Simple Methods for Estimation of Mean Residence Time and Steady-State Volume of Distribution from Continuous-Infusion Data

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The following equations are derived for amount of drug in the body (x_{bss}), volume of distribution (v_{ss}), and mean residence time in the body ($\bar{t}_b$) at steady state during a continuous constant rate infusion of drug.

$$x_{bss} = \frac{R}{c_{ss}} \int_0^\infty [c_{ss} - c(t)]dt = R \int_0^\infty \left[1 - \frac{c(t)}{c_{ss}}\right] dt$$

$$v_{ss} = \frac{x_{bss}}{c_{ss}} = \frac{R}{c_{ss}^2} \int_0^\infty [c_{ss} - c(t)]dt = \frac{R}{c_{ss}} \int_0^\infty \left[1 - \frac{c(t)}{c_{ss}}\right] dt$$

$$\bar{t}_b = \frac{x_{bss}}{R} = \frac{v_{ss}}{CL} = \frac{1}{c_{ss}} \int_0^\infty [c_{ss} - c(t)]dt = \int_0^\infty \left[1 - \frac{c(t)}{c_{ss}}\right] dt$$

where $c(t) \equiv$ drug concentration in the systemic circulation at time t following the start of a constant-rate infusion, $c_{ss} \equiv$ steady-state systemic drug concentration, and $R \equiv$ infusion rate. The equations are based on the assumption that the rate of drug elimination is proportional to the systemic drug concentration. The equations provide the basis for simple methods that are presented for estimating x_{bss}, v_{ss}, and $\bar{t}_b$ directly from experimental data. More general relationships are also derived for cases where the continuous infusion is preceded by other modes of administration, e.g., a bolus loading dose followed by a constant-rate infusion.

KEY WORDS: mean residence time; volume of distribution at steady state; intravenous infusion.

INTRODUCTION

Methods for the estimation of the mean residence time $\bar{t}_b$ and steady-state volume of distribution v_{ss} of a drug in the body have been developed for application to systemic drug concentration data resulting from most modes of drug administration including intravascular bolus, *truncated* constant-rate intravascular infusion, and extravascular administration (1–4). Less satisfactory methods are available for the case where drug is administered continuously for an indefinite time at a constant rate, e.g., a constant-rate i.v. infusion. Siegel (5) described a method for estimating $\bar{t}_b$ and v_{ss} using urinary excretion data resulting from such an infusion. Equations for v_{ss} applicable to systemic drug concentration data have been presented by Riegelman *et al.* (6) and Kowarski and Kowarski (7). However, both approaches are based on the assumption that steady state is achieved in a finite period of time, and their application requires that the infusion be continued until steady state is achieved. The equation of Riegelman *et al.* further requires that the infusion be stopped at steady state and that the concentration time course be observed during the postinfusion period. Another approach to this problem would be to reconstruct the bolus response from infusion data and then use existing methods for estimating v_{ss} and $\bar{t}_b$ from bolus data. Such a method can readily be constructed based on linear system analysis.[2] However, a method that can be applied more directly to the infusion data may offer some advantages with respect to simplicity and convenience.

The objectives of this article are rigorously to derive equations for v_{ss} and $\bar{t}_b$ in terms of the systemic drug concentration time course resulting from a continuous constant-rate infusion, to develop methods for the estimation of v_{ss} and $\bar{t}_b$ based on those equations, and to extend the equations to the more general case where the constant rate infusion is preceded by other modes of administration. The resulting equations and methods do not assume that steady state is achieved in a finite period of time and do not require measurement of postinfusion drug concentrations.

THEORY

The derivations presented here are based on the following assumptions:

1. It is assumed that the total rate of drug elimination is proportional to the systemic drug concentration, i.e.,

$$x_e' = \mathrm{CL}c \qquad (1)$$

where CL is a constant (the prime indicates differentiation).

2. It is assumed that the pharmacokinetic system is time invariant, at least to the extent that a constant-rate input will eventually result in a constant steady-state systemic drug concentration c_{ss} and a constant steady-state amount of drug in the body x_{bss}.

Case 1: Continuous Constant-Rate Infusion

In the case of a simple constant-rate infusion where $R \equiv$ infusion rate, mass balance dictates that $x_b' = R - x_e'$. Substituting Eq. (1) and the relationship $\mathrm{CL} = R/c_{ss}$ (which follows from assumptions 1 and 2 and the fact that the rate of elimination equals the input rate at steady state) into that relationship,

$$x_b' = \frac{R}{c_{ss}}(c_{ss} - c) = R\left(1 - \frac{c}{c_{ss}}\right) \qquad (2)$$

Integrating yields an equation for the amount of drug in the body,

$$x_b(t) = \frac{R}{c_{ss}} \int_0^t [c_{ss} - c(t)]dt = R \int_0^t \left[1 - \frac{c(t)}{c_{ss}}\right] dt \qquad (3)$$

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[2] For a time-invariant linear system, the unit impulse (bolus) response c_δ may be estimated according to $c_\delta = c'/R$, where c' is the derivative of the systemic drug concentration time course resulting from a constant-rate infusion (rate = R).

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Table I. List of Symbols

c	Drug concentration in the systemic circulation
CL	Total-body clearance
D_T	Amount of drug that reaches the systemic circulation during the interval $0 \leq t \leq T$
f	Rate of drug input (rate at which drug reaches the systemic circulation)
R	Rate of constant rate drug input
ss	Subscript denoting steady state, e.g., c_{ss} = systemic drug concentration at steady state
t	Elapsed time from the start of drug administration
T	Any time after which drug input occurs at the constant rate R
$\bar{t}_b$	Mean residence time
v_{ss}	Steady-state volume of distribution
x_b	Amount of drug in the body
x_e	Cumulative amount of drug eliminated from the body

The amount of drug in the body at steady state is obtained by taking the limit as $t \to \infty$,

$$x_{bss} = \lim_{t\to\infty} x_b(t) = \frac{R}{c_{ss}}\int_0^\infty [c_{ss} - c(t)]dt = R\int_0^\infty \left[1 - \frac{c(t)}{c_{ss}}\right] dt \tag{4}$$

Combining Eq. (4) with the definition of the steady-state volume of distribution,

$$v_{ss} = \frac{x_{bss}}{c_{ss}} = \frac{R}{c_{ss}^2}\int_0^\infty [c_{ss} - c(t)]dt = \frac{R}{c_{ss}}\int_0^\infty \left[1 - \frac{c(t)}{c_{ss}}\right] dt \tag{5}$$

It has previously been shown that $\bar{t}_b = x_{bss}/R = v_{ss}/\mathrm{CL}$ (1), so that

$$\bar{t}_b = \frac{x_{bss}}{R} = \frac{v_{ss}}{\mathrm{CL}} = \frac{1}{c_{ss}}\int_0^\infty [c_{ss} - c(t)]dt = \int_0^\infty \left[1 - \frac{c(t)}{c_{ss}}\right] dt \tag{6}$$

Similar equations have been presented previously for the blood volume and mean transit time of an indicator in a vascular bed (8). They had been derived for the case of a vascular bed with a single inlet and a single outlet in which a nonabsorbable chemical indicator is input at a constant rate at the inlet and the indicator concentration is measured at the outlet. In that setting blood flow, blood volume, and mean transit time through the vascular bed play analogous roles to CL, v_{ss}, and $\bar{t}_b$.

Case 2: Continuous Constant-Rate Infusion Preceded by Other Modes of Administration

For the case where a continuous constant rate infusion is preceded by other modes of administration, e.g., an i.v. bolus loading dose, the rate of drug input may be described by

$$f(t) = \begin{cases} \hat{f}(t), & 0 \leq t \leq T \\ R, & t > T \end{cases} \tag{7}$$

where T is any time after which drug input occurs at the constant rate, R, and $\hat{f}$ is the time course of the input rate prior to T. Proceeding as before, the mass balance relationship for x_b' now takes the form,

$$x_b'(t) = \begin{cases} \hat{f}(t) - \dfrac{R}{c_{ss}}c(t), 0 \leq t \leq T \\ R\left(1 - \dfrac{c}{c_{ss}}\right), \quad t > T \end{cases} \tag{8}$$

Integrating to obtain the amount of drug in the body,

$$x_b(t) = \begin{cases} \int_0^t \hat{f}(t)dt - \dfrac{R}{c_{ss}}\int_0^t c(t)dt, & 0 \leq t \leq T \\ \int_0^T \hat{f}(t)dt - \dfrac{R}{c_{ss}}\int_0^T c(t)dt & \\ \quad + R\int_T^t \left[1 - \dfrac{c(t)}{c_{ss}}\right] dt, & t > T \end{cases} \tag{9}$$

Let D_T denote the amount of drug that reaches the systemic circulation (e.g., the absorbed dose) during the interval $0 \leq t \leq T$, i.e., $D_T = \int_0^T \hat{f}(t)dt$. Also note that

$$\frac{R}{c_{ss}}\int_0^T c(t)dt = RT - R\int_0^T \left[1 - \frac{c(t)}{c_{ss}}\right] dt \tag{10}$$

Substituting (10) into Eq. (9),

$$x_b(t) = \begin{cases} \int_0^t \hat{f}(t)dt - \dfrac{R}{c_{ss}}\int_0^t c(t)dt, & 0 \leq t \leq T \\ D_T - RT + R\int_0^t \left[1 - \dfrac{c(t)}{d_{ss}}\right] dt, & t > T \end{cases} \tag{11}$$

The following equations for X_{bss}, v_{ss}, and $\bar{t}_b$ resulting from Eq. (11) are simple modifications of the equations derived above for case 1.

$$x_{bss} = \lim_{t\to\infty} x_b(t) = D_T - RT + \frac{R}{c_{ss}}\int_0^\infty [c_{ss} - c(t)]dt = D_T - RT + R\int_0^\infty \left[1 - \frac{c(t)}{c_{ss}}\right] dt \tag{12}$$

$$v_{ss} = \frac{x_{bss}}{c_{ss}} = \frac{D_T - RT}{c_{ss}} + \frac{R}{c_{ss}^2}\int_0^\infty [c_{ss} - c(t)]dt = \frac{D_T - RT}{c_{ss}} + \frac{R}{c_{ss}}\int_0^\infty \left[1 - \frac{c(t)}{c_{ss}}\right] dt \tag{13}$$

$$\bar{t}_b = \frac{x_{bss}}{R} = \frac{v_{ss}}{\mathrm{CL}} = \frac{D_T - RT}{R} + \frac{1}{c_{ss}}\int_0^\infty [c_{ss} - c(t)]dt = \frac{D_T - RT}{R} + \int_0^\infty \left[1 - \frac{c(t)}{c_{ss}}\right] dt \tag{14}$$

APPLICATION

The formulae derived above may be applied by fitting a suitable equation to the concentration time course during an infusion, e.g., an equation of the form,

$$c(t) = \sum_{i=1}^{n} b_i(1 - e^{-\beta_i t}) \tag{15}$$

The resulting equation is then substituted into the appropriate formulae. For the case when Eq. (15) describes the drug concentrations, the equations for $\bar{t}_b$ and v_{ss} become

$$\bar{t}_b = \left(\sum_{i=1}^{n} \frac{b_i}{\beta_i}\right) \Big/ \left(\sum_{i=1}^{n} b_i\right) \tag{16}$$

$$v_{ss} = \left(R \sum_{i=1}^{n} \frac{b_i}{\beta_i}\right) \Big/ \left(\sum_{i=1}^{n} b_i\right)^2 \tag{17}$$

Alternatively, a simple approach requiring less sophisticated computational methods is to replace the integrals with a suitable quadrature algorithm, e.g., trapezoidal rule; c and c_{ss} in the integrands are replaced by experimentally determined systemic drug concentrations. A procedure based on such an approach is outlined below for a continuous constant-rate infusion.

Estimation of c_{ss}

(a) If the sampling period is sufficiently long that steady state has been achieved, then c_{ss} may be estimated by averaging the observed systemic drug concentrations during steady state.

(b) Otherwise, fit an expression of the form,

$$c(t) = c_{ss}(1 - ae^{-\alpha t}) \tag{18}$$

to the terminal portion of the concentration data (region corresponding to the terminal monoexponential region of a bolus response). Equation (18) can be shown to be appropriate for any linear, time-invariant pharmacokinetic system that exhibits a terminal monoexponential concentration time course following a bolus input. In such cases α corresponds to the terminal elimination rate constant and usually $a \leq 1$.

Identification of the region in which Eq. (18) holds is somewhat more problematic than identification of the terminal monoexponential region following truncated inputs. One approach is to use a rate plot in the same manner as has been used for analysis of urine data, i.e., plot $\ln(\Delta c/\Delta t)$ vs t. In theory such a plot should exhibit a terminal linear region such that the slope $= -\alpha$ and the y intercept $= \ln(c_{ss}a\alpha)$. Thus, the terminal region is identified visually and an initial estimate of α may be obtained from the slope of the line. An alternative approach is to fit Eq. (18) to the data and then inspect for systematic deviations in the residuals. This may be facilitated by the use of a sigma-minus plot—plot both the observed and the calculated concentrations according to $\ln(c_{ss} - c)$ vs t {or equivalently, $\ln[1 - (c/c_{ss})]$ vs t}—in which such deviations would show as a calculated line that deviates from the trend of the terminal portion of the data. If systematic deviations are found, then one or more points are excluded from the initial part of the data and the procedure is repeated.

Estimation of $\bar{t}_b$

The integral may be partitioned into sampling and post-sampling regions,

$$\bar{t}_b = \int_0^{t_n} \left[1 - \frac{c(t)}{c_{ss}}\right] dt + \int_{t_n}^{\infty} \left[1 - \frac{c(t)}{c_{ss}}\right] dt \tag{19}$$

where t_n denotes the last sampling time.

(a) The integral over $(0,t_n)$ may be estimated by applying trapezoidal rule to the values of $1 - [c(t_i)/c_{ss}]$, where $c(t_i)$ denotes the experimental value at time t_i. A somewhat more convenient method results from the following identity:

$$\int_0^{t_n} \left[1 - \frac{c(t)}{c_{ss}}\right] dt = t_n - \frac{1}{c_{ss}} \int_0^{t_n} c(t)dt \tag{20}$$

Therefore, the integral over $(0,t_n)$ may be estimated by applying trapezoidal rule directly to the observed systemic drug concentrations and substituting the result in Eq. (20), i.e.,

$$\int_0^{t_n} \left[1 - \frac{c(t)}{c_{ss}}\right] dt \approx t_n - \frac{1}{c_{ss}} \cdot \frac{1}{2} \sum_{i=1}^{n} [c(t_i) + c(t_{i-1})](t_i - t_{i-1}) \tag{21}$$

where $t_0 = 0$.

(b) If steady state has been achieved by t_n, then $\int_{t_n}^{\infty} \{1 - [c(t)/c_{ss}]\}\, dt = 0$ and $\bar{t}_b$ is given by Eq. (21). Otherwise, the integral over (t_n,∞) may be estimated by substituting Eq. (18) for $c(t)$ and integrating to yield

$$\int_{t_n}^{\infty} \left[1 - \frac{c(t)}{c_{ss}}\right] dt = \frac{ae^{-\alpha t_n}}{\alpha} \tag{22}$$

$\bar{t}_b$ is then estimated as the sum of the results of applying Eqs. (21) and (22).

$$\bar{t}_b \approx t_n - \frac{1}{c_{ss}} \cdot \frac{1}{2} \sum_{i=1}^{n} [c(t_i) + c(t_{i-1})](t_i - t_{i-1}) + \frac{ae^{-\alpha t_n}}{\alpha} \tag{23}$$

Estimation of v_{ss}

Substitute previously determined values of c_{ss} and $\bar{t}_b$ into the following equation:

$$v_{ss} = \bar{t}_b \mathrm{CL} = \frac{R}{c_{ss}} \bar{t}_b \tag{24}$$

Several data sets were simulated by applying varying amounts of normally distributed random error to values calculated from the equations,

$$c(t) = R \sum_{i=1}^{3} \frac{a_i}{\alpha_i}(1 - e^{-\alpha_i t}), \qquad \text{i.v. infusion} \tag{25}$$

$$c(t) = D \sum_{i=1}^{3} a_i e^{-\alpha_i t}, \qquad \text{i.v. bolus} \tag{26}$$

where $R = 1$ mg/hr, $D = 25$ mg, $a_1 = 0.0282\ L^{-1}$, $\alpha_1 = 4.78\ hr^{-1}$, $a_2 = 0.0156\ L^{-1}$, $\alpha_2 = 0.226\ hr^{-1}$, $a_3 = 0.0061\ L^{-1}$, $\alpha_3 = 0.021\ hr^{-1}$. The sampling times were 0.5, 1, 2, 4, 6, 8, 12, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hr. The "true" values of $\bar{t}_b$ and v_{ss} based on these equations are $\bar{t}_b = 38.7$ hr and $v_{ss} = 106$ L. Both of the methods described above were used to estimate $\bar{t}_b$ and v_{ss} from the infusion data. To evaluate the effect of the overall sampling duration, the analyses were performed on subsets of the data formed by progressively excluding the later data points.

An equation of the form of Eq. (15) with $n = 2$ was fit to each infusion data set via weighted least-squares nonlinear regression (9). The use of $n > 2$ resulted in no substantial improvement in the fits. The squared residuals were weighted by c^{-2}. $\bar{t}_b$ and v_{ss} were then estimated according to Eqs. (16) and (17).

The values of c_{ss}, a, and α were estimated by fitting [weighted least-squares nonlinear regression (9)—weight = c^{-2}] an equation of the form of Eq. (18) to the terminal portion ($t \geq 12$ hr) of the "observed" concentration data. Equations (23) and (24) were applied to the infusion data to estimate $\bar{t}_b$ and v_{ss}.

$\bar{t}_b$ and v_{ss} were estimated from the bolus data according to $\bar{t}_b = \text{AUMC/AUC}$ and $v_{ss} = (D \cdot \text{AUMC})/\text{AUC}^2$ (1). AUC and AUMC are estimated by trapezoidal rule with extrapolation to infinity, i.e., $\text{AUC} = \text{AUC}(0 \rightarrow t_n) + [\hat{c}(t_n)/\alpha]$ and $\text{AUMC} = \text{AUMC}(0 \rightarrow t_n) + [t_n + (1/\alpha)][\hat{c}(t_n)/\alpha]$, where t_n is the last sampling time, $\hat{c}(t_n)$ is the calculated concentration at the last sampling time, and α is the terminal rate constant. α is estimated by fitting a monoexponential equation, $c(t) = ae^{-\alpha t}$, to the terminal monoexponential region of the bolus data and $\hat{c}(t_n) = ae^{-\alpha t_n}$. Summary statistics of the parameter estimates resulting from each of the methods are shown in Tables II–IV.

Table II. Estimation of Mean Residence Time in the Body ($\bar{t}_b$) and Volume of Distribution at Steady State (v_{ss}) from Simulated Infusion Data Using Eqs. (16) and (17)[a]

Error model[b]	Sampling period (hr)	$\bar{t}_b$ (hr) Mean	$\bar{t}_b$ (hr) SD	v_{ss} (L) Mean	v_{ss} (L) SD
$\sigma = 0.05c$	144	39.1	7.15	105.5	13.1
	168	38.4	6.40	104.5	12.5
	192	37.9	5.35	103.7	10.9
	216	38.3	4.52	104.4	9.50
	240	38.3	3.87	104.5	8.37
$\sigma = 0.1c$	144	53.1	23.8	126.3	36.4
	168	46.8	20.8	118.2	35.4
	192	42.4	14.7	112.2	27.9
	216	42.2	12.2	112.2	24.0
	240	41.3	9.78	110.9	20.4
$\sigma = 0.03692753c^{0.69897}$[c]	144	39.4	7.60	106.0	13.9
	168	38.4	6.39	104.5	12.6
	192	37.9	5.54	103.8	11.4
	216	38.4	4.74	104.6	10.1
	240	38.4	4.17	104.6	9.09

[a] Each mean and standard deviation is based on 10 simulated data sets.
[b] Standard deviation (σ) of normally distributed error.
[c] This results in coefficients of variation of 5% when $c = c_{ss}$ and 10% when $c = 0.1c_{ss}$.

Table III. Estimation of Mean Residence Time in the Body ($\bar{t}_b$) and Volume of Distribution at Steady State (v_{ss}) from Simulated Infusion Data Using Eqs. (23) and (24)

Error model[b]	Sampling period (hr)	$\bar{t}_b$ (hr) Mean	$\bar{t}_b$ (hr) SD	v_{ss} (L) Mean	v_{ss} (L) SD
$\sigma = 0.05c$	144	42.5	9.45	111.6	17.5
	168	40.8	7.81	109.1	15.4
	192	39.6	5.96	107.0	12.4
	216	39.9	5.19	107.8	11.0
	240	39.5	4.39	107.0	9.72
$\sigma = 0.1c$	144	57.5	27.3	131.1	44.2
	168	49.8	27.2	120.6	44.4
	192	42.8	16.8	111.1	32.4
	216	42.3	14.7	110.6	29.4
	240	40.5	11.3	107.4	24.9
$\sigma = 0.03692753c^{0.69897}$[c]	144	43.5	10.3	113.4	19.2
	168	41.5	8.58	110.3	17.0
	192	40.0	6.59	107.9	13.8
	216	40.3	5.81	108.5	12.3
	240	39.8	4.90	107.6	10.9

[a] Each mean and standard deviation is based on 10 simulated data sets.
[b] Standard deviation (σ) of normally distributed error.
[c] This results in coefficients of variation of 5% when $c = c_{ss}$ and 10% when $c = 0.1c_{ss}$.

The results indicate that the proposed methods are much less accurate and precise than the method used to analyze the bolus data. Accuracy and precision are highly dependent on the duration of sampling and the variability of the data. In cases where variability is relatively high, tolerable accuracy is obtained only if sampling is continued essentially to steady state. From these results it is concluded

Table IV. Estimation of Mean Residence Time in the Body ($\bar{t}_b$) and Volume of Distribution at Steady State (v_{ss}) from Simulated Bolus Data[a]

Error model[b]	Sampling period (hr)	$\bar{t}_b$ (hr) Mean	$\bar{t}_b$ (hr) SD	v_{ss} (L) Mean	v_{ss} (L) SD
$\sigma = 0.05c$	144	38.8	0.691	106.4	1.89
	168	38.8	0.457	106.3	1.55
	192	38.8	0.391	106.2	1.49
	216	38.8	0.375	106.3	1.38
	240	38.8	0.377	106.3	1.34
$\sigma = 0.1c$	144	39.1	1.38	106.7	3.72
	168	38.9	0.903	106.3	3.08
	192	38.8	0.754	106.2	2.92
	216	38.9	0.729	106.3	2.73
	240	38.9	0.734	106.3	2.64
$\sigma = 0.03692753c^{0.69897}$[c]	144	39.2	2.03	107.1	4.71
	168	38.9	1.41	106.5	3.87
	192	38.8	1.05	106.3	3.35
	216	39.0	0.924	106.6	2.90
	240	39.1	0.873	106.8	2.62

[a] Each mean and standard deviation is based on 10 simulated data sets.
[b] Standard deviation (σ) of normally distributed error.
[c] This results in coefficients of variation of 5% when $c = c_{ss}$ and 10% when $c = 0.1c_{ss}$.

that the proposed methods should be reserved for those cases where only infusion data are available.

DISCUSSION

The methods presented here for estimation of the mean residence time and steady-state volume of distribution based on systemic drug concentrations observed during a constant rate infusion are potentially useful additions to existing methods. However, they appear to be less accurate than methods used to estimate $\bar{t}_b$ and v_{ss} from bolus or truncated infusion data. Thus, the new methods are *not* recommended as a substitute for the more accurate approaches, but they are appropriate when only the results of a continuous infusion are available.

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