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When can the infusion period be safely ignored in the estimation of pharmacokinetic parameters of drugs in humans?

L. S. Freedman and P. Workman

MRC Clinical Oncology and Radiotherapeutics Unit, MRC Centre, Hills Road, Cambridge CB2 2QH, England

Summary. We describe a simple and rapid method to determine the amount by which the area under the curve (AUC) is underestimated when a drug is given by i.v. infusion, but the infusion period is ignored and the post-infusion data are analysed as if they derive from a bolus injection. Charts are provided that allow the investigator to determine the approximate underestimation for drugs following the one- and two-compartment models, and hence to decide whether it is acceptable to ignore the infusion period in a given case (e.g., underestimation $<5\%$ or 10%). Equations are also provided that allow the exact underestimation to be calculated, together with the true value of the AUC.

Introduction

In cancer chemotherapy, many drugs are given by i.v. infusion rather than by rapid bolus injection. This may be because of limited solubility in the injection vehicle, to avoid toxicological problems associated with high peak concentrations, or to maintain therapeutic concentrations for a sustained period. The infusion time may vary from a few minutes to several hours or days, depending on the drug, the dose and the clinical circumstances. Some investigators have opted to ignore the infusion period, particularly when this is short, and to analyse only the postinfusion data, treating these as if they derive from a bolus injection. This may have a significant effect on the estimated plasma pharmacokinetic parameters, including the area under the curve (AUC). Accurate assessment of the AUC is particularly important at present, in view of the proposals to base phase 1 dose escalations on rodent and human AUC values [1, 2].

We therefore felt it would be useful to provide a simple, rapid method to assess the acceptability of ignoring the infusion period for a given set of data. This paper first presents the pharmacokinetic equations for the bolus and infusion methods of administration and relates the corresponding parameters. It is then shown that the AUC is underestimated if the infusion period is ignored, and the percentage underestimation is given by a formula. Finally, graphs are presented that allow the investigator to judge quickly whether or not ignoring the infusion period will lead to serious underestimation of the AUC. The use of these graphs is demonstrated.

Offprint requests to: P. Workman

One-compartment model

The formulae given below both for one- and two-compartment models can be found in the textbooks of Wagner [7] and Gibaldi and Perrier [3]. They have also been given more explicitly by Loo and Riegelman [4]. We reproduce them here in a simplified form for the benefit of less mathematically inclined readers, and also to show the development of formulae for the percentage underestimation of the AUC.

Intravenous bolus injection. The serum concentration C (t) at time t after the injection is given by

$$C(t) = Ae^{-Kt} \tag{1}$$

The parameter A is the concentration at time zero and is equal to D/V, where D is the dose of drug given and V is the volume of the compartment. The parameter K is the elimination constant, and the half-life is given by ln(2)/K. The area under the curve (AUC) is given by A/K. Throughout this paper, the AUC is measured from zero time to infinity ($AUC_{0-\infty}$).

Intravenous infusion. Suppose the same amount of drug, D, is infused at a constant rate over time T. The serum concentration C (t) at time t from the start of infusion is then

$$C(t) = \frac{A(1-e^{-Kt})}{KT} \tag{2}$$

while infusion is continuing.

When infusion ceases, the concentration is

$$C(T) = \frac{A(1-e^{-KT})}{KT} \tag{3}$$

The concentration thereafter decreases according to the equation

$$C(t) = \frac{A(1-e^{-KT})}{KT} e^{-K(t-T)} \tag{4}$$

The elimination constant is K and the half-life for the post-infusion phase is ln(2)/K, as for the bolus injection. The AUC remains equal to A/K.

Intravenous infusion – ignoring the infusion period. If the investigator chooses to analyse only the post-infusion data and to ignore the infusion period, then Eq (4) will pertain and may be rewritten as

$$C(t') = A'e^{-Kt'} \tag{5}$$

$$\text{where } A' = \frac{A(1-e^{-KT})}{KT} \tag{6}$$

and t′ is time *measured from the end of infusion*. Thus, the post-infusion elimination curve should resemble that obtained from bolus injection of the drug, but with peak A′ instead of A. The relationship in Eq. (6) means that A′ is always less than A.

The elimination constant remains as K in Eq.(5), hence the estimation of this parameter is not affected by ignoring the infusion period; neither are half-life estimates affected.

The AUC, ignoring infusion, will equal A′/K and will underestimate the true AUC, A/K, because A′ is less than A. The resulting percentage underestimation of AUC will be $(1 - A'/A) \times 100\%$, which from Eq. (6) is dependent only on the value of KT. Figure 1 shows the percentage underestimation as related to KT. Critical values are: 5% underestimation if KT equals 0.103; 10% underestimation if KT equals 0.215; 20% underestimation if KT equals 0.465; 50% underestimation if KT equals 1.594. The smaller the value of KT, the less serious is the underestimation of the AUC. If the underestimation is sufficiently serious, then the investigator may calculate the correct AUC from

$$AUC = \frac{A'T}{1-e^{-KT}} \tag{7}$$

Two-compartment model

Intravenous bolus injection. The serum concentration C(t) at time t after the injection is given by

$$C(t) = Ae^{-\alpha t} + Be^{-\beta t} \tag{8}$$

The sum A + B represents the concentration at time zero and is equal to D/V, where D is the dose of the drug and V the volume of the central compartment. The parameter α is the distribution phase rate constant and β is the elimination phase rate constant. In general, we require that α is greater than β. The AUC is given by $A/\alpha + B/\beta$.

Intravenous infusion. Suppose the same amount of drug, D,

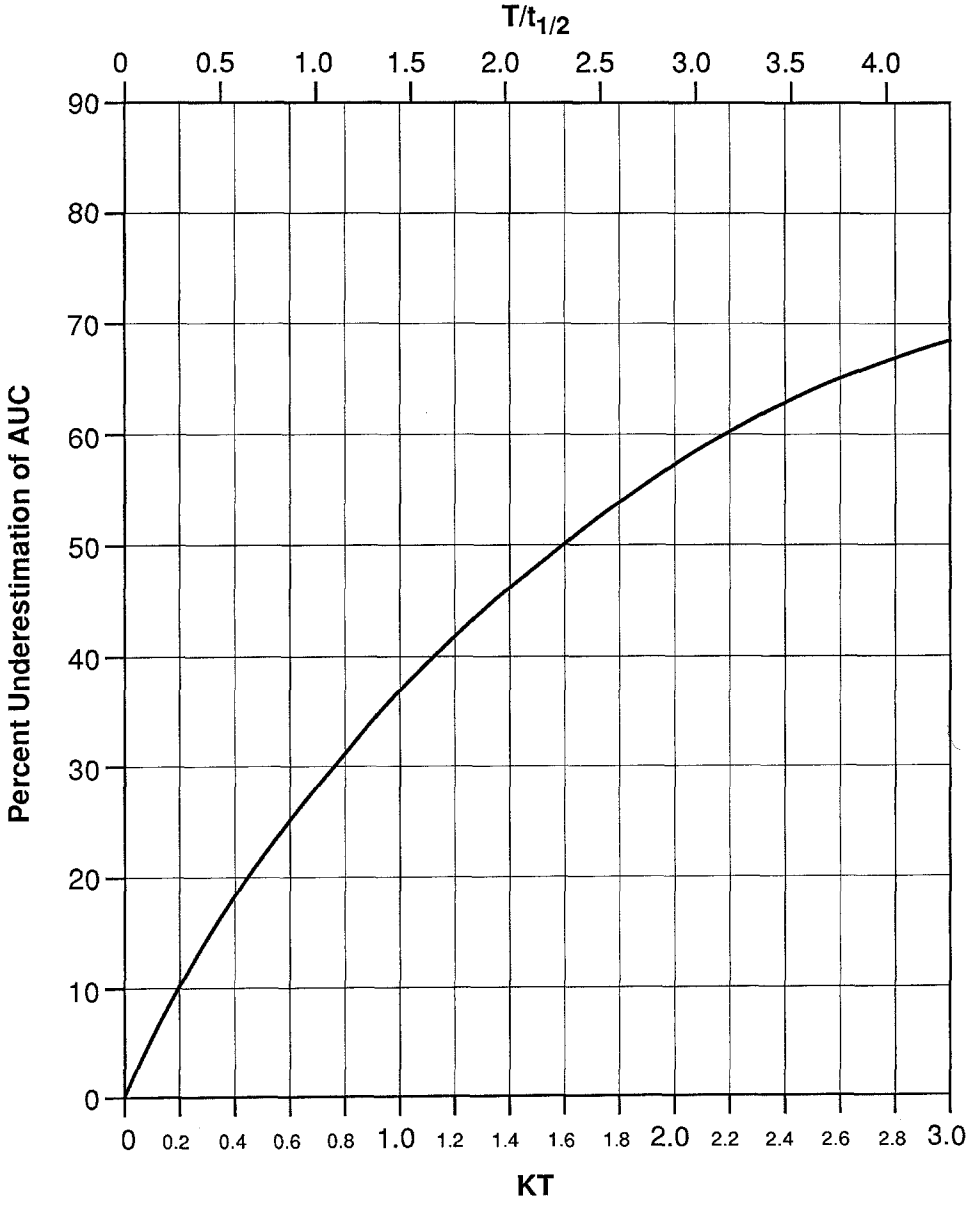

Fig. 1. Percentage underestimation of AUC, ignoring infusion period, for one-compartment model

is infused at a constant rate over time T. The serum concentration C (t) at time t from the start of infusion is then

$$C(t) = \frac{A(1-e^{-\alpha t})}{\alpha T} + \frac{B(1-e^{-\beta t})}{\beta T} \quad (9)$$

while infusion is continuing.

When infusion ceases, the concentration is

$$C(T) = \frac{A(1-e^{-\alpha T})}{\alpha T} + \frac{B(1-e^{-\beta T})}{\beta T} \quad (10)$$

The concentration thereafter decreases according to the equation

$$C(t) = \frac{A(1-e^{-\alpha T})}{\alpha T} e^{-\alpha(t-T)} + \frac{B(1-e^{-\beta T})}{\beta T} e^{-\beta(t-T)} \quad (11)$$

The distribution and elimination rate constants remain the same as for bolus injection. The AUC remains equal to $A/\alpha + B/\beta$.

Intravenous infusion – ignoring the infusion period. If the investigator chooses to analyse only the post-infusion data and to ignore the infusion period, then Eq. (11) will pertain and may be rewritten as

$$C(t') = A'e^{-\alpha t'} + B'e^{-\beta t'} \quad (12)$$

$$\text{where } A' = \frac{A(1-e^{-\alpha T})}{\alpha T} \quad (13)$$

$$B' = \frac{B(1-e^{-\beta T})}{\beta T} \quad (14)$$

and t' is time *measured from the end of infusion.* From Eq. (13) and (14) it can be shown that the ratio A'/B' is close to A/B for short infusion periods and decreases towards the value $A\beta/B\alpha$ with increasing infusion time T. Thus, the longer the infusion time, the less apparent will become the two-compartment nature of the kinetics when judged on the basis of the post-infusion data. The Eqs. (13) and (14) also mean that the peak (A' + B') is always less than the peak observed after bolus injection (A + B).

The distribution and elimination rate constants in Eq. (12) remain as α and β respectively, so that estimation of these parameters is not affected by ignoring the infusion period.

The AUC, ignoring infusion, will equal $A'/\alpha + B'/\beta$. This will underestimate the true AUC, $A/\alpha + B/\beta$, because A' is less than A and B' is less than B. The resulting percentage underestimation of AUC will be

$$\left[1 - \frac{A'/\alpha + B'/\beta}{A/\alpha + B/\beta}\right] \times 100\% \quad (15)$$

Expression (15) is dependent on three quantities: αT, βT and A'/B'. In fact, one may rewrite it as

$$\left[1 - \frac{(A'/B')\frac{1}{\alpha T} + \frac{1}{\beta T}}{(A'/B')\frac{e^{\alpha T}}{e^{\alpha T}-1} + \frac{e^{\beta T}}{e^{\beta T}-1}}\right] \times 100\% \quad (16)$$

Knowing these three quantities, from Eq. (16) one may calculate the percentage underestimation of AUC resulting from ignoring the infusion period. Figures 2–5 provide quick checks on the percentage underestimation of AUC. Their use will be explained in the next section.

If the underestimation is sufficiently small, then the investigator will be reassured that little has been lost by ignoring the infusion period. Otherwise, the investigator may calculate the correct AUC from

$$AUC = T\left[\frac{A'}{1-e^{-\alpha T}} + \frac{B'}{1-e^{-\beta T}}\right] \quad (17)$$

Examples

One-compartment model. Consider four drugs with respective half-lives of 30 min ($K = 1.386\ h^{-1}$), 1 h ($K = 0.693\ h^{-1}$), 3 h ($K = 0.231\ h^{-1}$) and 6 h ($K = 0.116\ h^{-1}$). Suppose that each of these drugs was being given by infusion over periods of 10 min, 30 min, 1 h or 2 h. Table 1 shows the percentage underestimation of the true AUC if calculated ignoring the infusion time. These values can also be read directly from Fig. 1. It can be seen that a 10% underestimate occurs when the infusion time is one-third of the half-life. The estimate of AUC is grossly in error (underestimate of over 25%) when the infusion time is greater than or equal to the half-life of the drug.

Two-compartment model. (a) Consider a drug which has a distribution half-life of 20 min ($\alpha = 2.079\ h^{-1}$) and an elimination half-life of 4 h ($\beta = 0.173\ h^{-1}$). Suppose that the drug was infused over 10 min (T = 0.167 h) and analysis carried out on the post-infusion data indicated that A'/B' = 2.

Equation (16) may be used to calculate that the true AUC would be underestimated by 3.3% if the infusion period were ignored. Alternatively, Fig. 2–5 may be consulted. Figure 2 allows the investigator to determine whether or not the underestimation exceeds 5%. First αT and βT are determined; in this case they are 0.346 and 0.029 respectively. The point on the graph determined by these coordinates is then located and its position in respect to the appropriate A'/B' curve is observed. In our case, A'/B' = 2 and the point lies *below* the corresponding curve. Hence the underestimation of AUC is less than 5%.

Table 1. Percentage underestimation (%U) of AUC in the one-compartment model if infusion period is ignored

Half-life [h] ($t_{1/2}$)	K	Time of infusion (T) [min]											
		10			30			60			120		
		$T/t_{1/2}$	KT	%U	$T/t_{1/2}$	KT	%U	$T/t_{1/2}$	KT	%U	$T/t_{1/2}$	KT	%U
0.5	1.386	0.333	0.231	10.7	1.0	0.693	27.9	2.0	1.386	45.9	4.0	2.772	66.2
1.0	0.693	0.167	0.116	5.6	0.5	0.347	15.5	1.0	0.693	27.9	2.0	1.386	45.9
3.0	0.231	0.056	0.038	1.9	0.167	0.116	5.6	0.333	0.231	10.7	0.667	0.462	19.9
6.0	0.116	0.028	0.019	1.0	0.083	0.058	2.8	0.167	0.116	5.6	0.333	0.231	10.7

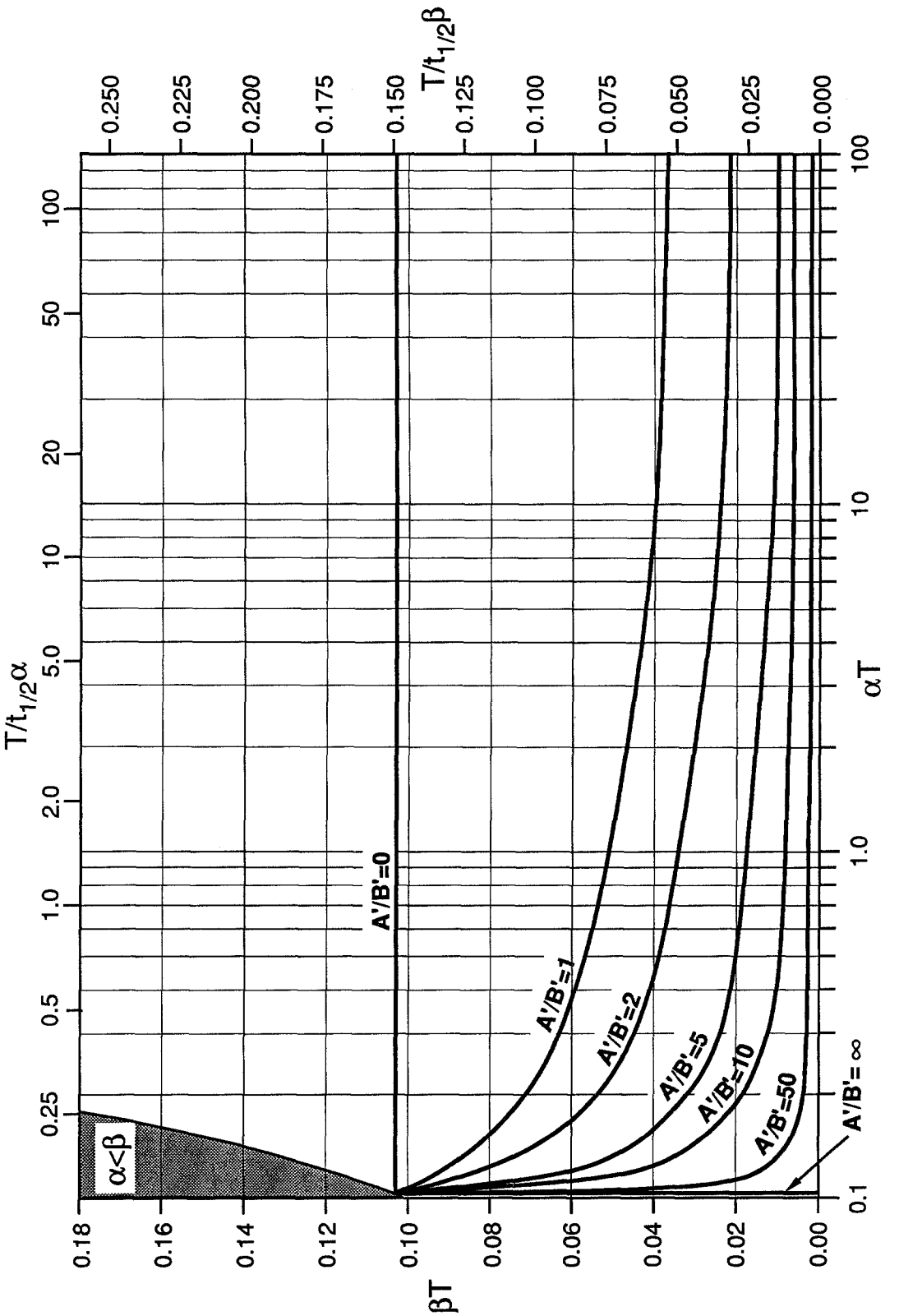

Fig. 2. Chart to decide whether percentage underestimation of AUC, ignoring infusion period, for two-compartment model is greater than 5%. Note: If $\alpha T < 0.103$, or, equivalently, $T/t_{1/2\alpha} < 0.148$, underestimation is always less than 5%. Above the line corresponding to the appropriate A'/B' the AUC is underestimated by > 5%

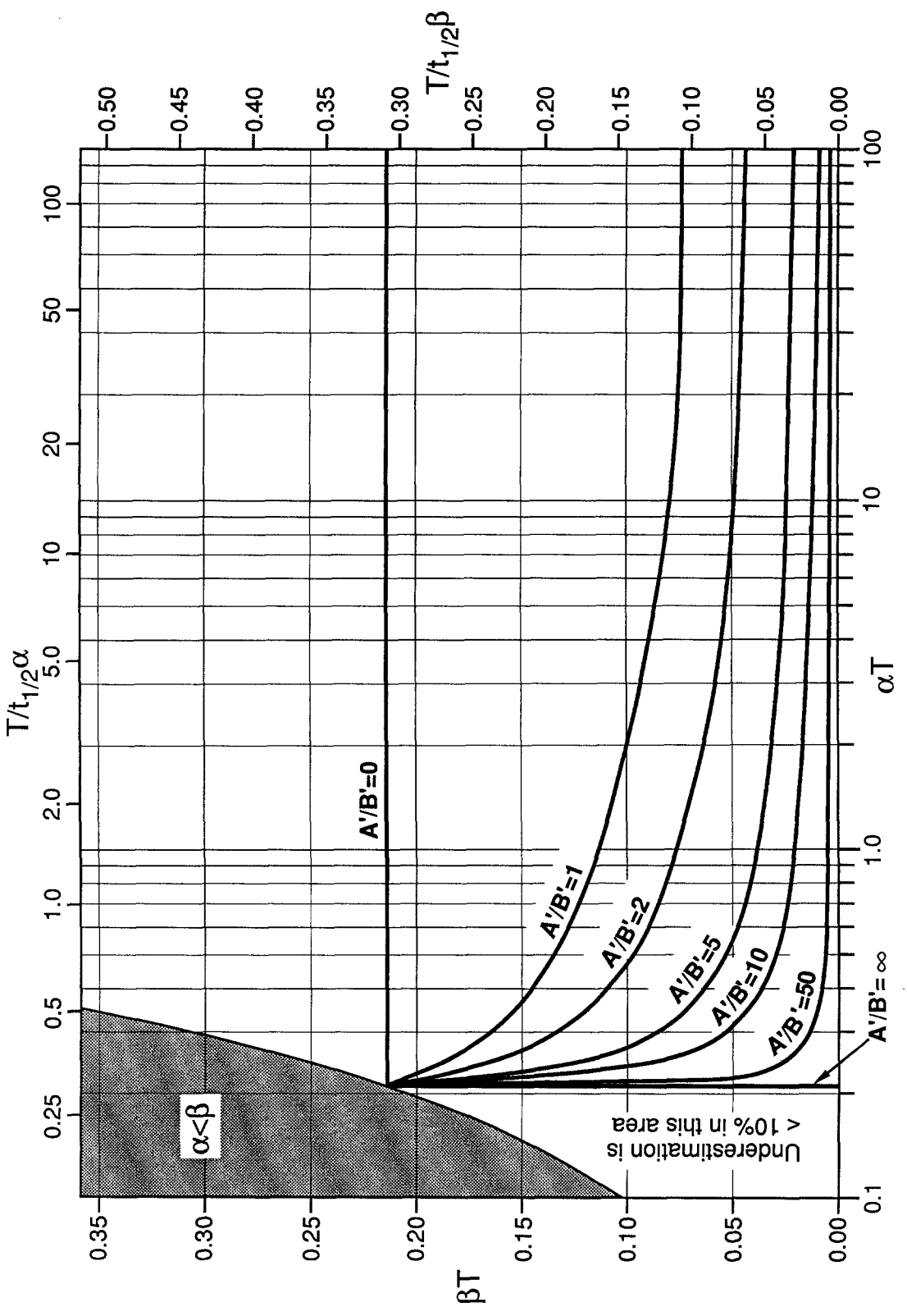

Fig. 3. Chart to decide whether percentage underestimation of AUC, ignoring infusion period, for two-compartmental model is greater than 10%. Above the line corresponding to the appropriate A′/B′ the AUC is underestimated by $> 10\%$

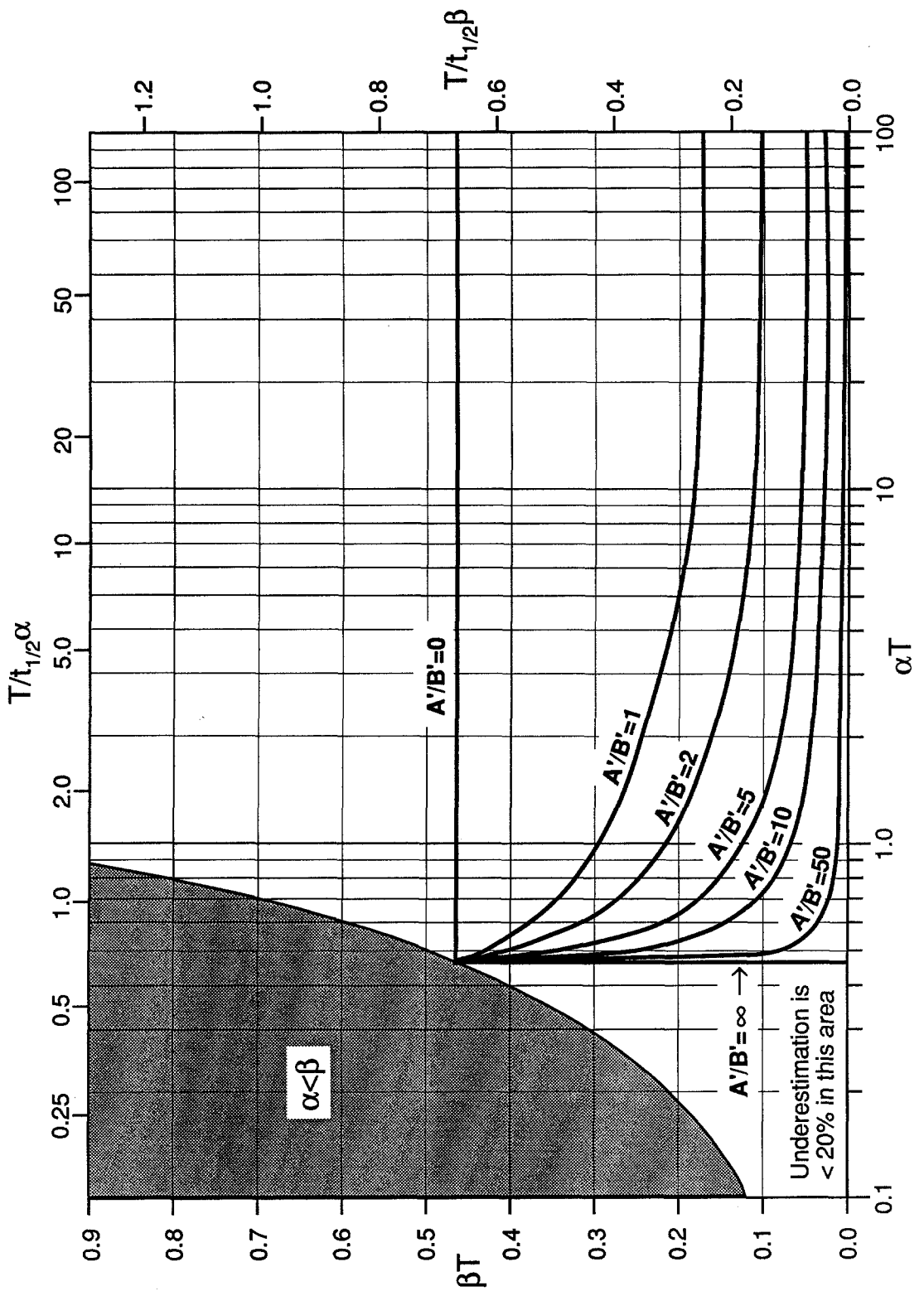

Fig. 4. Chart to decide whether percentage underestimation of AUC, ignoring infusion period, for two-compartmental model is greater than 20%. Above the line corresponding to the appropriate A′/B′ the AUC is underestimated by > 20%

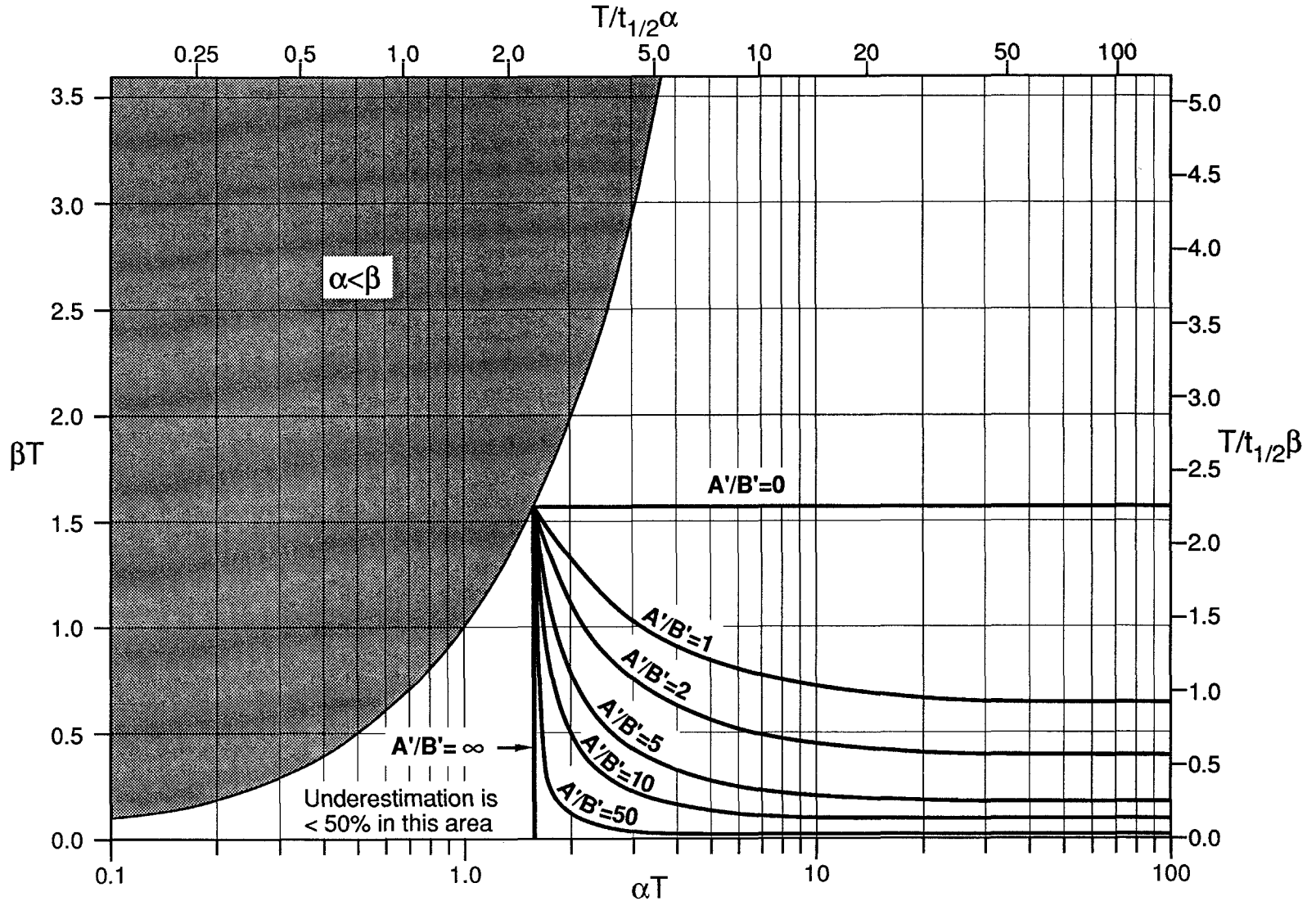

Fig. 5. Chart to decide whether percentage underestimation of AUC, ignoring infusion period, for two-compartmental model is greater than 50%. Above the line corresponding to the appropriated A′/B′ the AUC is underestimated by $>50\%$

In contrast, if A′/B′ had equalled 50 instead of 2, the point would have fallen *above* the curve, indicating an underestimation of more than 5%. In the latter case, the investigator may wish to discover whether the underestimation, now known to be greater than 5%, is in fact greater than 10%. Use of Fig. 3 in an analogous way to Fig. 2 will provide the answer. The point again lies above the curve corresponding to A′/B′ = 50, hence the underestimation *is* greater than 10%. To find out whether underestimation is also greater than 20%, Fig. 4 should be consulted. In fact, on this graph, the point falls to the left of the vertical line corresponding to A′/B′ = ∞. In this area, underestimation is below 20% for all values of A′/B′. Direct calculation from Eq. (16) shows that the actual underestimation is 13%. Figure 5 allows one to determine whether the underestimation exceeds 50%.

(b) Suppose that it was necessary to extend the infusion time of the drug to 1 h. We revert to the example where for a 20 min infusion A′/B′ = 2. The reader is cautioned that with the extension of infusion, not only will αT and βT be increased 3-fold, but the value of A′/B′ is expected to change. If it is desirable to know *in advance* whether the infusion period may be safely ignored, the investigator will need to calculate the value of A′/B′ expected to pertain with an infusion period of 1 h. This may be done using Eqs. (13) and (14) in our example, and the result is that A′/B′ changes from 2 to 1.11. However, the simplest approach is to use the value of A′/B′ calculated directly from the post-infusion data gathered after the 1-h infusion. Figures 2–5 may now be consulted using the new values of A′/B′ (1.11), αT (2.079) and βT (0.173).

Figures 2 and 3 show the point with co-ordinates (2.079, 0.173) to lie above the curve corresponding to A′/B′ = 1, indicating that underestimation is greater than 10%. Figure 4 shows the same point to lie below the curve corresponding to A′/B′ = 1 and close enough to the curve A′/B′ = 2 to be confident that it would also lie below the curve for the actual value of A′/B′ (1.11), which is not shown in the figure. Thus, the underestimation is above 10% but below 20%. Direct calculation from Eq. (16) shows that the actual figure is 17%.

Finally, it should be noted that the quantities αT and βT are proportional to the ratio of infusion period (T) to distribution half-life and elimination half-life respectively. For those investigators who prefer to think in terms of these ratios, alternative scales are provided in Figs. 1–5. Thus, the point αT = 0.346 (see *Two-compartment model* under *Examples*) is equivalent to a ratio $T/t_{½\alpha}$ equal to 0.5 (10 min/20 min), whereas the point βT is equivalent to a ratio $T/t_{½\beta}$ of 0.0417 (10 min/240 min). Using the alternative scales provided, the point of interest is located on the graph by co-ordinates (0.5, 0.0417).

Application to two clinical studies

(a) *Pharmacokinetics of high-dose BCNU in man.* Eight patients with malignant disease were given a 10-min i.v. infusion of BCNU, doses ranging from 200 mg/m² to 800 mg/m² [5]. The time course from the end of infusion was plotted and a two-compartment model was needed to describe the elimination of the drug. The parameters of the model were estimated using a non-linear weighted least squares technique. Table 2 shows the estimates of A′, B′, α and β.

Table 2. Pharmacokinetic data for 8 patients receiving a 10-min infusion of BCNU

Dose (mg/m²)	Two-compartment model parameters					Parameters for reading Fig. 2–5		
	A′	α	B′	β	%U	αT	βT	A′/B′
200	1.33	1.20	0.393	0.271	5.5	0.20	0.045	3.4
300	4.50	2.36	0.835	0.361	10.0	0.39	0.060	5.4
300	5.49	2.53	0.984	0.173	6.8	0.42	0.029	5.6
800	11.5	1.97	0.356	0.181	11.8	0.33	0.030	32.3
800	7.62	1.34	0.170	0.163	9.1	0.22	0.027	44.8
800	14.2	1.71	0.629	0.187	10.0	0.29	0.031	22.6
800	6.01	1.40	0.0649	0.118	9.8	0.23	0.020	92.6
800	20.5	0.735	3.00	0.188	4.4	0.12	0.031	6.8

Table 3. Pharmacokinetic data for 10 patients receiving a 10-min infusion of SR-2508

Dose (g/m²)	Two-compartment model parameters					Parameters for reading Fig. 2–5		
	A′	α	B′	β	%U	αT	βT	A′/B′
0.5	46.8	4.60	20.6	0.161	4.2	0.77	0.027	2.3
0.5	23.1	1.40	11.9	0.151	3.0	0.23	0.025	1.9
0.5	26.5	0.678	3.91	0.0885	3.0	0.11	0.015	6.8
0.5	35.1	2.31	17.2	0.104	2.5	0.39	0.017	2.0
1.0	49.3	2.06	19.7	0.146	3.6	0.34	0.024	2.5
1.0	59.6	2.46	27.0	0.139	3.3	0.41	0.023	2.2
2.0	72.7	2.49	82.7	0.0990	1.5	0.42	0.017	0.9
2.0	105.8	2.46	65.1	0.159	3.2	0.41	0.027	1.6
0.5	11.8	1.36	12.5	0.120	1.8	0.23	0.020	0.9
0.5	33.3	1.88	17.4	0.144	3.1	0.31	0.024	1.9

Reference to Figs. 2–4 or calculation of the percentage underestimation (%U) from Eq. (16) shows that, by ignoring the infusion time part of the curve, underestimation would have been between 10% and 20% for one patient, between 5% and 10% for six patients and under 5% for the remaining patient. Thus, in our view, correction would be needed for seven of the eight patients.

(b) *Pharmacokinetics of Ro 03-8799 and SR 2508 in man.* Ten patients with malignant disease received 10-min i.v. infusions of single doses of these radiosensitizers simultaneously [6]. Doses of SR 2508 ranged from 0.5 to 2.0 g/m^2. A two-compartment model was fitted to the time course, and the estimated parameters for SR 2508 are shown in Table 3. Reference to Fig. 2 or calculation of %U shows that for all ten patients the AUC was underestimated by less than 5% if infusion time was ignored. Similar results were found for Ro 03 8799.

Discussion

Cancer chemotherapeutic agents are often given by i.v. infusion. It is clear that if only the post-infusion data are analysed the AUC will be underestimated in all cases. Although implicit in equations published previously [3, 4, 7], this underestimation has not been emphasized elsewhere. We show here that the degree of underestimation will be dependent upon the infusion time and the pharmacokinetic parameters for the particular drug and subject, and we provide a simple way of judging the seriousness of the underestimation.

If the infusion period is very long (e.g. several hours), the investigator is likely to collect samples during the infusion period and the AUC will be estimated from a complete data set. The most common problem is likely to be where the infusion is relatively short and logistic or ethical problems prevent sampling during this period. To cater for this situation, we felt it would be useful to provide a method for the investigator to determine easily and rapidly the approximate amount by which the calculated AUC will be in error when the infusion period is ignored. Charts are provided for this purpose, allowing the investigator to decide the level at which the error is acceptable (e.g. $< 5\%$ or 10%) and whether to make a correction for the underestimate. This can be done using Eqs. (7) or (17). These procedures can be carried out on an individual patient basis.

Ideally a new drug should be given as an i.v. bolus injection to provide an initially accurate characterisation of its pharmacokinetics and to estimate the parameters for the appropriate model. Also, where possible, samples should be taken during an i.v. infusion, even if the time is considered to be relatively short. Where this is not possible, the tables and equations presented here should prove useful.

If a long series of calculations is required, this could be readily automated using a programmable calculator. An alternative would be to use a computer that includes infusion time as a variable in the pharmacokinetic model (for example, AUTOAN; see pp 434–437 in [7]), or to employ a short subroutine to calculate A, B, true AUC and the %U of AUC when interfaced with a standard statistical package[1]. The present paper allows the investigator to decide whether this is necessary.

Because of the recent proposals to base phase 1 dose escalations on rodent and human AUC values [1, 2], accurate assessment of AUC is of considerable practical as well as academic importance. It should be remembered that an AUC determined from an individual patient's data is already subject to non-negligible sampling error. Our view is that it is unacceptable to introduce an additional systematic error in excess of 5% by ignoring the infusion time, especially since the error can be quite easily corrected.

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[1] For example, we have written such a subroutine to be used in conjunction with Subroutine VCO5AD of the Harwell Subroutine Library for nonlinear regression analysis (details available from the authors on request)