

$$\hat{k} = \frac{1}{t} W\left(\frac{Rt}{\bar{V}\,\bar{C}_t}\right) \tag{8}$$

where $\bar{C}_t$ is the mean concentration at time *t* and we set $\bar{V}$ equal to 0.5 mg/kg × (mean actual body weight for the group) [7]. The quantity $\hat{k}$ in Eq. (8) is an *estimate* of $\bar{k}$, but it does not directly follow from Eq. (4), since Eq. (4) relates quantities of a single individual and not average quantities. Nonetheless the quantity $\hat{k}$ is a plausible construct and in Fig. 4 Bi and 4Bii

we plot $\hat{k}$ as red or blue dots, and we comment (below) on possible errors associated with using $\hat{k}$ as an estimate of $\bar{k}$.

We have also compared our estimates of the mean value of *k* to those predicted using the following population-based pharmacokinetic model that is currently used in clinical practice [7]

$$k^{theo} = \frac{0.04 \times IBW \times f_1 \times f_2 \ldots\ldots f_n}{V}. \quad (9)$$

In this equation, $k^{theo} =$ predicted value of k for theophylline, $V =$ volume of distribution, $IBW =$ patient's ideal body weight, $f_n =$ patient/disease/lifestyle factors, that scale k according to the influence of that factor on drug elimination (for example, cardiac failure has $f = 0.5$, hence if cardiac failure is present, it reduces the estimate of k to 50% of its value in the absence of cardiac failure).

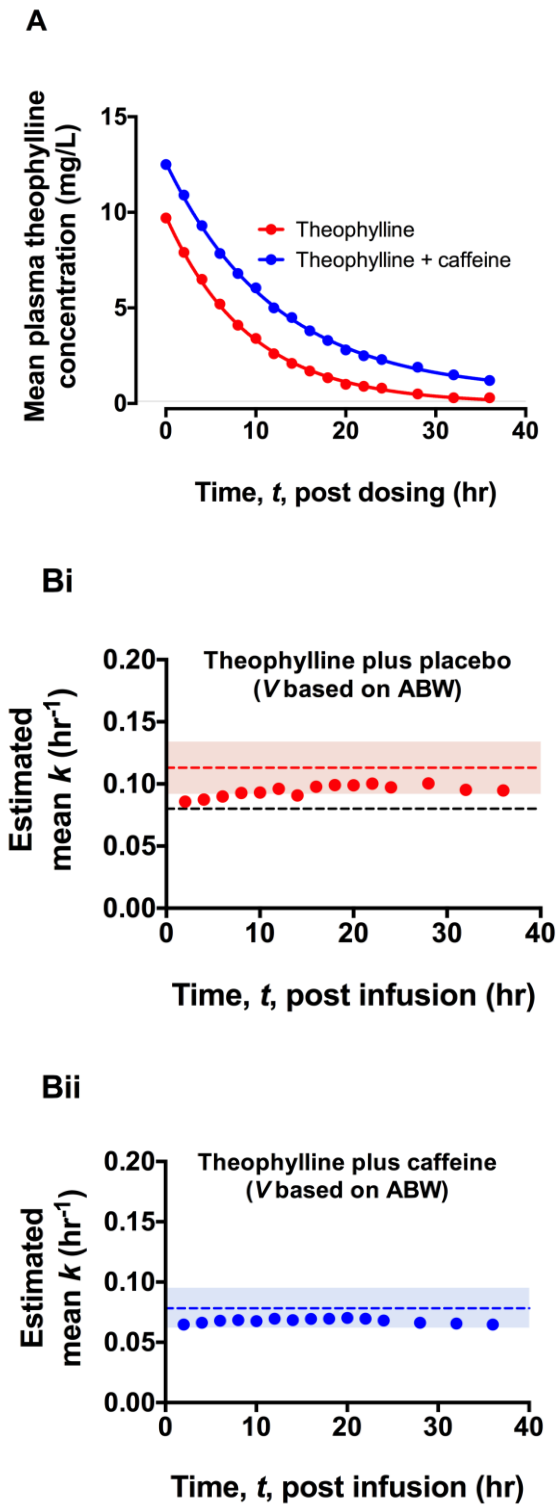

A
Mean plasma theophylline concentration (mg/L)
15
10
5
0
0
10
20
30
40
Theophylline
Theophylline + caffeine
Time, t, post dosing (hr)
Bi
Theophylline plus placebo
(V based on ABW)
Estimated mean k (hr-1)
0.20
0.15
0.10
0.05
0.00
0
10
20
30
40
Time, t, post infusion (hr)
Bii
Theophylline plus caffeine
(V based on ABW)
Estimated mean k (hr-1)
0.20
0.15
0.10
0.05
0.00
0
10
20
30
40
Time, t, post infusion (hr)

Figure 4

Figure 4 Caption: Application of Eq. (4) to published data (Jonkman *et al* [6]) on theophylline. Panel A: Plots of data from [6] showing exponential decline of theophylline in the plasma concentration over time in patients without co-administered caffeine (red) and with co-administered caffeine (blue). Data have been fitted with a single exponential curve. Panel Bi: Properties of theophylline without co-administered caffeine. We plot the estimate $\hat{k}$ of the mean elimination rate-constant following from Eq. (8) as red dots. The dashed red line indicates the experimentally determined mean value of this constant, $\bar{k}$, and the shaded area gives its standard deviation. The dashed black line indicates the estimated value of k from a population-based pharmacokinetic model given in Eq. (9). Panel Bii: Properties of theophylline with co-administered caffeine. We plot the estimate $\hat{k}$ (Eq. (8)) as blue dots. The dashed blue line indicates the experimentally determined mean value of *k*, namely $\bar{k}$, and the shaded area gives its standard deviation. In the figure we use the abbreviation ABW for *actual body weight*.

From Fig. 4Bi and 4Bii, it can be seen that the majority of values of $\hat{k}$ (following from Eq. (8)) fall within one standard deviation of the experimentally determined $\bar{k}$. Additionally, however, we note that the values of $\hat{k}$ for different times in Fig. 4 can be seen to underestimate the values of $\bar{k}$ in both the control and caffeine groups.

To understand if this moderately small bias is related to the form of our estimate of $\bar{k}$, namely $\hat{k}$ (Eq. (8)), which amongst other things depends on the mean concentration of the drug, we

performed the following simulation.

We fixed the dose rate, *R*, but for each individual we randomly generated statistically independent normally distributed values of *k* and *V*. For individual *i* we write these values as k_i and V_i, respectively, and we used these values to calculate $C_t^{(i)}$, the concentration of the drug in individual *i* at time *t* according to Eq. (2) . Application of Eq. (4) to each $C_t^{(i)}$, for any *t*, produced the exact result for k_i, as expected. However, when we used our estimate $\hat{k}$ of Eq. (8), we found a small but consistent underestimate of $\bar{k}$ at all times. Furthermore, the $\hat{k}$ values obtained also contain some time dependence (data not shown).
This simulation study may explain some of the underestimate of $\bar{k}$ that occurs by using $\hat{k}$ in its place.

Two other factors may also contribute to the underestimate of $\bar{k}$. First, the value for *V* used in our analysis was based on the mean actual body weight of participants in the Jonkman paper. As theophylline in reasonably hydrophilic, *V* should ideally be estimated using ideal (or lean) body weight. Using actual body weight typically overestimates *V*, resulting in an underestimate of *k*. As no data regarding patient's height was presented in the original paper we were unable to calculate *ideal* body weight. Second, in both arms of the study, a single bolus loading dose of theophylline was administered prior to commencing the continuous intravenous infusion. This dose was not factored in to our 'dose rate', *R*, as it should have been cleared before the intravenous infusion was stopped. However, there is a possibility that a small amount of this loading dose was still present during the early plasma

measurements, which would have also led to a small underestimate of *k* (due to a slight increase in *R*).

Despite the moderately small bias in our estimates of *k*, it nevertheless appears that they are more accurate than the estimate made using the pharmacokinetic model described above (Eq. (8)) that is currently used in clinical practice. This may be because our approach only utilises the patient parameter V, which shows relatively little patient-to-patient variation. The elimination rate, k, on the other hand shows considerable patient-to-patient variation due to multiple factors which of necessity have to be incorporated into traditional population based pharmacokinetic models. Indeed, the more f_n factors present in Eq. (8), the less accurate the estimate is likely to be, due to accumulation of errors from different factors in the final answer.

Figure 4Bii illustrates how estimates of the mean value of k, using our model, predicted the value within one standard deviation of the experimentally determined mean value, for all post drug administration times in the theophylline plus caffeine group. What is of particular interest here is that *no pharmacokinetic prediction* of k can be currently made using Eq. (9) due to the fact that there is no population data to reflect the impact of theophylline - caffeine interaction. It should also be noted that justification for basing Eq. (4) on an exponential function is reflected by the reasonable match of a single exponential to the data in Fig 4A.

2.2.2 Case 2: Cyclosporin - during the initial dosing period

Cyclosporin is another example of a drug that has a narrow therapeutic window. It is an immunosuppressant that is most commonly used to prevent organ rejection after transplant surgery [8]. To reduce the risk of toxicity, blood cyclosporin levels are routinely monitored. In the following application of Eq. (6) we have used data presented in a paper by Gupta *et al.* (1987) [9] in which the pharmacokinetics of a constant rate cylosporin infusion were determined in patients that had undergone renal transplant surgery.

The initial part of the study involved administering cyclosporin to 5 patients, at a dose rate of $R = 7$ mg/kg/day over a 72 hour period. Blood cyclosporin measurements vs. time are only presented for $n = 1$ patients, but nevertheless, we have applied our model of predicting k with a single blood concentration measurement to these data and compared them to the experimentally determined k in the paper. For the purpose of this exercise we used the V provided in the paper for this individual patient (patient 5).

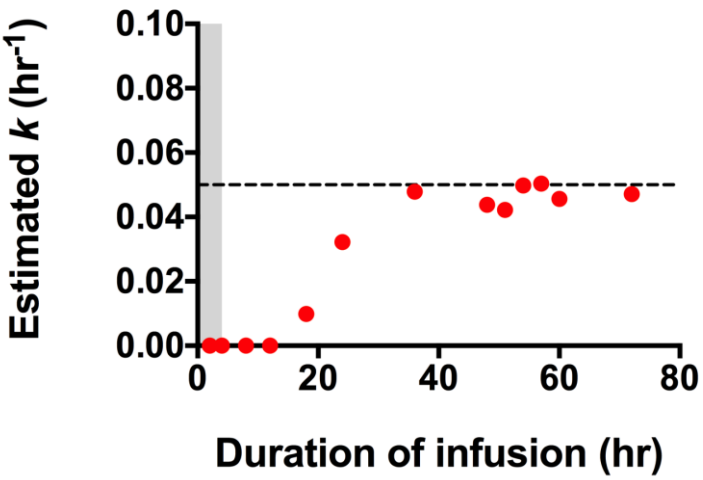


Figure 5

Figure 5 Caption: Application of Eq. (6) of Scenario 2 to published data (Gupta *et al*, 1987 [9]). The elimination rate constant k has been estimated using single plasma concentrations taken at various times during the period of constant-rate cyclosporin (7 mg/kg/day). The shaded grey area represents the theoretical alpha distribution phase of cyclosporin. It appears however that the alpha distribution phase may be extended in this patient

---

As seen in Figure 5, our estimation of k using Eq. (6) is reasonably accurate for samples taken at all times >18 hours post-infusion. However, at earlier sampling times the accuracy of the estimate is heavily biased towards lower than expected values of *k*. One simple reason for this observation could be that during the early stages of administration the drug had not fully equilibrated with other non-vascular compartments, during a period of time referred to as the alpha-distribution phase [10]. This would lead to higher than expected values of C_t, resulting in an underestimate of *k*. However, published data suggest that the alpha-distribution phase of

cyclosporin should be complete within approximately 5 hours (grey shaded area in Figure 5) and it is clear from Figure 5 that bias in our estimate exceeds this time.

In an attempt to understand what factors, other than a prolonged alpha-distribution phase, may have influenced the bias at early times, we generated concentration vs. time curves for a drug with an arbitary dose rate of 1 mg/hr, an arbitary volume of distribution, *V*, of 1 L, and a value of *k* of 0.05 hr^{-1} (i.e., similar to that of cyclosporin). The C_t values were generated using Eq. (5), where $C_{ss} = \frac{R}{Vk}$. First, we used these concentration values to estimate *k* using Eq. (6), which we found to be exact. Next, to see if an intrinsic error in the drug assay procedure may have contributed to the bias, we applied a ±6% error to the values of C_t, and repeated our estimations of *k* using Eq. (6) (±6% is the reported measurement error in the ciclosporin assay [11]). This error led to a large bias in *k* at early measurement times, which behaves exponentially (Figure 6A) and converges to the true value of *k* ± 6% error as the time of measurement increases. Repeating this procedure with a range of *k*-values, the level of bias at any particular time was found to be inversely proportional to the *k* value of the drug (Figure 6B). With regards to our estimated *k* for ciclosporin, in Figure 6A we see that the level of bias in the estimate *k* reduces exponentially with the time of measurement to a point at approximately 27 hours where the estimated *k* is within ~10% of the true *k* value. This is in accordance with the time at which we observe our estimated *k* in Figure 5 to approach the experimentally determined *k*. Additional analyses are provided in the Appendix C, to determine an optimal time to sample C_t to ensure a minimal level of bias.

Following green text seems to be taking the paper a bit away from straight comparison of model and data.

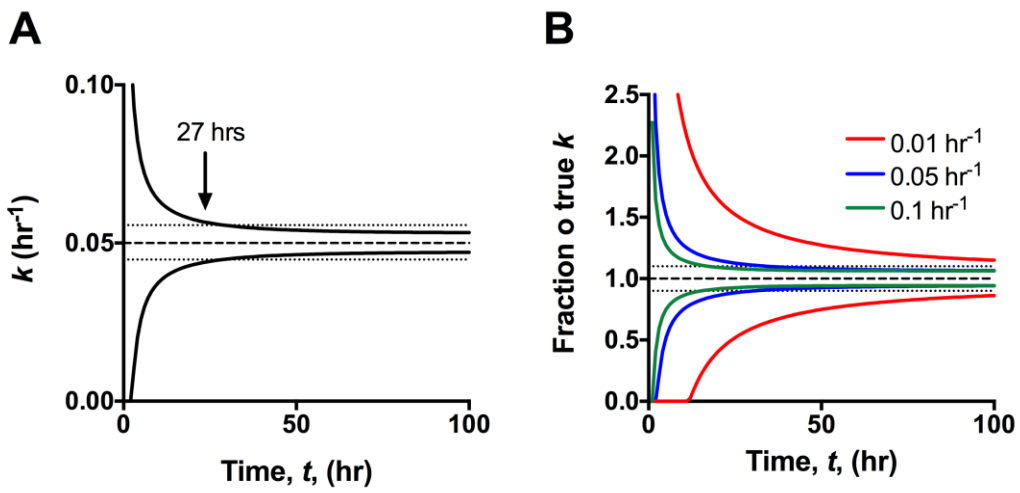


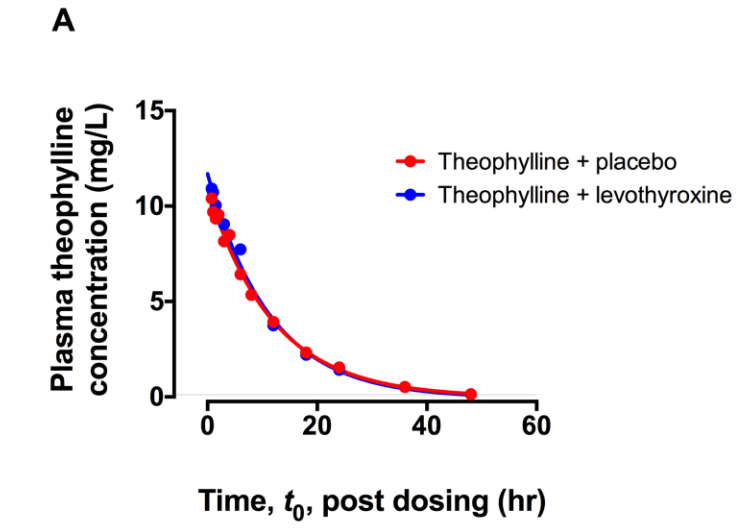
Figure 6

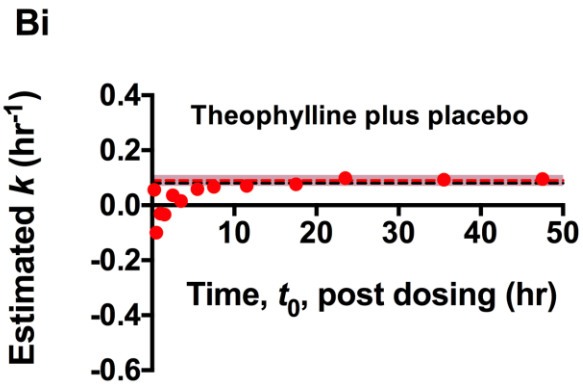
Figure 6 Caption. Bias in the estimation of 'k' using Equation (6) on simulated data. Panel A: Relationship between the estimated 'k' and the time of measurement when there is a ±6% error in plasma drug concentration measurement. Dotted lines indicate 10% level of bias. Panel B: Relationship between the ratio of observed to true *k* when there is a ±6% error in C, and the time of measurement. The data is shown for different values of the true *k*.

2.2.3 Case 3: Theophylline - post dosing without the steady state having been reached

In this final example, we have selected a study in which theophylline was administered intravenously at a dose rate of $R = 9$ mg/kg/hr, over a period of 30 mins, in two groups of patients: a group co-administered placebo, and a group co-administered levothyroxine [12]. Following the intravenous infusion of theophylline, plasma samples were analysed at several times over the next 50 hours. The study subsequently compared pharmacokinetic parameters (e.g. k) to determine if an interaction between the two drugs existed. As the duration of the infusion in this study was only 30 mins, the plasma concentration will not have established the steady state concentration by the time the infusion was stopped (it would take approximately 40 hours of continuous infusion to reach steady state). This means that we are unable to use Eq. (4) to estimate k from a single plasma concentration measurement. We therefore utilised Eq. (7) of Scenario 3.

As can be seen from Figure 7, a reasonably accurate k was estimated (i.e. within the standard deviation of the k calculated as part of the study) when plasma samples taken at times between 5.5 hours and 48 hours were used in both groups. At times prior to this, the estimates deviate substantially from the k values calculated as part of the study. Again, this may be due to an alpha-distribution phase, which was not included in our analysis.


A
Plasma theophylline concentration (mg/L)
15
10
5
0
0
20
40
60
Theophylline + placebo
Theophylline + levothyroxine
Time, t_0, post dosing (hr)


Bi
Estimated k (hr^{-1})
0.4
0.2
0.0
-0.2
-0.4
-0.6
10
20
30
40
50
Theophylline plus placebo
Time, t_0, post dosing (hr)

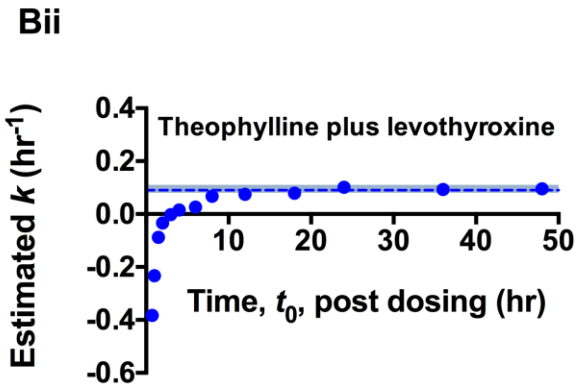

Bii
Estimated k (hr^{-1})
0.4
0.2
0.0
-0.2
-0.4
-0.6
10
20
30
40
50
Theophylline plus levothyroxine
Time, t_0, post dosing (hr)

Figure 7

Figure 7 Caption: Estimation of k using a single post dose plasma drug concentration, when steady state has not been achieved. Panel A: Plot of plasma concentration vs. time in theophylline $\pm$ levothyroxine groups extracted from a paper by Gisclon *et al.* [12]. Plasma concentrations of theophylline were measured at times following cessation of a 30 min infusion of theophylline at a dose of 9 mg/kg/hr. Panels Bi and Bii: In this example, Eq. (7) of Scenario 3 has been applied to the data reproduced in Panel A (where Panel Bi represents the patient group receiveing theophylline and placebo, and Panel Bii represents the patient group taking theophylline and levothyroxine). The coloured dots, and shaded area indicate the mean k, and standard deviation around the mean k, respectively, that were calculated during the study. The dashed black lines indicate the estimates of k using the population-based PK equation (Eq. (8)). The volume of distribution, V, used in the calculations was 0.5 L/kg.

As in the previous case, in order to determine a) what factors influence this bias, and to identify an optimal measurement time to obtain an accurate estimate of *k* we performed a series of investigations similar to those discssued above. In these investigations, we produced a series of concentration values vs. time using the following equation: $C_t = \frac{R}{Vk}(1 - e^{-kt_1})e^{-kt_0}$. The initial infusion time (t_1) was set to 0.5 hr (i.e. identical to t_1 in the Gisclon paper), *R* was set to 1 mg/hr, *V* was set to 1 L, and *k* to 0.08 hr^{-1}. As in case 2, when we used these concentration values to predict *k* at each time we found the equations produced exact results. Next we applied a ±6% error to each of the concentrations and re-ran our estimation using Eq. (7). As

in case 2, we found a simlar relationship between bias and the measurement time (Figure 8A), that was dependent upon *k* (Figure 8Bi). However the reduced far quicklier in this scenario. In fact, by increasing the value of t_1 the level of bias reduces until a point at which bias is negliable. In Figure 8A the level of bias reduces exponentially with the time of measurement; at 6.8 hours the estimated *k* is within ~10% of the true *k*, which is in accordance with the bias observed in our estimates in Figure 7B. Additional analyses are provided in Appendix C, to determine an optimal time to sample C_t to ensure a minimal level of bias.

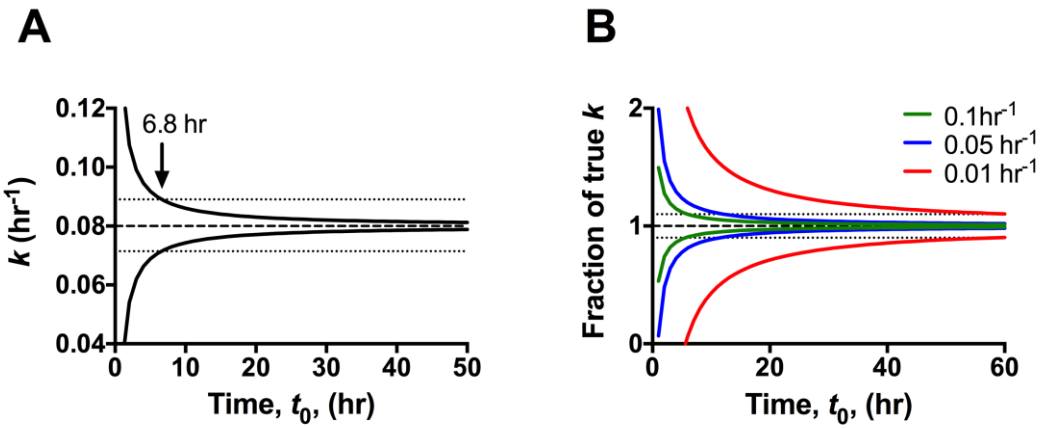


Figure 8

Figure 8 Caption. Bias in the estimation of *k* using Equation (7). Panel A: Relationship between the estimated *k* and the time of measurement when a ±6% error exists in the plasma drug concentration measurement. Dotted lines indicate 10% level of bias. Panel B: Relationship between the ratio of observed to true *k* when there is a ±6% error in C , and the time of measurement. Data is shown different values of true 'k'.

3 Discussion

The gold standard for achieving a full evaluation of pharmacokinetic parameters remains a careful measurement of plasma levels of the drug under investigation at multiple times. With a complete and accurate determination of the elimination of a drug from the plasma, important pharmacokinetic parameters such as the elimination rate constant (k) or volume of distribution (V) can be accurately determined. Whilst this approach is valuable in the clinical laboratory, it is an impractical approach in the normal clinical setting. Taking multiple blood samples is a problem for at-risk patient groups such as premature neonates who have a very low circulatory volume, or patients where obtaining venous access is difficult, or dangerous. In addition, kinetic parameters obtained under laboratory conditions, often in young healthy male volunteers, may not be reflective of sick, frail and elderly patients. For this reason, using population data to estimate patient plasma drug concentrations can often be an unreliable guide [13], especially is they include parameters that provide an estimation of renal function [14]. Correction of kinetic parameters such as drug clearance (Cl) by multiplying by a standard correction factor can go some way to rectifying this problem, but often vulnerable patients with multiple co-morbidities end up with a calculated clearance that is not reflective of the true value.

Consider, as an example, a frail elderly 45 Kg female patient, who smokes, has congestive cardiac failure and severe obstructive pulmonary disease, who has been prescribed theophylline. Based on population data her clearance should be 1.8 L/ hr, but this has to be modified by a factor of 1.6 because she smokes, by 0.4 because she has congestive cardiac

failure and by 0.8 because she has severe obstructive pulmonary disease, yielding a clearance of 0.92 L/hr. Multiplication by so many factors, which may or may not be fully applicable to our patient, ultimately makes the estimate unreliable [7]. What is required is a personalised estimate of the patient's own clearance.

Clearance is equal to the elimination rate constant (k) multiplied by the volume of distribution (V), and is sensitive to multiple pathophysiological changes observed in patients. This is because the elimination rate constant is a composite rate constant derived from hepatic metabolism ($k_{hepatic}$), renal excretion (k_{renal}), biliary excretion (k_{bil}) plus other routes of elimination (k_{other}). The volume of distribution is more predictable, being largely dependent on ideal body weight. Estimating the elimination rate constant (k) of a drug in a patient with just one blood sample will help the clinician develop a personalized medicine approach to vulnerable patients.

Our approach minimizes the need to utilize population data to estimate k; we only rely on population data to estimate V, and then k can be reliably estimated for the patient with just one blood sample measurement that is taken at a known time. We have used this approach on historic studies to illustrate the utility and the current limitations of our approach. The estimated k values obtained agree reasonably with the values obtained historically using standard drug-time profile measurements.

The estimated k has a tendency to be underestimated in plasma samples taken soon after the

last dose of the drug (Figures 5 and 6) but seems to improve with time. This may be a reflection of a prolonged alpha distribution phase which is observed in drugs which are best described by a two-compartment rather than the one compartment model used in this paper [10]. A two-compartment model is used where the administered drug takes time to distribute throughout the body. Thus, there is an initial volume of distribution (V_i) and a total volume distribution (V_d). Because we estimate k from V and a plasma sample, any uncertainty around V will affect our estimate of k. For most drugs, however, a one-compartment model is sufficient to describe the plasma concentration time-course, and for drugs where the alpha distribution phase is important, (e.g., digoxin) sampling at a later time will improve the estimate of k.

The approach presented in this work will be useful in a number of settings, especially in clinical areas where patients require close monitoring and have unstable organ function, for example, intensive care units. The advantages for its application in such settings include the following. Firstly, it gives a more reliable estimate of drug clearance for patients with multiple pathologies and does not rely on proxy or lagging markers of hepatic and renal function. Secondly, it could potentially reduce the need for repeated samples to be analysed as part of a traditional therapeutic drug monitoring regimen. Thirdly, by accurately determining k, these models allows the prediction of when a patient will completely (99.9%) clear a drug from the body, and determines when a drug concentration will reach steady state. This time is approximately equal to $5/k$.

Another area where this model could be useful is in the clinical trial setting. Here, there is an

opportunity for the clinical burden, cost, and danger associated with taking multiple blood samples to be reduced by utilising these models. In terms of cost, and regular access to drug assaying facilities this approach may also be of value in developing countries, or in field hospitals for example.

Our mathematical modelling approach does, however, have some practical drawbacks and limitations. The first of which is that it currently cannot be used with orally administered drugs, because the proportion of orally administered drug that enters the systemic circulation (bioavailability) in the *individual* patient is unknown. Data from the literature could of course be used, but this may introduce an additional source of error into the estimate. Secondly, accurate recordings of timing in relation to plasma sampling and drug cessation is important. Thirdly, this approach is currently restricted to continuous infusion. Nonetheless, for clinicians struggling with the use of drugs with a low therapeutic index, in a high intensity situation, the model will help in clinical decision making.

4. Methods

4.1 Literature search

Our mathematical models were tested on patient data published in the literature, which was searched using the National Library of Medicine search engine Pubmed. We restricted our literature search to the following commonly used drugs with a low therapeutic index: theophylline, cyclosporin, digoxin, and vancomycin. These drugs typically necessitate the application of therapeutic drug monitoring, and require a working knowledge of the elimination rate constant.

Our literature search was further refined to manuscripts (or the associated supplementary material) that provided either raw data on plasma concentration vs. time of these drugs, or plots where the data could be easily extracted. The plasma concentration vs. time data also had to reflect at lease one of the three scenarios for which our models are applicable: (1) the exponential decay period following steady state (2) the initial dosing period, and (3) an exponential decay following a period of drug administration during which the plasma concentration had not reached steady state. The publication also had to provide information regarding the dose rate, volume of distribution, patient weight, and time of plasma sampling. Estimated values for k using the equations outlined in this manuscript were then compared to k values generated experimentally in the selected paper.

The manuscripts which met these criteria were in excess of 20 years old. It was not possible to contact authors to obtain raw data, as they had ceased publishing.

4.2 Data analysis

Estimates of k using our mathematical models were presented in graphical form in Graphpad Prism v6.00.

Key Points

- The elimination rate constant, k, is a parameter which can be used by clinicians to design suitable dosage regimens for high-risk drugs. It describes the rate at which a drug is eliminated from the body, and is dependent upon both drug, and patient factors. Unfortunately, it is currently impractical to obtain a 'personal' k for each patient that uses multiple-blood samples, and estimates which use population data, or lagging proxy markers, are error-prone.
- Our study therefore asked the following question: can a single plasma drug concentration measurement be used to estimate a patient's 'personal' elimination rate constant?
- Our study describes a mathematical method which can be used to calculate *k* using a single plasma drug concentration that reflects intrinsic drug and patient factors. This model may be adopted by clinicians working in areas where high-risk drugs are used, for example, intensive care units, to ensure the safe and effective use of medicines.

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Author's contributions

(1) substantial contributions to conception or design of the work (DW, GS, MA);

(2) drafting of the work (DW, GS, MA) or revising it critically for important intellectual content (MA);

(3) all the Authors approved the submitted final version to be published and

(4) all the Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

(5) all authors confirm that they have no actual or potential conflicts of interest.

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Appendices

Appendix A

In this appendix we give the mathematical details of determining k from Eq. (5) of the main text, which for convenience we have reproduced here: $C_t = \frac{R}{Vk}(1 - e^{-kt})$. We begin by isolating e^{-kt} with the result $e^{-kt} = 1 - \frac{VkC_t}{R}$ and this equation can be rewritten as $e^{kt}\left(1 - \frac{VkC_t}{R}\right) = 1$ which in turn is equivalent to $\left(kt - \frac{Rt}{VC_t}\right)e^{kt} = -\frac{Rt}{VC_t}$. Multiplying the left and right sides by $e^{-\frac{Rt}{VC_t}}$ yields $\left(kt - \frac{Rt}{VC_t}\right)e^{kt-\frac{Rt}{VC_t}} = -\frac{Rt}{VC_t}e^{-\frac{Rt}{VC_t}}$. This equation is of the form $xe^x = y$ and the relevant solution for x is $x = W(y)$ where $W(y)$ is (the principal branch of) the Lambert W function [15]. We thus obtain $kt - \frac{Rt}{VC_t} = W\left(-\frac{Rt}{VC_t}e^{-\frac{Rt}{VC_t}}\right)$ which yields the result $k = \frac{R}{VC_t} + \frac{1}{t}W\left(-\frac{Rt}{VC_t}e^{-\frac{Rt}{VC_t}}\right)$ that is given in the main text.

Appendix B

In this appendix we provide the arguments leading to the equation that governs k in a scenario where a single plasma sample is taken at a time post drug administration, *without* assuming plasma drug concentration has reached steady state. We then derive the general form for the solution of k that solves this equation. For analytical insight, we present an approximation for k.

To begin, we note that during drug administration, which takes place from time 0 to time t_1, the plasma concentration of the drug rises from 0 to the value $\frac{R}{Vk}(1 - e^{-kt_1})$, where R is the dose rate, V is the apparent volume of distribution, and k is the elimination rate constant. After drug administration ceases, the plasma concentration of the drug decreases exponentially, at a rate of k. Thus at a further time t_0 *after* cessation of drug administration (i.e., at a time $t_1 + t_0$ after initial drug administration), the plasma concentration is written as C_{t_0} (a more consistent, but cumbersome notation that we do *not* adopt would be $C_{t_1+t_0}$) and is given by $C_{t_0} = \frac{R}{Vk}(1 - e^{-kt_1})e^{-kt_0}$. We rewrite this equation as

$$1 = \frac{(1-e^{-kt_1})e^{-kt_0}}{\left(\frac{VC_{t_0}k}{R}\right)} \qquad \text{(B1)}$$

and for the purpose of solving this equation, we work with the scaled quantities

$$K = \frac{C_{t_0} V k}{R}, \qquad T_0 = \frac{R t_0}{C_{t_0} V}, \qquad T_1 = \frac{R t_1}{C_{t_0} V}. \tag{B2}$$

Eq. (B1) then becomes

$$1 = \frac{\left(1 - e^{-K T_1}\right)}{K} e^{-K T_0}. \tag{B3}$$

This equation involves only K, T_0 and T_1, and hence shows that K depends only on T_0 and T_1 and no other quantities. We can therefore write

$$K = K(T_0, T_1). \tag{B4}$$

It follows that underlying the problem of determining k is the function $K(T_0, T_1)$ that depends on two variables. Given the form of $K(T_0, T_1)$, the result for k, for arbitrary values of R, V, C_t, t_0 and t_1 is, via Eqs. (B2) and (B4),

$$k = \frac{R}{C_{t_0} V} K\left(\frac{R t_0}{C_{t_0} V}, \frac{R t_1}{C_{t_0} V}\right). \tag{B5}$$

The function $K = K(T_0, T_1)$, which obeys Eq. (B3), does not have a solution in terms of known functions. In the absence of an exact solution of $K(T_0, T_1)$ we[2] can determine its value *numerically*.

[2] We only know the form of $K(T_0, T_1)$ in the special cases $K(T_0, \infty) = W(T_0)/T_0$, which corresponds to the result for Scenario 1, and $K(0, T_1) = 1 + W(-T_1 e^{-T_1})/T_1$, which corresponds to the result for Scenario 2.

Before we discuss the numerical approach, we need to note that $K(T_0, T_1)$ is defined for all $T_0 \geq 0$ but only for

$$T_1 > 1. \tag{B6}$$

To see this, we rewrite Eq. (B3) as $1 = T_1 \frac{1-e^{-KT_1}}{KT_1} e^{-KT_0}$ and using (i) $\frac{1-e^{-x}}{x} < 1$ (which applies for $x > 0$), and (ii) $e^{-KT_0} \leq 1$ yields $1 = T_1 \frac{1-e^{-KT_1}}{KT_1} e^{-KT_0} < T_1$, thereby indicating the restriction on T_1 of Eq. (B6).

For the numerical approach, we proceed as follows.

Given values of t_1 and t_0, we first evaluate the quantities $T_0 = \frac{Rt_0}{C_{t_0}V}$ and $T_1 = \frac{Rt_1}{C_{t_0}V}$. For these values of T_0 and T_1 we determine the value of $K(T_0, T_1)$ by numerically solving Eq. (B3) for K. This may be achieved using standard numerical software packages, or by proceeding with an iterative approach, using the simplest method [1]. That is, with $f(K) = K - (1 - e^{-KT_1})e^{-KT_0}$ and $f_1(K) = df(K)/dK = 1 + T_0 e^{-KT_0} - (T_1 + T_0)e^{-K(T_1+T_0)}$ we iteratively look for the solution of $f(K) = 0$ using the Newton method[3] $K_{j+1} = K_j - f(K_j)/f_1(K_j)$. In practise, an initial value of $K_0 = 0.5$ worked satisfactorily (there was reasonably rapid convergence) for $0.02 \leq T_0 \leq 50$ and $1.02 \leq T_1 \leq 50$, and we could terminate the iteration when, e.g., K_{j+1}

[3] The Newton method is, with $f(K) = K - (1 - e^{-KT_1})e^{-KT_0}$ and $f_1(K) = df(K)/dK = 1 + T_0 e^{-KT_0} - (T_1 + T_0)e^{-K(T_1+T_0)}$ given by iterating $K_{j+1} = K_j - f(K_j)/f_1(K_j)$.

differed from K_j by less than 10^{-10}.

In addition to the numerical results, some analytical insights into k may be gained from approximations of $K(T_0, T_1)$. We consider two distinct approximations.

Approximation 1

To derive an first approximation of $K(T_0, T_1)$, we start with Eq. (B3), and write it in the form $e^{KT_0} = T_1 \frac{1-e^{-KT_1}}{KT_1}$ which then yields

$$KT_0 = \ln(T_1) + \ln\left(\frac{1-e^{-KT_1}}{KT_1}\right). \quad \text{(B7)}$$

Assuming KT_1 is small ($\ll 1$) we expand the term $\ln\left(\frac{1-e^{-KT_1}}{KT_1}\right)$ on the right hand side of Eq. (B3) in powers of KT_1 and obtain $\ln\left(\frac{1-e^{-KT_1}}{KT_1}\right) = -\frac{KT_1}{2} + \frac{(KT_1)^2}{24} - \frac{(KT_1)^4}{2880} + \ldots$. The smallness of the coefficient of $(KT_1)^4$ suggests that a good approximation of $\ln\left(\frac{1-e^{-KT_1}}{KT_1}\right)$ is the quadratic function $\ln\left(\frac{1-e^{-KT_1}}{KT_1}\right) \simeq -\frac{KT_1}{2} + \frac{(KT_1)^2}{24}$. This yields the following approximation for Eq. (B7):

$$KT_0 = \ln(T_1) - \frac{KT_1}{2} + \frac{(KT_1)^2}{24} \quad \text{(B8)}$$

which is a quadratic equation in K. Solving Eq. (B8) for K, we use the smaller root, which correctly yields $K = 0$ when $T_1 = 1$, to obtain the approximation of $K(T_0, T_1)$ that we write as $K_1(T_0, T_1)$, and is given by

$$K_1(T_0,T_1)=\frac{6}{T_1^2}\left[(2T_0+T_1)-\sqrt{(2T_0+T_1)^2-\frac{2}{3}T_1^2\ln(T_1)}\right]$$

$$=\frac{4\ln(T_1)}{(2T_0+T_1)+\sqrt{(2T_0+T_1)^2-\frac{2}{3}T_1^2\ln(T_1)}}. \qquad \text{(B9)}$$

We give values of $K_1(T_0,T_1)$ in Table S1.

T_0	T_1	$K_1(T_0,T_1)$	$K_2(T_0,T_1)$	$K(T_0,T_1)$
0.2	1.2	0.232	0.569	0.232
	2.0	0.633	0.708	0.632
	5.0	0.929	0.834	0.833
	10.0	complex	0.844	0.844
	50.0	complex	0.845	0.845
1.0	1.2	0.114	0.348	0.114
	2.0	0.357	0.438	0.357
	5.0	0.550	0.546	0.543
	10.0	complex	0.566	0.566
	50.0	complex	0.567	0.567
5.0	1.2	0.033	0.137	0.033
	2.0	0.116	0.173	0.116
	5.0	0.221	0.231	0.221
	10.0	0.258	0.257	0.256
	50.0	complex	0.265	0.265
10.0	1.2	0.017	0.083	0.017
	2.0	0.063	0.104	0.063
	5.0	0.130	0.141	0.130
	10.0	0.161	0.163	0.161
	50.0	complex	0.175	0.175
50.0	1.2	0.004	0.022	0.004
	2.0	0.014	0.027	0.014
	5.0	0.031	0.038	0.031
	10.0	0.042	0.045	0.042
	50.0	0.057	0.056	0.056

Table S1

Table S1 Caption: For a range of different values of T_0 and T_1, this table contains results for two approximations of the function $K(T_0,T_1)$, written $K_1(T_0,T_1)$ and $K_2(T_0,T_1)$. These are given in Eqs. (B9) and (B13), respectively. For comparison, the table also contains the

corresponding exact values of $K(T_0, T_1)$. Note that those entries of the table labelled "complex", correspond to when the approximation yielded a complex number, and hence cannot be used.

Approximation 2

Another approximation of $K(T_0, T_1)$ can be obtained by writing Eq. (B3) as

$$KT_0 e^{KT_0} = T_0(1 - e^{-KT_1}) \tag{B10}$$

We note that given $y = xe^x$ with $x \geq -1$, an equivalent statement is $x = W(y)$ where $W(x)$ is (the principal branch of) the Lambert W function [1]. Thus we can write Eq. (B10) in the equivalent form

$$K = \frac{1}{T_0} W\big(T_0(1 - e^{-KT_1})\big). \tag{B11}$$

This is not an explicit solution for $K \equiv K(T_0, T_1)$ because K appears on both sides of the equation. It should be noted, however, that the value of K, assuming drug infusion was continued until a steady state level of the drug was effectively reached, corresponds to setting $T_1 = \infty$ in Eq. (B11). This leads to $K(T_0, \infty) = W(T_0)/T_0$ which *is* an explicit solution for K that holds in this special case. We shall write the explicit form for K that holds when the steady state level of the drug in the body is achieved

$$K_{ss}(T_0) \equiv K(T_0, \infty) = \frac{1}{T_0} W(T_0). \tag{B12}$$

For large but non-infinite values of T_1 a plausible approximation for K is to set $K = K_{ss}(T_0)$ on the right hand side of Eq. (B11). This leads to our second approximation of $K(T_0, T_1)$, that we write as $K_2(T_0, T_1)$, and is given by

$$K_2(T_0, T_1) = \frac{1}{T_0} W\left(T_0\left(1 - e^{-K_{ss}(T_0)T_1}\right)\right)$$

$$= \frac{1}{T_0} W\left(T_0\left(1 - e^{-W(T_0)T_1/T_0}\right)\right). \tag{B13}$$

We give values of $K_1(T_0, T_1)$ in Table S1.

From Table S1 we can see the quality of the approximations for different T_0 and T_1. The use of $K_1(T_0, T_1)$ for $T_1 < 4.5$ and[4] $K_2(T_0, T_1)$ for $T_1 \geq 4.5$ works tolerably well - see Table S1. This suggests a single (combined) approximation for $K(T_0, T_1)$ that is given by

$$K_{approx}(T_0, T_1) \simeq \begin{cases} K_1(T_0, T_1), & T_1 < 4.5 \\ K_2(T_0, T_1), & T_1 \geq 4.5 \end{cases} \tag{B14}$$

[4] The value $T_1 = 4.5$ for the upper T_1 value of validity of K_1 is not completely arbitrary; we note that in Eq. (B9), the argument of the square root will not go negative for all $T_0 \geq 0$ if $T_1^2 - \frac{2}{3} T_1^2 \ln(T_1) \geq 0$. This corresponds to $\ln(T_1) \leq 3/2$ i.e., $T_1 \leq e^{3/2} \simeq 4.5$.

and we give this single approximation in Table S2.

T_0	T_1	$K_{approx}(T_0, T_1)$	$K(T_0, T_1)$	absolute error
0.2	1.2	0.232	0.232	< 0.1%
	2.0	0.633	0.632	0.1%
	5.0	0.834	0.833	<0.1%
	10.0	0.844	0.844	<0.1%
	50.0	0.845	0.845	<0.1%
1.0	1.2	0.114	0.114	<0.1%
	2.0	0.357	0.357	<0.1%
	5.0	0.546	0.543	0.5%
	10.0	0.566	0.566	<0.1%
	50.0	0.567	0.567	<0.1%
5.0	1.2	0.033	0.033	<0.1%
	2.0	0.116	0.116	<0.1%
	5.0	0.231	0.221	4.5%
	10.0	0.257	0.256	0.3%
	50.0	0.265	0.265	<0.1%
10.0	1.2	0.017	0.017	<0.1%
	2.0	0.063	0.063	<0.1%
	5.0	0.141	0.130	8.7%
	10.0	0.163	0.161	1.2%
	50.0	0.175	0.175	<0.1%
50.0	1.2	0.004	0.004	<0.1%
	2.0	0.014	0.014	<0.1%
	5.0	0.038	0.031	23.0%
	10.0	0.045	0.042	7.8%
	50.0	0.056	0.056	<0.1%

Table S2

Table S2 Caption: Single approximation of the function $K(T_0, T_1)$, written $K_{*approx}(T_0, T_1)$, is given in Eq. (B14). This table contains values of $K_{*approx}(T_0, T_1)$ for some different values of T_0 and T_1. The table also contains the corresponding exact values of $K(T_0, T_1)$ and the percentage error in the approximate values.

We note that in terms of the original quantities, we have $k = \frac{R}{C_{t_0}V} K\left(\frac{Rt_0}{C_{t_0}V}, \frac{Rt_1}{C_{t_0}V}\right)$ and using $K_{approx}(T_0, T_1)$ of Eq. (B14) then yields an approximation for k.

Appendix C

With the knowledge that the bias in our estimate of k in case Case 2 is dependent upon both the intrinsic error in measuring C_t, and the drug's k, it raises the question: is there an optimal time for taking a single measurement of C_t in order to estimate k, within a certain, agreed level of error. If we presume that an acceptable level of error would be within ±5% of the ±6% error used above (which is equal to an approximate overall error of ±10%) we can identify the time at which the estimate of k using Eq. (6) reaches this acceptable level of error, and look at the releationship between this time, and the true value of k. A plot of this optimal measurement time vs. half-life (which is 0.693/k), reveals a linear relationship (Figure 6C), with a slope of approximately 2. The equation of the resulting plot can be used to identify the optimal time to take a single measurement for *any* drug (Figure S1) as long as a rough estimate of $t_{1/2}$ (i.e. 0.693/k) is known. The rough estimate of $t_{1/2}$ could of course come from the literature. We have chosen to express the relationship in terms of $t_{1/2}$ as k is typically reported in this form in the literature. The optimal time to take a single measurement of cyclosporin (with a previously reported k of 0.05 hr^{-1}) in order to estimate k using Eq. (6) would be 27 hours, which is in accordance with the data presented in Figure 5. It must be noted however, that this relationship is dependent upon the intrinsic error of the assay and any interpatient variability, and may need to be adjusted for less accurate assay methods.

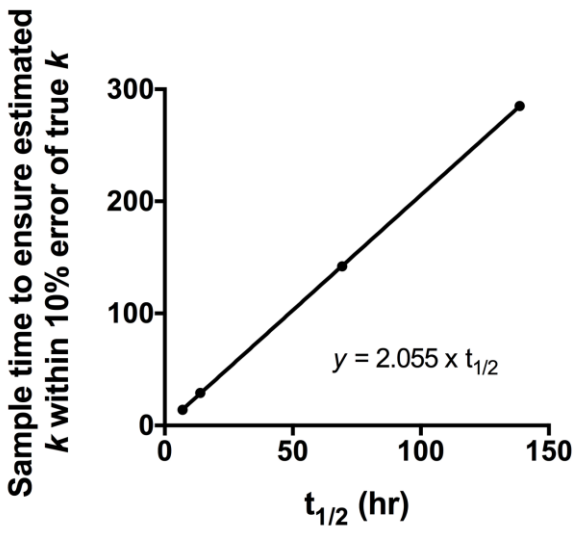

Figure S1

Figure S1 Caption: Plot showing linear relationship between the optimal measurement time and a drug's half-life ($t_{1/2}$) to ensure a <10% error and a drug's $t_{1/2}$, when estimating *k* using Eq. (6) (i.e. during the initial stages of drug administration up to steady state).

In Case 3, we performed a similar analysis in an attempt to find an optimal measurement time to estimate *k* with a ±10% overall error. In doing so, we found a linear relationship between *k* and the optimal measurement time such that 0.8 x $t_{1/2}$ should estimate *k* with <10% error (Figure S2).

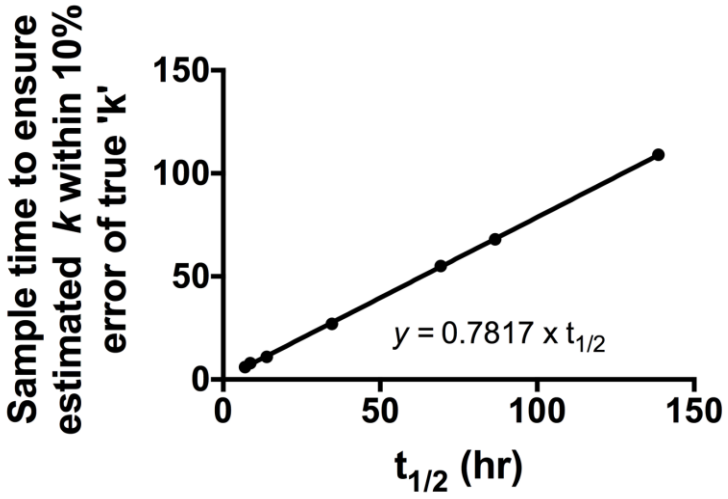

Figure S2

Figure S2 caption: Plot showing linear relationship between the optimal measurement time and a drug's half-life ($t_{1/2}$) to ensure a <10% error and a drug's $t_{1/2}$, when estimating *k* using Eq. (7) (i.e. follow drug administration assuming steady state has not been reached).