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SCIENTIFIC COMMENTARY

Mean Residence Time in Peripheral Tissue: A Linear Disposition Parameter Useful for Evaluating a Drug's Tissue Distribution

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The tendency of drugs to distribute in peripheral tissue has traditionally been described by the use of various volume of distribution terms. Recently there has been an interest in applying statistical moments principles in pharmacokinetics (1–5). The moments technique has been employed to evaluate the mean residence time of a drug in the "body," i.e., the tendency of the drug to remain in the systemic circulation space and the peripheral tissue space without a differentiation of the distribution tendencies in these spaces. The purposes of this communication are (a) to propose a method of evaluating a drug's affinity for peripheral tissue distribution in terms of the mean residence time in peripheral tissue, (b) to present a formula enabling the mean residence time in peripheral tissue to be evaluated from systemic drug level data from an i.v. administration, (c) to discuss the limitations and assumptions behind the methods, and (d) to demonstrate the method using several drugs.

The following derivations are aimed at showing that the mean residence time $\bar{t}_p$ of molecules in peripheral tissue of a drug having a linear disposition and a systemic elimination can be calculated simply according to:

$$\bar{t}_p = \frac{AUMC}{AUC} - \frac{AUC}{c(0)} \tag{1}$$

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where

$$AUMC = \int_0^\infty tc(t)\, dt \tag{2}$$

and

$$AUC = \int_0^\infty c(t)\, dt \tag{3}$$

The calculations (Eqs. 1-3) are done on the basis of the systemic drug level $c(t)$ resulting from an arbitrary i.v. bolus dose. The mean residence time of drug molecules in the "body," $\bar{t}_b$, is, as shown in Appendix A, the sum of the mean residence time in the systemic circulation, $\bar{t}_s$, and the mean residence time in the peripheral tissue, $\bar{t}_p$:

$$\bar{t}_b = \bar{t}_s + \bar{t}_p \tag{4}$$

It is well known that the mean residence time in the body can be calculated according to the following expression:

$$\bar{t}_b = \frac{AUMC}{AUC} \tag{5}$$

(see refs. 1-3). However, it is apparently not generally realized that the calculation of $\bar{t}_b$ from systemic drug level data is based not only on the linear disposition[3] assumption, but also on the assumption that the drug is not eliminated from peripheral tissue. Appendix B presents a formal derivation of Eq. (5) to show why this additional requirement must be met.

It will now be proven for a drug with a linear disposition (as defined) that the mean residence time of drug molecules in the systemic circulation is simply given by

$$\bar{t}_s = \frac{AUC}{c(0)} \tag{6}$$

Once this equation has been verified then Eq. (1) is proven by substituting Eqs. (5) and (6) into Eq. (4). Equation (6) may be derived as follows. Consider $n(0)$ molecules injected ($t = 0$) systemically in an i.v. bolus fashion. Then the number of molecules in the systemic circulation at time t is

$$n(t) = V \cdot c(t)/M \tag{7}$$

[3]Linear drug disposition in this context is defined in the general sense that the systemic drug level follows the superposition principle with respect to the rate by which the drug reaches the general systemic circulation.

where M is the molecule weight of the molecules. The total sum for all molecules of the time spans the molecules spend in the systemic circulation is

$$T_s = \int_0^\infty n(t)\, dt \tag{8}$$

This is the total time spent there by $n(0) = D/M$ molecules. Thus the mean residence time of the molecules in the systemic circulation is

$$\bar{t}_s = \frac{T_s}{n(0)} = \frac{\int_0^\infty n(t)\, dt}{n(0)} = \frac{V/M \int_0^\infty c(t)\, dt}{D/M} = \frac{AUC}{c(0)} \tag{9}$$

which verifies Eq. (6). Equation (1) then follows from Eqs. (4)-(6).

A careful analysis of the derivations above and in the appendix reveals the following facts. First, the mean residence time in the body, $\bar{t}_b$, and the mean residence time in the system circulation, $\bar{t}_s$, are unique disposition parameters for drugs with a linear disposition. Second, the $\bar{t}_b$ parameter (and therefore also $\bar{t}_p$) cannot be exactly calculated *from systemic drug level data* if a peripheral drug elimination takes place. It can readily be shown by a derivation similar to the derivation of $\bar{t}_s$ above that the mean residence time in the "body" is given by

$$\bar{t}_b = \frac{\int_0^\infty A_b(t)\, dt}{D} \tag{10}$$

so that

$$\bar{t}_p = \frac{\int_0^\infty A_b(t)\, dt}{D} - \frac{AUC}{c(0)} \tag{11}$$

Equations (10) and (11) are valid irrespective of whether a peripheral drug elimination takes place. However, contrary to Eqs. (1) and (5), the above expressions (Eqs. 10 and 11) are of a conceptual rather than practical significance since it is usually not possible to determine the amount of drug in the "body," $A_b(t)$. Third, it is evident from the derivations that the mean residence time of the drug in the systemic circulation can be calculated according to Eq. (6) irrespective of peripheral or nonperipheral drug elimination. The derivations above show how $\bar{t}_b$, $\bar{t}_p$, and $\bar{t}_s$ can be calculated from an i.v. bolus response $c(t)$. Appendix C shows how the same parameters can be obtained from a constant rate i.v. infusion response.

EXAMPLES

The mean residence time in the peripheral tissue was calculated using four drugs which appear to have a linear drug disposition (Table I). The

Table I. Intravenous Bolus Response According to Eq. (16)

Drug	Source	A_1 (mg/L)	α_1 (min^{-1})	A_2 (mg/L)	α_2 (min^{-1})	$\bar{t}_p$ (hr)	$\bar{t}_b$ (hr)	$\bar{t}_p/\bar{t}_b$
Propylthiouracil	Ref. 4, subject 6	22.3	0.139	12.1	8.00E−3	1.09	1.90	0.571
Theophylline	Ref. 5	12.0	9.67E−2	18.0	2.67E−3	2.32	6.13	0.378
Hexobarbital	Ref. 6, subject K.H.	13.7	6.62E−2	4.94	2.73E−3	3.70	5.50	0.673
Digoxin	Ref. 7, subject R.R.M.	2.27E−2	3.35E−2	8.30E−4	3.00E−4	42.3	44.7	0.945

calculations are based on an ordinary two exponential least squares approximation of the i.v. bolus drug level response:

$$c(t) = A_1\, e^{-\alpha_1 t} + A_2\, e^{-\alpha_2 t} \tag{12}$$

(see refs. 6–9). Equation (16) leads to the following simple expressions:

$$AUMC = A_1/\alpha_1^2 + A_2/\alpha_2^2 \tag{13}$$

$$AUC = A_1/\alpha_1 + A_1/\alpha_2 \tag{14}$$

$$c(0) = A_1 + A_2 \tag{15}$$

used in calculating $\bar{t}_p$ (Eq. 1).

Equations (12)–(15) require the A_i, α_i parameters to be determined by "curve pealing" of the i.v. bolus data, or more accurately, by curve fitting. Alternatively, the $AUMC$ and the AUC may be determined directly from the raw data by a suitable numerical quadrature method. The simplest quadrature method is based on a collocation polynomial of first degree for which the following algorithm is readily derived:

$$AUMC_{t_i}^{t_{i+1}} \equiv \int_{t_i}^{t_{i+1}} tc(t)\, dt \simeq K_1(t_{i+1}^3 - t_i^3) + K_2(t_{i+1}^2 - t_i^2) \tag{16}$$

where

$$K_1 = \frac{c_{i+1} - c_i}{3(t_{i+1} - t_i)} \tag{17}$$

and

$$K_2 = (c_i - K_1 t_i)/2 \tag{18}$$

Then $AUMC$ is calculated according to

$$AUMC = AUMC_0^{t_1} + AUMC_{t_1}^{t_2} + \cdots + AUMC_{t_m}^{\infty} \tag{19}$$

where the last term in Eq. (19) is given by

$$AUMC_{t_m}^{\infty} \simeq c_m(t_m/\beta + 1/\beta^2) \tag{20}$$

which is called the "tail end moment." Equation (20) is calculated from the last data point (t_m, c_m) under the assumption that the drug level declines in a single exponential fashion beyond that point, i.e., $c(t) \simeq c_m\, e^{-\beta(t-t_m)}$, $t > t_m$. It is also assumed that β can suitably be determined from the data.

Although it is beyond the scope of this short communication to deal with a comparison of numerical methods for evaluating $\bar{t}_p$ (Eq. 1), it is likely true that a least squares or other regression method tends to provide more reliable estimates of $\bar{t}_p$ than a quadrature method such as the one above, which essentially ignores the error in the data. Furthermore, the

problem of extrapolation ($t \to 0$, $t \to \infty$) also appears to be better handled by a regression approach since an exact fit to the first and last data points, which often are inaccurately determined, provides a poor basis for extrapolation. Furthermore, a sum of exponentials (Eq. 12) is intrinsically less erratic in extrapolations than quadrature polynomials.

If a drug elimination takes place from peripheral tissue for some of these drugs (Table I), the moment expression in Eq. (1) will be a biased approximation of the mean peripheral residence time. As such, the expression is still valuable as a measure of the relative distribution of drug between the systemic circulation and peripheral tissue, but it cannot be interpreted as a mean residence time. It is probably true for most drugs that the elimination practically can be considered to take place from the systemic circulation due to the relatively rapid perfusion of the main eliminating organs. Thus, $\bar{t}_p$ should be a valuable parameter for most drugs with a linear disposition.

The question whether a *significant* peripheral elimination takes place appears difficult to resolve by a kinetic analysis involving only systemic drug level data. Some peripheral elimination is expected to take place for most drugs since virtually all drugs distribute into the gastrointestinal lumen content and are naturally eliminated to some extent by the transit of the G.I. content. For drugs with a pronounced enterohepatic recycling, this form of peripheral elimination may be significant, particularly in cases where it involves an intermediate complexation or other intermediate transformation of the drug with a slow absorption rate. The affinity of the drug for the G.I. content also plays a role. For example, it was demonstrated in humans that the elimination rate of phenobarbital following a short i.v. infusion is substantially increased by the introduction of activated charcoal in the G.I. lumen content (10). Drug's G.I. affinity to "normal meals" may only be determined by quantifying the amount of *unchanged* drug which is excreted with the feces. The extent of "elimination" with the feces is commonly determined by simple radiotracer methodology. However, since this procedure measures total drug including metabolites excreted from the systemic circulation, true elimination by this route cannot be evaluated. In the quite limited cases where the unchanged drug has been quantified in the feces, usually only a relatively small fraction of the drug was determined. Thus, it is likely true that the bias in determination of $\bar{t}_p$ according to Eq. (1) caused by the intrinsic G.I. elimination is small for most drugs.

APPENDIX A

Let t_{si} and t_{pi} denote the times the ith drug molecule spends in the systemic circulation and the peripheral tissue, respectively, then $(t_{si} + t_{pi})$ is

the total time the molecule spends in the body, and the mean residence in the body becomes for n molecules:

$$\begin{aligned}\bar{t}_b &= [(t_{s1}+t_{p1})+(t_{s2}+t_{p2})+\cdots+(t_{sn}+t_{pn})]/n \\ &= (t_{s1}+t_{s2}+\cdots+t_{sn})/n+(t_{p1}+t_{p2}+\cdots+t_{pn})/n \\ &= \bar{t}_s+\bar{t}_p\end{aligned} \tag{1A}$$

APPENDIX B

Let $A_b(t)$ define the amount of unchanged drug in the "body" (i.e., residing in the systemic circulation or in the peripheral tissues) which has not yet been eliminated. Let $A_e(t)$ define the amount of drug which has been eliminated from the "body" (i.e., metabolized, chemically degraded, or excreted), and D the i.v. bolus dose injected. From mass balance principles it follows that

$$D = A_b(t)+A_e(t) \tag{B1}$$

Let t_b denote the random variable describing the residence time in the "body" for a drug molecule. The probability distribution function for the random variable t_b, which will be denoted $G(t)$, is equal to the probability that t_b for a molecule is less than or equal to given time t:

$$G(t) = Pr(t_b \leq t) \tag{B2}$$

Noting that $t_b \leq t$ for a molecule that has been eliminated at time t and $t_b > t$ for a molecule which has not been eliminated at time t, it follows that

$$G(t) = A_e(t)/D \tag{B3}$$

The probability density function of t_b, the derivative of $G(t)$, is

$$h(t) \equiv \frac{dG(t)}{dt} = \frac{1}{D}\frac{dA_e(t)}{dt} \tag{B4}$$

The mathematical expectation of t_b, which is the mean residence time $\bar{t}_b$ of drug molecules in the "body," is then given by

$$E(t_b) \equiv \bar{t}_b = \int_{-\infty}^{\infty} h(t)\,t\,dt = \int_0^{\infty} h(t)\,t\,dt \tag{B5}$$

From Eqs. (B4) and (B5) it follows that

$$\bar{t}_b = \frac{1}{D}\int_0^{\infty} t\frac{dA_e(t)}{dt}\,dt \tag{B6}$$

The body clearance may be defined as

$$Cl(t) \equiv \frac{dA_e/dt}{c(t)} \tag{B7}$$

Combining Eqs. (B6) and (B7) gives

$$\bar{t}_b = \frac{1}{D}\int_0^\infty tCl(t)c(t)\,dt \tag{B8}$$

If the drug is only eliminated from the systemic circulation and the elimination is by a first order process, then the body clearance (Eq. B7) is constant, and Eq. (B8) may in this, and only this, case be written:

$$\bar{t}_b = \frac{Cl}{D}\int_0^\infty tc(t)\,dt = \frac{Cl}{D}AUMC \tag{B9}$$

Furthermore, in this case Eq. (B7) is simply integrated to give

$$\int_0^\infty A_e(t)\,dt = D = Cl \cdot AUC \tag{B10}$$

Substituting $Cl = D/AUC$ (Eq. B10) into Eq. (B9) proves Eq. (5).

APPENDIX C

Due to the dose independence of the $\bar{t}_b$, $\bar{t}_p$, and $\bar{t}_s$ parameters, the i.v. bolus response $c(t)$ used for the calculations of these parameters can be replaced by the unit impulse response $c_\delta(t)$. The unit impulse response can simply be obtained from the response $c_R(t)$ to constant rate ($= R$) infusion of the drug according to

$$c_\delta(t) = \frac{1}{R} \cdot \frac{dc_R(t)}{dt} \qquad t > 0 \tag{C1}$$

Alternatively, both the infusion phase response and the postinfusion phase ($t > T > 0$) response may be combined for a more comprehensive determination of $c_\delta(t)$ according to:

$$c_\delta(t) - c_\delta(t-T)_+ = \frac{1}{R} \cdot \frac{dc_R(t)}{dt} \tag{C2}$$

where

$$c_\delta(t-T)_+ = c_\delta(t-T) \qquad \text{for } t > T \tag{C3}$$

$$c_\delta(t-T)_+ = 0 \qquad \text{for } t \le T \tag{C4}$$

Equations (C1)–(C4) are useful when dealing with drugs which cannot be given by an i.v. bolus injection due to excessive side effects from such a rapid injection.

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