Title: Improved estimates of mean pharmacokinetic parameters for increased accuracy in dosing and reduced risk to patients.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

Pharmacokinetic equations, which relate different parameters of a single individual, are often applied in clinical practice to reported mean values, with the aim of estimating the mean value of an unreported parameter. There appear to be no discussions of errors associated with this practice.

WHAT THIS STUDY ADDS

In this study we establish how this practice generally leads to errors in estimates of mean parameter values, due to population heterogeneity. We provide details of inequalities which apply for a number of pharmacokinetic equations, and produce approximations which can be used to improve the accuracy of parameter estimates, in clinical practice.

Improved estimates of mean pharmacokinetic parameters for increased accuracy in dosing and reduced risk to patients

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ABSTRACT

AIM: Pharmacokinetic equations, which relate different parameters of a single individual, are often applied to reported mean parameter-values, with the aim of estimating the mean value of an unreported parameter. Due to population heterogeneity this approach generally leads to errors in their estimation. We provide details of this source of error. Our aim is to take into account the effects of population heterogeneity in commonly used pharmacokinetic models. This provides improved estimates and knowledge of the concentration of a drug in the plasma over time.

METHODS: Inequalities and approximations for corrected mean estimates are derived. These results are then applied to published clinical-trial data to illustrate their accuracy in practical situations.

RESULTS: By using mean values within the pharmacokinetic equations for a single individual, we show that estimates of mean parameter-values, for a variety of dosing regimens, generally have errors. Using published clinical trial data, we show that such estimates can systematically deviate from the exact mean value by up to 19%. We provide analytical results, which amount to inequalities when there are systematic deviations from exact results, along with approximate results that improve the accuracy of estimates.

CONCLUSIONS: Medical, pharmacy and nursing students should be educated about errors and inequalities that can arise when transforming reported mean values of pharmacokinetic parameters into the mean values of parameters that are required, but not reported. Using approximate results, that correct the estimates of mean parameter values so that they more accurately reflect the actual average values may provide a practical solution.

Introduction

The therapeutic and toxicological responses of a patient to a drug are typically related to the concentration of the drug in the patient's blood-plasma. An aim of clinical pharmacokinetics is to predict the conditions under which the concentration of a drug lies within the *therapeutic window*, namely the range of concentrations running from the smallest value producing a therapeutic effect, to the largest value that is not toxic[1]. Clinical pharmacokinetics achieves such predictions by the construction of mathematical models that describe how the blood-plasma concentration of a drug in a patient (*concentration* for short) changes over time. Such a model, containing appropriate values of the pharmacokinetic parameters, can be used directly during a patient's treatment, to calculate the required dose and frequency of a drug. That is, the model allows determination of the regimen that treads the path between the patient's successful therapeutic response and their risk of harm.

In this work we provide corrections for the estimates of parameters that enter pharmacokinetic models for drugs that undergo *first order elimination* and involve distribution into a *single compartment*. The rationale for studying such models is that: (i) the majority of drugs used in clinical practice involve first order elimination where, in the absence of drug infusion, the rate of decrease of a drug's concentration is directly proportional to the concentration itself[2], and (ii) most drugs either exhibit single-compartment kinetics, or distribute rapidly into peripheral compartments[2], thereby allowing the behaviour to be effectively modelled with a single-compartment. We recognise that when there is an extended distribution time, or when elimination is not solely from the central compartment, some adjustment may be required for the results presented in this work.

In single compartment models there are several parameters that reflect important physicochemical properties of both the drug administered and the physiology (or pathology) of the patient. These include the following.

1. The apparent volume of distribution, V. This is the proportionality constant that relates the amount of the drug in the body, X, to the plasma concentration of the drug, C. That is, $X = V \times C$.

2. The clearance, Cl. This is defined as the volume of plasma that is cleared of the drug per unit time.

3. The elimination rate constant, k. This describes the fraction of the total amount of the drug in the body (or the fraction of the blood-plasma concentration) that is cleared per unit time.

4. The half-life, $t_{1/2}$. This is the time it takes for the drug plasma concentration to fall to half its initial value (in the absence of drug administration). The half life can be calculated from knowledge of the elimination rate constant, k, via

$$t_{1/2} = \frac{\ln(2)}{k} \tag{1}$$

where $\ln(2)$ is the natural logarithm of 2, and has an approximate value of 0.693.

Population estimates of these four parameters have been determined in clinical trials for a wide range of therapeutically used drugs, and are typically reported in the form of 'sample mean $\pm$ sample standard deviation'. From these results, other results can be estimated, such as 95% confidence intervals. The results reported for population mean values can be applied directly to an individual patient, with the understanding that there will generally be differences with the patient's actual kinetic parameters, leading to differences between the calculated and actual drug concentrations within the patient. It is possible, using non-linear mixed effect modelling software, to determine more accurate, *personalised* pharmacokinetic parameters for individual patients.[3] However, in clinical practice this approach is rarely employed. A typical approach, that is used 'at the patient's bedside', involves finding basic pharmacokinetic parameters, such as mean values, from the literature, and then incorporating these parameters into basic calculations.

Nevertheless, whilst population statistics of pharmacokinetic parameters (such as mean values) are often present in reports of clinical trials, such reports rarely present *all* relevant parameters. For example, a study may report the mean value of the clearance, Cl, but not the mean value of the elimination constant, k, or, it may report the mean value of k, but not the mean half life, $t_{1/2}$. In these instances, the reported mean values of population parameters can apparently be used to determine the mean value of an unreported parameter. The method is to directly use the reported mean values within the standard pharmacokinetic equations, *apparently producing* the mean value of an unreported parameter, despite the fact that the equations were only designed to relate parameters of an individual.

As an illustration, it is natural to estimate the mean value of the half life, written $\bar{t}_{1/2}$ (denoting mean values by an overbar) from the mean value of the elimination constant, $\bar{k}$, by the substitution of mean values into Eq. (1) with the result $\bar{t}_{1/2} = \ln(2)/\bar{k}$. Indeed this approach is routinely presented in textbooks[2,4], and taught in pharmacokinetic classes in medical and pharmacy schools. As a consequence this approach is often adopted when solving pharmaceutical problems in the clinical environment. But is it *correct* to relate or estimate mean values in this manner? We show in this paper that while, for a particular patient, *their* half life, $t_{1/2}$, is related to *their* elimination constant, k, via Eq. (1), it is not generally correct to infer that the mean values of $t_{1/2}$ and k of a population are related via the equation $\bar{t}_{1/2} = \ln(2)/\bar{k}$. This issue arises because of population heterogeneity, where different individuals generally have different pharmacokinetic parameters (here, k values), and that there is a non-linear relationship connecting the parameters (here, $t_{1/2}$ depends non-linearly on k).

We establish in this work that some of the relationships between pharmacokinetic parameters in an individual become *inequalities* when applied to mean values of a population. This includes the case of $t_{1/2}$ and k (which are related by Eq. (1)), where an inequality relates the mean values of $t_{1/2}$ and k, with $\bar{t}_{1/2}$ generally exceeding $\ln(2)/\bar{k}$.

Some of the formulae of pharmacokinetics are more complicated than the one relating $t_{1/2}$ and k, and may not lead to an inequality. We show, however, that irrespective of the presence or absence of an inequality, approximate results can be derived, for various statistics of pharmacokinetic parameters, which provide more accurate estimates than the results obtained by assuming that a relationship, which holds between parameters of an individual, also applies to mean values.

Let us now state the aim of this work. This is to take into account the effects of population heterogeneity in the most basic and commonly used of pharmacokinetic models, to allow improved estimation and knowledge of the concentration of a drug in the blood-plasma, so it can be controlled to lie within the therapeutic window. To this end, we derive inequalities and approximations for a number of quantities of direct pharmacokinetic interest. We draw upon clinical datasets to illustrate: (i) the magnitude of the effects that can arise in the inequalities, and (ii) the quality of the approximate results derived. While the results we present have a somewhat broad applicability, an important application is to the set of drugs where the therapeutic window is narrow. In the Discussion, we provide suggestions for ways this issue may be managed, to the benefit of clinical practice.

Throughout this work we shall use t to denote the time, an overbar denote a population average, and we will often refer to the blood-plasma concentration of a drug just as its *concentration*.

Results

Properties of an individual patient

Drug Regimen 1: constant infusion

We begin by considering an individual patient who was constantly infused with a drug for an interval of time prior to $t = 0$, with the infusion stopped at $t = 0$. We assume the interval of infusion, prior to $t = 0$, was sufficiently long that the blood-plasma concentration of the drug achieved a steady-state value by $t = 0$. We work under the assumption that the behaviour of the drug is described by a single-compartment model with a first order elimination process[2]. It then follows that for any post-infusion time t (i.e., for any $t \geq 0$), the concentration of the drug, written C_t, is given by

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

where C_{ss} is the steady-state concentration (which was established by $t = 0$) and k is the drug elimination constant. The form of the steady-state concentration is given by

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

where R is the drug infusion dose rate and V is the apparent volume of distribution. For completeness, we give a derivation of Eqs. (2) and (3) in part A of the Supplementary Material. Generally, the parameters k and V depend on both the particular drug administered and the particular patient under consideration.

The time it takes for a drug's concentration to fall to half its initial value is its half life, $t_{1/2}$, which is given in Eq. (1) in terms of the elimination constant, k (see part A of the Supplementary Material for details). The dependence of the half life on the elimination constant means the half life itself depends on the particular drug and the particular patient.

Drug Regimen 2: bolus doses

We now consider a patient under a different drug regimen where, at regular time intervals, the patient was administered a drug (either intravenously or orally) in the form of identical boluses. As in the case of Drug Regimen 1, we assume the drug was distributed into a single compartment, and eliminated via a first-order process.

After administration of an appreciable number of doses of the drug, the blood-plasma concentration of the drug settles down to a *steady-state* behaviour, where it changes periodically over time[1] (see part A of the Supplementary Material for details). In the steady state the concentration of the drug varies between a minimum (or trough) value, denoted $C_{ss,\min}$, and a maximum (or peak) value, $C_{ss,\max}$. The minimum value occurs immediately prior to administration of a bolus, and the maximum occurs just after administration.

With D, the dose of the drug that is administered in each bolus, and τ the time interval between each administration, the *time averaged* concentration of the drug in the steady state is given by

$$C_{ss,\text{ave}} = \frac{D}{\tau} \frac{1}{Vk} \tag{4}$$

(see part A of the Supplementary Material) where again V is the volume of distribution and k is the elimination rate constant. We shall often refer to $C_{ss,\text{ave}}$ as the *average* concentration. We note that the quantity D/τ associated with Regimen 2 is the analogue of the infusion rate R of Regimen 1.

At steady state, the trough value of the drug's concentration is given by

$$C_{ss,\min} = \frac{D}{V} \frac{e^{-k\tau}}{1-e^{-k\tau}} \tag{5}$$

and its peak value is

$$C_{ss,\max} = \frac{D}{V} \frac{1}{1-e^{-k\tau}} \tag{6}$$

(see part A of the Supplementary Material for details).

The periodically changing steady-state concentration has the following additional two properties.

1. The amount the peak value lies above the average is greater than the amount the trough value lies below the average, i.e.,

$$C_{ss,\max} - C_{ss,\text{ave}} > C_{ss,\text{ave}} - C_{ss,\min} \tag{7}$$

(see part A of the Supplementary Material).

[1] Prior to reaching steady-state behaviour, the concentration is the sum of two terms, one changing periodically with time, the other decreasing exponentially.

2. The proportion of time the concentration lies above the average value, written P_+, is given by

$$P_+ = \frac{1}{k\tau}\ln\left(\frac{k\tau}{1-e^{-k\tau}}\right) \tag{8}$$

(see part A of the Supplementary Material). The value of P_+ is smaller than $\frac{1}{2}$, meaning that in the steady state, the concentration exceeds $C_{ss,\text{ave}}$ for less than half the time.

Heterogeneous population of patients

We now consider a *population* of patients which, as a general feature, exhibits heterogeneity. Thus when a given drug is administered, different patients will generally have different apparent volumes of distribution, V, and different elimination rate constants, k. For such a heterogeneous population we can consider a particular patient to have been randomly picked from the population of patients and, as a consequence, the values of k and V for the patient are randomly picked in an appropriate way. But what constitutes an appropriate way? It is commonly argued that the clearance, Cl, and the apparent volume, V, are independent parameters, in the sense that a change in one of these parameters can occur, without the other being affected[4,5], but there are exceptions to this rule[2]. The clearance, Cl, is related to k and V via

$$Cl = kV. \tag{9}$$

In this work we shall proceed under the common situation that Cl and V are statistically independent parameters that describe the behaviour of a drug in a patient. We thus take the view that for a particular patient, their clearance value was randomly picked from a distribution of Cl values, and completely independently, the patient's apparent volume was randomly picked from a distribution of V values. This identification of Cl and V as the independent parameters is important in what follows. It leads to the direct implication that the parameters k and V are not independent of one another. Indeed writing Eq. (9) in the form $k = Cl/V$ indicates that large V values lead to small k values, and suggests that in a population of individuals the quantities k and V are *negatively correlated*. This is indeed what is found, with a negative covariance between k and V (see part B of the Supplementary Material) which is approximately given by

$$\text{Cov}(k,V) \simeq -\bar{k}\bar{V}\frac{\text{Var}(V)}{\bar{V}^2} \tag{10}$$

where[3] $\bar{k}$ and $\bar{V}$ are the mean values of k and V, respectively, while $\text{Var}(V)$ denotes the variance of V. Some of our conclusions would be significantly altered if k and V were independent parameters, since then the covariance of k and V is zero, and, for example, Eq. (10) would not apply.

Inequalities and Approximations: Drug Regimen 1

We now go from the results for individuals, involving constant drug infusion, that are given in Eqs. 1 - 8 to statistics describing a heterogeneous population. For some of the results for parameters of individuals, given above in the first section of the Results, entitled **Properties of an individual patient**, the corresponding mean values in a heterogenous population satisfy *inequalities* that apply irrespective of the origin of the data used, and so may arise from a relatively small-scale study or from a large, population-wide, study.

The inequalities we present have their origin in a basic property of a random variable X that takes *non-negative* values. With an overbar denoting the mean value, so $\bar{X}$ denotes the mean value of X, the basic property is

$$\overline{\left(\tfrac{1}{X}\right)} \geq \tfrac{1}{\bar{X}} \tag{11}$$

which can also be written as $\overline{X^{-1}} \geq \left(\overline{X}\right)^{-1}$.[7] Equation (11) says that the average value of X^{-1} will equal or exceed $1/\bar{X}$. To illustrate this, suppose that X just takes the values 1, 4 and 10 with equal probability, then $\overline{\left(\frac{1}{X}\right)} = \frac{9}{20}$ but $\frac{1}{\bar{X}} = \frac{4}{20}$, thereby providing a particular example of $\overline{\left(\frac{1}{X}\right)} \geq \frac{1}{\bar{X}}$. Equation (11) reduces to an equality only if there is no variation in the values that X takes, and for practical purposes, Eq. (11) can be taken as an *inequality*, since in real datasets there will be variation in X under normal circumstances. The inequality in Eq. (11) arises from convexity (i.e., curvature) of $1/X$.[7]

[2] An example where the clearance of a drug, Cl, and the volume of distribution, V, do not behave independently occurs when the drug digoxin is used in patients with renal dysfunction; in this case, concerted changes in Cl and V occur. These changes arise from decreased glomerular filtration and renal blood flow (leading to reduced elimination), and altered tissue penetration and drug binding (leading to a reduced volume of distribution)[6].

[3] The approximation given in Eq. (10) applies when deviations of V from its mean value are typically small. For full details, including the exact result for $\text{Cov}(k,V)$, see part B of the Supplementary Material.

In addition to inequalities, we can derive *approximate results* for some of the basic statistics describing a heterogeneous population. We derive approximations under the assumption that deviations (typically of k and V) from their mean values are small, to the extent that we calculate results where only the leading term in deviations from the mean are included. We shall often refer to such results as *small deviation approximations*. The approximate results we shall derive can, like the inequalities, apply to data from, e.g., a relatively small-scale study or a large population-wide study.

In practice the quantities k and V are often the ones that are estimated and the results we shall present are given in terms of statistics of k and V.

Half life of the drug, $t_{1/2}$

For a given patient, with a given value of their elimination constant, k, the half life is given by Eq. (1). For a *set* of patients, with generally different values of k, we directly employ Eq. (11) and find the *mean half life*satisfies the inequality:

$$\bar{t}_{1/2} \geq \frac{\ln(2)}{\bar{k}} \tag{12}$$

where $\ln(2) \simeq 0.693$. Thus, in a finite sample of patients where k values have been recorded, or in a very large (population-wide) dataset, Eq. (12) tells us that the mean half life will generally exceed the result $\ln(2)/\bar{k}$ which involves the mean value of k for the dataset used. The amount by which $\bar{t}_{1/2}$ exceeds $\ln(2)/\bar{k}$ can be substantial (see later).

To find an approximation for the mean value of $t_{1/2}$ we proceed by assuming that deviations of k from its mean value are typically small. If we neglect *all* deviations of k from its mean value then $\bar{t}_{1/2}$ follows from Eq. (1) with k replaced by its mean value, $\bar{k}$. This leads to to $\bar{t}_{1/2} \simeq \ln(2)/\bar{k}$. We go beyond this simplistic approximation by including deviations of k from its mean value. With $\mathrm{Var}(k)$ the *variance* of k (which is a measure of deviations of k from its mean value) the approximation of the mean half life, that includes the leading effect of deviations, is

$$\bar{t}_{1/2} \simeq \left(\frac{\ln(2)}{\bar{k}}\right) \times \left[1 + \frac{\mathrm{Var}(k)}{\bar{k}^2}\right] \tag{13}$$

(see part C of the Supplementary Material).

Consider now the variance of the half life. This vanishes if k has no deviations from its mean value, however including the leading effect of deviations of k from its mean value yields

$$\mathrm{Var}\left(t_{1/2}\right) \simeq \left(\frac{\ln(2)}{\bar{k}}\right)^2 \times \left[\frac{\mathrm{Var}(k)}{\bar{k}^2}\right] \tag{14}$$

(see part C of the Supplementary Material).

While we have given, above, results for the mean and variance of the half life, $t_{1/2}$, in terms of properties of the elimination constant, k, we note that the relation in Eq. (1), between $t_{1/2}$ and k, can be rewritten as $k = \ln(2)/t_{1/2}$. This equation, which amounts to an interchange of $t_{1/2}$ and k within Eq. (1), allows us to determine statistical properties of k given properties of $t_{1/2}$. In particular, interchanging $t_{1/2}$ and k in Eqs. (12), (13) and (14) yields three results for properties for k in terms of statistics of $t_{1/2}$. For example, Eq. (12) yields

$$\bar{k} \geq \frac{\ln(2)}{\bar{t}_{1/2}}. \tag{15}$$

Steady-state value of the concentration, C_{ss}

For different patients that have all been subject to an identical continuous dose rate of R of a drug prior to $t = 0$, the steady-state value of the concentration, C_{ss}, will differ from patient to patient. We write Eq. (3) in the form $C_{ss} = R/Cl$, determine the average of this equation, and then directly employ Eq. (11) to obtain $\bar{C}_{ss} \geq R/\overline{Cl}$. In terms of statistics of k and V we find that $\bar{C}_{ss} \geq \frac{R\overline{V^{-1}}}{\bar{k}}$ (see part C of the Supplementary Material) and using Eq. (11) on $\overline{V^{-1}}$ in this inequality for $\bar{C}_{ss}$ yields a further inequality, thus

$$\bar{C}_{ss} \geq \frac{R\overline{V^{-1}}}{\bar{k}} \geq \frac{R}{\bar{V}\bar{k}}. \tag{16}$$

We now assume that in the population of patients, both k and V typically have small deviations from their mean values. We then determine approximations of the mean and variance of the steady-state concentration by including the leading effects of deviations of k and V from their mean values and obtain the results

$$\bar{C}_{ss} \simeq \left(\frac{R}{\bar{k}\bar{V}}\right) \times \left[1 + \frac{\mathrm{Var}(k)}{\bar{k}^2}\right] \tag{17}$$

and

$$\mathrm{Var}\left(C_{ss}\right) \simeq \left(\frac{R}{\bar{k}\bar{V}}\right)^2 \times \left[\frac{\mathrm{Var}(k)}{\bar{k}^2} - \frac{\mathrm{Var}(V)}{\bar{V}^2}\right], \tag{18}$$

respectively (see part C of the Supplementary Material).

Drug-concentration at time t, namely C_t

The blood plasma drug concentration at time t is given by Eq. (2). For this quantity, an inequality for C_t does not apply for all t (see part C of the Supplementary Material).

We can, however, still obtain small deviation approximations for the mean and variance of C_t. We find

$$\bar{C}_t \simeq \left(\frac{R}{\bar{k}\bar{V}} e^{-\bar{k}t}\right) \times \left[1 + \left(1 + \bar{k}t + \tfrac{1}{2}\left(\bar{k}t\right)^2\right)\frac{\mathrm{Var}(k)}{\bar{k}^2} - \bar{k}t\,\frac{\mathrm{Var}(V)}{\bar{V}^2}\right] \tag{19}$$

and

$$\mathrm{Var}\left(C_t\right) \simeq \left(\frac{R}{\bar{k}\bar{V}} e^{-\bar{k}t}\right)^2 \times \left[\left(1+\bar{k}t\right)^2 \frac{\mathrm{Var}(k)}{\bar{k}^2} - \left(1+2\bar{k}t\right)\frac{\mathrm{Var}(V)}{\bar{V}^2}\right], \tag{20}$$

respectively (see part C of the Supplementary Material).

Clearance, Cl

Under the assumptions of the analysis carried out, the clearance, Cl, is an independent quantity. However, in terms of statistics of k and V we find that the clearance satisfies the inequality

$$\overline{Cl} \leq \bar{k} \times \bar{V} \tag{21}$$

(see part C of the Supplementary Material). The inequality in Eq. (21) goes in the *opposite direction* to the previous inequalities given in Eqs. (12) and (16).

Small deviation approximations for the mean and variance of Cl are

$$\overline{Cl} \simeq \left(\bar{k}\bar{V}\right) \times \left[1 - \frac{\mathrm{Var}(V)}{\bar{V}^2}\right] \tag{22}$$

and

$$\mathrm{Var}(Cl) \simeq \left(\bar{k}\bar{V}\right)^2 \times \left[\frac{\mathrm{Var}(k)}{\bar{k}^2} - \frac{\mathrm{Var}(V)}{\bar{V}^2}\right], \tag{23}$$

respectively (see part C of the Supplementary Material).

Inequalities and Approximations: Drug Regimen 2

We now consider results for a set of heterogeneous individuals subject to periodic bolus drug administration.

Time averaged concentration, $C_{ss,\mathrm{ave}}$

The form given in Eq. (4) for $C_{ss,\mathrm{ave}}$ has the same general form as the steady-state concentration in Drug Regimen 1, namely Eq. (3), but with the drug infusion dose rate, R, replaced by the bolus dose divided by the time interval between each administration, i.e., D/τ. Thus all such results can thus be directly taken over to Drug Regimen 2 and we find the mean obeys

$$\bar{C}_{ss,\mathrm{ave}} \geq \frac{D\overline{V^{-1}}}{k\tau} \geq \frac{D}{k\tau\bar{V}}. \tag{24}$$

Small deviation approximations for the mean and variance of $C_{ss,\mathrm{ave}}$ are

$$\bar{C}_{ss,\mathrm{ave}} \simeq \left(\frac{D}{\bar{k}\tau\bar{V}}\right) \times \left[1 + \frac{\mathrm{Var}(k)}{\bar{k}^2}\right] \tag{25}$$

and

$$\mathrm{Var}\left(C_{ss,\mathrm{ave}}\right) \simeq \left(\frac{D}{\bar{k}\tau\bar{V}}\right)^2 \times \left[\frac{\mathrm{Var}(k)}{\bar{k}^2} - \frac{\mathrm{Var}(V)}{\bar{V}^2}\right], \tag{26}$$

respectively.

Trough value of the concentration, $C_{ss,\min}$

For this quantity, an inequality for does not apply for all τ (see part C of the Supplementary Material).

Small deviation approximations for the mean and variance of $C_{ss,\min}$ are

$$\bar{C}_{ss,\min} \simeq \left(\frac{D}{\bar{V}}\frac{e^{-\bar{k}\tau}}{1-e^{-\bar{k}\tau}}\right) \times \left[1+\frac{1+e^{-\bar{k}\tau}}{2}\left(\frac{\bar{k}\tau}{1-e^{-\bar{k}\tau}}\right)^2 \frac{\mathrm{Var}(k)}{\bar{k}^2} + \frac{1-\bar{k}\tau-e^{-\bar{k}\tau}}{1-e^{-\bar{k}\tau}}\frac{\mathrm{Var}(V)}{\bar{V}^2}\right] \tag{27}$$

and

$$\mathrm{Var}\left(C_{ss,\min}\right) \simeq \left(\frac{D}{\bar{V}}\frac{e^{-\bar{k}\tau}}{1-e^{-\bar{k}\tau}}\right)^2 \times \left[\left(\frac{\bar{k}\tau}{1-e^{-\bar{k}\tau}}\right)^2 \frac{\mathrm{Var}(k)}{\bar{k}^2} + \frac{1-2\bar{k}\tau-e^{-\bar{k}\tau}}{1-e^{-\bar{k}\tau}}\frac{\mathrm{Var}(V)}{\bar{V}^2}\right], \tag{28}$$

respectively (see part C of the Supplementary Material).

Peak value of the concentration, $C_{ss,\max}$

For this quantity, an inequality for does not apply for all τ (see part C of the Supplementary Material).

Small deviation approximations for the mean and variance of $C_{ss,\max}$ are

$$\bar{C}_{ss,\max} \simeq \left(\frac{D}{\bar{V}}\frac{1}{1-e^{-\bar{k}\tau}}\right) \times \left[1+\frac{\left(1+e^{-\bar{k}\tau}\right)e^{-\bar{k}\tau}}{2}\left(\frac{\bar{k}\tau}{1-e^{-\bar{k}\tau}}\right)^2 \frac{\mathrm{Var}(k)}{\bar{k}^2} + \frac{1-(1+\bar{k}\tau)e^{-\bar{k}\tau}}{1-e^{-\bar{k}\tau}}\frac{\mathrm{Var}(V)}{\bar{V}^2}\right] \tag{29}$$

and

$$\mathrm{Var}\left(C_{ss,\max}\right) \simeq \left(\frac{D}{\bar{V}}\frac{1}{1-e^{-\bar{k}\tau}}\right)^2 \times \left[\left(\frac{\bar{k}\tau e^{-\bar{k}\tau}}{1-e^{-\bar{k}\tau}}\right)^2 \frac{\mathrm{Var}(k)}{\bar{k}^2} + \frac{1-(1+2\bar{k}\tau)e^{-\bar{k}\tau}}{1-e^{-\bar{k}\tau}}\frac{\mathrm{Var}(V)}{\bar{V}^2}\right], \tag{30}$$

respectively (see part C of the Supplementary Material).

Application of results to clinical datasets

There are two questions we wish to address. The first concerns inequalities. We would like to know, in some actual case studies, the extent to which the average values, presented above for $t_{1/2}$, k (from rearranging Eq. (12)), C_{ss}, Cl and $C_{ss,\mathrm{ave}}$, deviate from satisfying the equalities that the parameters of an individual satisfy. We shall provide examples of clinical datasets that show that there can be considerable deviations from equalities.

The second question concerns approximations. We would like to know the extent to which the approximations we have presented above, for the means and variances of $t_{1/2}$, C_{ss}, C_t, Cl, $C_{ss,\mathrm{ave}}$, $C_{ss,\min}$ and $C_{ss,\max}$, capture/characterise actual results? We shall provide examples of clinical datasets that allow us to illustrate the accuracy of the approximations.

Inequalities - Drug Regimen 1

To illustrate the working of the inequalities for average values of $t_{1/2}$, C_{ss} and Cl, as given in Eqs. (12), (16) and (21), respectively, we have drawn upon data presented in a paper by Kessler *et al.* (1986)[8] in which the authors studied the effect of either acute myocardial infarction (MI), or congestive heart failure (CCF) on the pharmacokinetics of procainamide (an anti-arrhythmic drug). Study participants were allocated to one of three groups: a control group, a group with participants who had recently suffered an acute MI, and a third group containing participants with CCF. All patients then received continuous infusion of procainamide at a rate of 25 mg/min, until either: (i) a total dose of 1000 mg had been reached, or (ii) an adverse drug reaction had developed, or (iii) there was a sufficient therapeutic response, prior to 1000 mg being reached. Blood was drawn at regular intervals during dosing, and analysed to determine pharmacokinetic parameters of individual participants.

For the purpose of this illustration we shall consider only the participants in the control group.

In the paper of Kessler *et al.* (1986)[8] we note that: (i) $t_{1/2}$ was determined from the equation $t_{1/2} = \ln(2)/k$, with k estimated from the data (by non-linear regression of the curve of procainamide concentration versus time), but k itself was not directly reported; (ii) Cl was estimated by dividing the total dose administered (TD) by the area under the curve of procainamide concentration versus time (AUC); (iii) V was determined from $V = TD \times t_{1/2}/\left[AUC \times \ln(2)\right]$.

Details of the three pharmacokinetic parameters $t_{1/2}$, Cl and V of the individual participants are provided in Table 1, under the heading 'from Kessler et al. (1986)'. These were converted from quantities 'per unit weight', to values for each individual,

by multiplying by the weight given for each participant. In Table 1 we omitted Participant 1 as an unrepresentative outlier[4]. Also included in Table 1 are values of quantities that were calculated from the reported values of the parameters $t_{1/2}$, Cl and V. These are values of k, which were determined in the most direct way from $k = \ln(2)/t_{1/2}$, values of C_{ss} and C_t (at time $t = 2$ h), which were calculated from Eqs. (3) and[5] (2), respectively.

In Table 2 we provide examples of the inequalities that $t_{1/2}$, C_{ss} and Cl obey, using the mean values given in Table 1.

Note that in accordance with Eq. (21), the inequality for Cl goes in the opposite direction to the inequalities for $t_{1/2}$ and C_{ss}, and this is the origin of the negative deviation for Cl that appears in Table 2.

Inequalities - Drug Regimen 2

For Drug Regimen 2 we have established a pair of inequalities for the time averaged concentration in the steady state, $C_{ss,\text{ave}}$, as given in Eq. (24)[6]. To illustrate the working of these inequalities for $C_{ss,\text{ave}}$, we have drawn upon data presented in a paper by Bowles *et. al.* (1988)[11] in which two groups of healthy individuals were orally administered a salt of the bronchodilator theophylline (aminophylline) at a dose of 200 mg every 8 hours[7]. In one group, participants were co-administered the antibiotic norfloxacin, while in the other group participants were administered a placebo. Participants received aminophylline for 4 days, after which serial blood tests were taken and analysed for theophylline concentrations. The study aimed to assess the impact of norfloxacin on the pharmacokinetics of theophylline. For the purpose of this illustration we shall consider only the participants in the control group.

In the paper by Bowles *et. al.* (1988)[11], the authors calculated: (i) the clearance for each participant, Cl, from the ratio $Cl = D \times 0.8/AUC_{0-8h}$, namely the 'dose administered, each bolus', divided by the 'area, for the dosage interval, under the plasma concentration versus time curve', and (ii) the elimination rate constant, k, and half-life, $t_{1/2}$ (by linear regression of the curve of plasma concentration versus time). The paper did not directly report the volume of distribution for each participant, but we derived this using a rearranged form of Eq. (9), namely $V = Cl/k$. We then used the resulting V values to calculate the results for time-averaged steady-state concentration, $C_{ss,\text{ave}}$, from Eq. (4).

The reported values of the pharmacokinetic parameters k and Cl of the individual participants are provided in Table 3, under the heading 'from Bowles et al. (1988)'. We also included, in Table 3, values of quantities that were calculated using these two pharmacokinetic parameters. These are values of V for each participant, which were calculated using a rearranged form of Eq. (9), namely $V = Cl/k$, along with values of $C_{ss,\text{ave}}$, $C_{ss,\text{min}}$ and $C_{ss,\text{max}}$, which were calculated from Eqs. (4), (5) and (6), respectively.

In Table 4 we provide an example of the two inequalities that $C_{ss,\text{ave}}$ obeys, using mean values given in Table 3.

Approximations - Drug Regimen 1

We have given small deviation approximations for the means and variances of $t_{1/2}$, C_{ss}, C_t and Cl, under Drug Regimen 1, and corresponding results for $C_{ss,\text{ave}}$, $C_{ss,\text{min}}$ and $C_{ss,\text{max}}$, under Drug Regimen 2. Now, we calculate exact results for these quantities, that arise from the data, and compare these with the corresponding approximations. For example, the final column of Table 1 contains values of C_t for 9 participants, that arose from the clinical dataset of Kessler et al. (1986)[8]. We can calculate the *exact mean* of these 9 values of C_t, and compare this result with the approximate result for the mean: (i) neglecting any deviations of the parameters k and V from their mean values (as given by $\bar{C}_t \simeq \frac{R}{\bar{k}\bar{V}} e^{-\bar{k}t}$), and (ii) keeping the leading effects of deviations of the parameters k and V, as given in Eq. (19). In this way, we obtain an indication of the quality of the approximations and gain an understanding of the importance of the deviations of k and V from their mean values, in a heterogeneous population.

In Table 5 and Table 6 we compare exact and approximate means and variances respectively from the data by Kessler et al.[8]

Approximations - Drug Regimen 2

In Table 7 and Table 8 we compare exact and approximate means and variances from the data by Bowles et al.[11]

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[4]Patient 1 is identified as an outlier by Grubb's outlier test ($G = 2.322$, $\alpha = 0.05$)[9]. Consistent with this, Patient 1 is an outlier in both clearance and age, lying greater than two standard deviations from the mean of both of these quantities. Finally, with inclusion of Patient 1, the Pearson correlation coefficient[10] between V and Cl is 0.69, and the p-value, for the null hypothesis of no correlation against the alternative of a non-zero correlation, is 0.03. This p-value would cause us to reject the generally accepted hypothesis of independence of V and Cl. By contrast, with omission of Patient 1, we find a Pearson correlation coefficient of 0.28 and a p-value of 0.47.

[5]We could have derived C_{ss} from R/Cl rather than $R/(Vk)$. However, for all participants except Patient 10, the difference was of of the order of 2% or smaller.

[6]In addition to these inequalities, inequalities also exist, as in Drug Regimen 1, between $t_{1/2}$ and k according to Eqs. (12) and (15), and between Cl, V and k according to Eq. (21).

[7]Generally, any dose of aminophylline has to be multiplied by a *salt factor* of 0.8 to determine the dose of therapeutically active theophylline that the aminophylline contains[4].

Discussion

Pharmacokinetic equations relate different parameters that characterise an individual. In this paper we have established results for *statistics* of pharmacokinetic parameters (such as the mean and variance) of a population of individuals, with the results taking the form of inequalities and approximations.

One of the findings of this work is that relations between statistics of pharmacokinetic parameters, such as mean values, do not generally follow by replacing the parameters of an individual, within a pharmacokinetic equation, by mean values of the parameters. An illustrative example of this concerns the half life, $t_{1/2}$. Despite the fact that $t_{1/2} = \ln(2)/k$, we have shown that the mean half life, $\bar{t}_{1/2}$, does not generally follow from $\bar{t}_{1/2} = \ln(2)/\bar{k}$ where $\bar{k}$ is the mean value of k. This finding has wider implications for the way we use knowledge of the statistics of some pharmacokinetic parameters, to determine statistics of other pharmacokinetic parameters. Thus, if we know the value of $\bar{k}$ and estimate $\bar{t}_{1/2}$ using $\bar{t}_{1/2} = \ln(2)/\bar{k}$, then the value of $\bar{t}_{1/2}$ obtained will generally *deviate* from the actual (or true) mean value of the half life. For some pharmacokinetic equations there is a systematic direction of the deviation, with an inequality generally holding between the estimated and actual results. For other pharmacokinetic equations, no systematic direction of the deviation holds for all parameter values - so no inequality generally applies. We note that in some cases, the deviation between calculated and actual results can be quite pronounced, and we discuss below how such deviations may lead to an increased risk of medication-related harm through inappropriate design of a dosage regimen.

In general, the design of continuous dosage regimens are based on a number of principles. Firstly, a clinician must decide upon a target *steady state* concentration. This will lie somewhere within the therapeutic range of the drug selected, but the severity of the condition being treated and other clinical or drug-related factors (e.g. drug interactions) may determine where in that range the target is set.

Once the target concentration is identified, it is necessary to calculate the continuous dose rate, R, which maintains this concentration. Following from Eq. (3) , the calculation involves multiplying the target steady state concentration, C_{ss}, by the clearance in the form $k \times V$. However, in clinical practice, mean values of k and V are sometimes used in the calculation, and such a usage can, as described in this work, lead to a value of the clearance that overestimates the actual value of the clearance that is required for the selected target concentration (see Eq. (21)). This then leads to a dose rate that is itself overestimated, and when applied to a patient, produces a steady state concentration that is larger than originally identified.

In Table 2 we can see that for the data of Kessler et al.[8], the actual mean clearance, $\overline{Cl}$, was in accordance with Eq. (21), and smaller than the product of the population averages of k and V, namely $\bar{k} \times \bar{V}$. For this dataset, the actual value of $\overline{Cl}$, was 4% smaller than $\bar{k} \times \bar{V}$.

In some cases a clinician may decide to commence drug therapy using a standard published dosage regimen. Using Eq. (3) the clinician can then predict the steady state concentration that this regimen would achieve. However, predicting the mean steady state concentration, $\overline{C}_{ss}$, using, for example, the mean values of k and V in the plausible (but generally incorrect) formula $\bar{C}_{ss} = R/\left(\bar{V}\bar{k}\right)$ (cf. Eq. (16)), means that the value of $\overline{C}_{ss}$ that this formula predicts, is smaller the actual mean value. For the data of Kessler et al.[8] the value of $\overline{C}_{ss}$ given in Table 2, which would arise from the equation $\bar{C}_{ss} = R/\left(\bar{V}\bar{k}\right)$, is approximately 20% smaller than the actual mean steady state concentration. Such an erroneous prediction for $\overline{C}_{ss}$ could result in a patient's actual steady state blood plasma drug concentration being higher than the value predicted. Furthermore, if, in the absence of response to the drug, the clinician increases the dose, this could lead to a yet higher plasma concentration that could lie in the toxic range.

There is a further point we wish to make, regarding continuous intravenous infusion kinetics. It covers the case where a standard published dosage regimen is used, and assumes the only statistic available to the clinician is the mean elimination rate constant, $\bar{k}$. We note that the time taken for the concentration to reach e.g., 95% of the steady state value is solely dependent upon the half life of the drug. In an initially drug-free individual, a concentration of 95% of the steady state value is achieved after a time of $\frac{\ln(20)}{\ln(2)} \times t_{1/2} \simeq 4.32 \times t_{1/2}$ (see part A of the Supplementary Material for details). However, as found in the data of Kessler et al., an estimate of $\bar{t}_{1/2}$, based on the generally incorrect equation $\bar{t}_{1/2} = \ln(2)/\bar{k}$, can be substantially smaller than the actual value of $\bar{t}_{1/2}$ (see Table 2). This difference between estimated and actual values of $\bar{t}_{1/2}$ has the consequence that it may take longer to approach a steady state concentration (and hence a therapeutic concentration) than the estimated $\bar{t}_{1/2}$ would suggest. Additionally, if the mean steady state concentration, $\bar{C}_{ss}$, is estimated from the incorrect result $\bar{C}_{ss} = R/(\bar{V}\bar{k})$, then the estimate will generally be smaller than the true $\bar{C}_{ss}$. As a consequence, at the time when the plasma drug concentration is expected to be at 95% of the steady state value, the concentration may actually be at, or above the desired steady state value. If a plasma drug level taken at this time confirms attainment of the steady state value then clinical monitoring may be reduced/terminated. However, the patient's plasma drug concentration will actually increase for a further period of time until the steady state is genuinely achieved, making toxicity more likely. For the case of intermittent bolus administration, similar considerations apply.

As another clinical scenario of interest, consider a patient taking a drug with low therapeutic index, who presents with

signs of drug toxicity. If the plasma drug concentration is taken, and found to exceed the therapeutic range, then the clinician will stop the dose. The clinician will need to know the time it will take for the plasma drug concentration to fall back to the therapeutic range, at which point dosing can be restarted, albeit at a lower rate. In order to estimate this time, the clinician needs to first have an estimate of the elimination rate constant k. For an 'average' patient the population mean value for k would naturally be used. The plasma concentration of the drug at time t is then given by the equation

$$C_t = C_0 e^{-kt} \tag{31}$$

where C_0 is the concentration at time 0. The clinician would substitute both the measured plasma concentration, C_0, and the target concentration, C_t, into Eq. (31) and solve for t to estimate the required time. A commonly encountered problem, however, is that a mean value of k may not be readily available in the literature. A practical solution would be to transform the mean value of $t_{1/2}$ (which *is* usually readily available) into k, using the equation $k = \ln(2)/t_{1/2}$, which is a rewrite of Eq. (1). However, we now know, from the present work, that using mean values in this equation for k leads to a systematic underestimate of k, which results in an overestimate of the time taken for the plasma concentration to fall to a particular target value. As an illustration of this, we have simulated a small population of $n = 10$ patients, by randomly generating k values for each individual (details given in Figure 1 Caption), and then determining the individual values of $t_{1/2}$ (calculated from $t_{1/2} = \ln(2)/k$). In this simulation, we take the therapeutic range of the drug to be $5 - 15$ mg/L, and the initial toxic plasma concentration to be 20 mg/L, and we find that when the mean value of k (i.e. $\bar{k}$) is used in Eq. (31) that the time taken to reach 5 mg/L is approximately 11 h. If, on the other hand, we use $\ln(2)/\bar{t}_{1/2}$ in place of k in Eq. (31) we find that the plasma concentration is predicted to reach 5 mg/L after approximately 15 h. During this additional 4 h period, the patient's drug concentration will dip below the therapeutic threshold. If the drug in question were an antibiotic, an antiviral, an antiretroviral or an immunosuppressant then it could lead to treatment failure (possibly drug resistance in the case of antimicrobial/viral/retroviral therapy). Figure (**??**) shows the plasma vs. time profile for the 10 simulated patients, and the estimates of the time taken to reach 5 mg/L using either $\bar{k}$ or $\ln(2)/\bar{t}_{1/2}$ in place of k in Eq. (31).

When we apply population averages to individual patients, we are making the assumption that the patients have pharmacokinetic parameters that are close to the average values reported in (or inferred from) a clinical trial. This will generally lead to a discrepancy between the observed and predicted concentrations of a drug in the blood plasma of a patient, unless a personalised approach is used[12].

A second source of error, however, is the discrepancy that occurs when we transform the mean values of known pharmacokinetic parameters into the mean values of unknown pharmacokinetic parameters. This need arises because not all parameters are reported in a clinical trial. Indeed, we are seeing more clinical trials being conducted, especially in special patient groups, e.g., those with renal impairment, or at the extremes of age, with no consistency in the types of pharmacokinetic parameters that are documented. This means that clinicians may frequently have to transform parameters to obtain data that can answer their particular therapeutic question.

There are perhaps three obvious resolutions to the above issues. The first would be to determine personalised pharmacokinetic parameter values for individual patients using non-linear mixed effect modelling software.[3] Although this is routinely used in clinical trials, and in some hospital laboratories, it is not common practice in the day to day clinical care of patients as it requires expensive software, and expertise in its use. The second approach is for publishers/referees to insist that researchers present population averages for *all* pharmacokinetic parameters, not just a subset of the parameters. The third, and perhaps easiest to implement, is to develop a method to correct the value of parameters that have been calculated from population statistics, so that they more accurately reflect the actual average values. In Part C of the Supplementary Material we set out a series of approximations which can be used in clinical practice to correct the results that arise by using mean values of parameters in pharmacokinetic equations that apply only to the parameter-values of an individual. As we have shown in the results section, when applied to published clinical trial data, these approximations lead to more accurate estimates of the true mean-value of a pharmacokinetic parameter. Alongside education of healthcare professionals regarding this issue, the application of these approximations in the clinical setting may thus reduce calculational errors, and the consequential risk of supra- or sub-therapeutic drug concentrations, which will have a positive impact on patient care. The calculations that we provide in the Supplementary Material are relatively simple, and can be easily coded in commonly used software programmes such as Microsoft Excel, making its clinical utility virtually universal. The authors have provided a sample Microsoft Excel spreadsheet as Supplementary Material which contains the formulae for approximations for continuous and bolus dosing mean and variance PK mean parameters. These can be used by readers to calculate values for drugs of their choice.

In conclusion, we believe that it is important for the next generation of pharmacy, medical, and nursing students, to be educated about errors and inequalities that can arise when transforming reported mean values of pharmacokinetic parameters into the mean values of parameters that are required but not reported. These errors are a potential source of error in dosing and a source of risk and harm to patients that can both be reduced.

The practice of transforming population averages of pharmacokinetic parameters, to other parameters, without taking into

account the deviation of parameters from their mean values, is common in some pharmacokinetic textbooks (see e.g.,[2]), and we hope this paper will stimulate a review of the relevant literature.

Methods

Literature search and data analysis

Medline (Pubmed, NCBI) was searched for relevant clinical trials that presented raw data of pharmacokinetic parameters for drugs with a narrow therapeutic window. Simulations were conducted in Microsoft Excel, and data analysed and presented in Matlab and Graphpad Prism (GraphPad Prism version 8.3.1 for Mac, GraphPad Software, La Jolla California USA, www.graphpad.com.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org[13], and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019 a,b).

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Author contributions statement

GS and DW contributed equally to all aspects of the manuscript: conception, writing, and analysis.

Additional information

The authors declare no competing interests.

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List of figure legends

Figure 1

Illustration of the systematic error that occurs when the time taken for a drug to decay from an initial value to a secondary value follows from using the generally incorrect estimate $\bar{k} = \ln(2)/\bar{t}_{1/2}$ **Panel A** Plasma concentration vs. time profiles for $n = 10$ random values of k that were drawn from a uniform distribution over the interval 0.04 h^{-1} to 0.2 h^{-1}. **Panel B:** The plasma concentration vs. time profiles, where either $\bar{k}$ (in blue) or the estimate $\ln(2)/\bar{t}_{1/2}$ (in red) were used in place of k in Eq. (31). The initial concentration used for the figure (C_0) was 20 mg/L. With a therapeutic range of the drug of $5-15$ mg/L, the effect of estimating k, for an 'average' patient, using $\ln(2)/\bar{t}_{1/2}$, instead of $\bar{k}$, is to overestimate the time it takes for the plasma concentration to fall to 5 mg/L (red curve). The discrepancy between actual and estimated times to reach 5 mg/L (before another dose is required) is approximately 4 h and is shown by the grey shaded area. During this time, the actual plasma concentration lies below the minimum effective therapeutic concentration.

List of tables

	from Kessler et al. (1986)			calculated quantities		
Participant	$t_{1/2}$ (h)	Cl (L/h)	V (L)	k (1/h)	C_{ss} (mg/L)	C_t for $t = 2$h (mg/L)
2	3.2	40.0	189	0.22	36.6	23.8
3	2.5	31.0	113	0.28	47.9	27.5
4	1.2	59.1	100	0.58	26.0	8.2
5	1.1	71.8	116	0.63	20.5	5.8
6	2.0	64.2	182	0.35	23.8	11.9
7	2.2	32.7	104	0.32	45.8	24.4
8	4.3	21.4	130	0.16	71.6	51.9
9	2.2	35.0	113	0.32	42.1	22.4
10	3.3	16.9	96	0.21	74.4	48.9
mean	2.4	41.3	127	0.34	43.2	25.0
std. dev.	1.0	19.3	35	0.16	19.5	16.3

Table 1. Reported values of the pharmacokinetic parameters $t_{1/2}$, Cl and V presented in Kessler *et al.* (1986)[8] for 9 control participants who received intravenous procainamide at a rate of $R = 25$ mg/min. The table also contains values of k, C_{ss}, V^{-1} and C_t (for $t = 2$ h), which were calculated from the reported pharmacokinetic parameters of the participants, along with means and standard deviations (abbreviated to std. dev.) of all quantities

quantity	inequality	left side of the inequality	right side of the inequality	% deviation of left and right sides
$t_{1/2}$ (h)	Eq. (12)	2.4	2.0	16
C_{ss} (mg/L)	Eq. (16)	43.2	(36.8, 34.9)	(15, 19)
Cl (L/h)	Eq. (21)	41.3	43.0	−4

Table 2. Examples of the working of the inequalities derived in this work for Drug Regimen 1. Using the mean values given in Table 1, that arise from the data in the paper by Kessler *et al.* (1986)[8], along with the mean value of V^{-1} of 8.31×10^{-3}, we have compared the left and right hand sides of the different inequalities. The column labelled '% deviation of left and right sides' contains the percentage difference between the left and right sides of the inequalities. The steady-state concentration, C_{ss}, satisfies *two* inequalities (Eq. (16)), which have the form $\bar{C}_{ss} \geq a \geq b$, and we give results for this in the table, writing the right side of the inequality as (a, b)

	from Bowles et al. (1988)		calculated quantities			
Participant	k (1/h)	Cl (L/h)	V (L)	$C_{ss,\text{ave}}$ (mg/L)	$C_{ss,\text{min}}$ (mg/L)	$C_{ss,\text{max}}$ (mg/L)
1	0.144	3.01	20.9	6.64	3.54	11.19
2	0.073	2.19	30.0	9.13	6.72	12.06
3	0.096	3.39	35.3	5.90	3.92	8.45
4	0.099	2.29	23.1	8.73	5.73	12.64
5	0.146	4.44	30.4	4.50	2.37	7.64
6	0.113	2.78	24.6	7.19	4.43	10.93
7	0.056	2.74	48.9	7.30	5.79	9.06
8	0.066	2.17	32.9	9.22	7.00	11.86
9	0.104	2.82	27.1	7.09	4.55	10.45
10	0.072	2.66	36.9	7.52	5.56	9.89
mean	0.097	2.85	31.0	7.32	4.96	10.42
std. dev.	0.031	0.68	8.2	1.47	1.46	1.64

Table 3. Reported values of the pharmacokinetic parameters k and Cl, presented in Bowles *et al.* (1988)[11] for 10 control participants who received 200 mg of theophylline (aminophylline) every $\tau = 8$ hours. The amount of aminophylline administered each dose was $D = 200$ mg$\times 0.8$ where 0.8 is the salt factor. The table also contains values of V, $C_{ss,\text{ave}}$, $C_{ss,\text{min}}$ and $C_{ss,\text{max}}$, which were calculated from the pharmacokinetic parameters of the participants. The means and standard deviations of all quantities are provided in the final two rows of the table

quantity	inequality	left side of the inequality	right side of the inequality	% deviation of left and right sides
$C_{ss,\text{ave}}$ (mg/L)	Eq. (24)	7.32	(7.04, 6.65)	(4, 9)

Table 4. Example of the working of the inequalities derived in this work for Drug Regimen 2. Using mean values given in Table 3, that arise from the data in the paper by Bowles et al. (1988), we have compared the left and right hand sides of the inequalities for the time averaged steady-state concentration, $C_{ss,\text{ave}}$, given in Eq. (24). This equation contains two inequalities, which have the form $C_{ss,\text{ave}} \geq a \geq b$, and we give results for this in the table, writing the right side of the inequality as (a, b).

quantity	equation	exact mean	approx. neglecting deviations	approx. including leading deviations
$\bar{t}_{1/2}$ (h)	Eq. (13)	2.4	2.0	2.5
$\bar{C}_{ss}$ (mg/L)	Eq. (17)	43.2	34.9	42.8
$\bar{C}_t$ (mg/L)	Eq. (19)	25.0	17.7	24.5
$\overline{Cl}$ (L/h)	Eq. (22)	41.3	43.0	39.8

Table 5. Exact results for mean values of $t_{1/2}$, C_{ss}, C_t (with $t = 2$ h) and Cl, that arise from the data of Kessler *et al.* (1986)[8], are compared with approximate results. The approximate results are given where we neglect any deviations of k and V from their mean values (for example, determining $\bar{t}_{1/2}$ from the equation $\bar{t}_{1/2} = \ln(2)/\bar{k}$) and where we include the leading effect of deviations (for example, determining $\bar{t}_{1/2}$ from Eq. (13)). The table was constructed using entries of Table 1.

quantity	approximation	exact variance	approx. from leading deviations
$\text{Var}(t_{1/2})$ (h^2)	Eq. (14)	1.05	0.96
$\text{Var}(C_{ss})$ ((mg)^2/L^2)	Eq. (18)	3.80×10^2	1.87×10^2
$\text{Var}(C_t)$ ((mg)^2/L^2)	Eq. (20)	2.66×10^2	1.47×10^2
$\text{Var}(Cl)$ (L^2/h^2)	Eq. (23)	3.52×10^2	2.85×10^2

Table 6. Exact results for the variances, that arise from the data of Kessler *et al.* (1986)[8], are compared with approximate results that include the leading effect of deviations of k and V from their mean values. The table was constructed using entries of Table 1.

quantity	approximation	exact mean	approx. neglecting deviations	approx. including leading deviations
$\bar{C}_{ss,\mathrm{ave}}$ (mg/L)	Eq. (25)	7.32	6.65	7.34
$\bar{C}_{ss,\mathrm{min}}$ (mg/L)	Eq. (27)	4.96	4.40	4.96
$\bar{C}_{ss,\mathrm{max}}$ (mg/L)	Eq. (29)	10.42	9.56	10.47

Table 7. Exact results for mean values of $C_{ss,\mathrm{ave}}$, $C_{ss,\mathrm{min}}$ and $C_{ss,\mathrm{max}}$, that arise from the data of Bowles *et al.* (1988), are compared with approximate results. The approximate results are given where we neglect any deviations of k and V from their mean values (for example, by determining $\bar{C}_{ss,\mathrm{ave}}$ from the equation $\bar{C}_{ss,\mathrm{ave}} = D/\left(\bar{k}\tau\bar{V}D\right)$) and where we include the leading effect of deviations (for example, by determining $\bar{C}_{ss,\mathrm{ave}}$ from Eq. (25)). The table was constructed using entries of Table 3.

quantity	approximation	exact variance	approx. from leading deviations
$\mathrm{Var}(C_{ss,\mathrm{ave}})$ $((\mathrm{mg})^2/\mathrm{L}^2)$	Eq. (26)	2.15	1.52
$\mathrm{Var}(C_{ss,\mathrm{min}})$ $((\mathrm{mg})^2/\mathrm{L}^2)$	Eq. (28)	2.13	1.64
$\mathrm{Var}(C_{ss,\mathrm{max}})$ $((\mathrm{mg})^2/\mathrm{L}^2)$	Eq. (30)	2.70	2.10

Table 8. Exact results for the variances that arise from the data of Bowles *et al.* (1988), are compared with approximate results that include the leading effect of deviations of k and V from their mean values. The table was constructed using entries of Table