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The possible range of values for apparent volume of distribution at steady-state when disposition may be characterized by a tri-exponential function

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Summary

The inability to calculate a definitive value for apparent volume of distribution at steady state is discussed and a method presented whereby the possible minimum and maximum values for V_{ss} may be determined for a drug obeying linear kinetics whose disposition may be characterized by means of a tri-exponential equation.

Introduction

The use of compartmental models to describe the kinetics of drug disposition has become less common in recent years with many pharmacokineticists preferring a non-compartmental approach.

Four methods available for the estimation of V_{ss} which do not require detailed compartmental analysis (Riegelman et al., 1968; Wagner, 1976; Benet and Galeazzi, 1979; Rowland, 1982) have recently been reviewed (Collier, 1983). These methods, apart from assuming that linear kinetics apply, all assume drug to be eliminated only via the central compartment and must therefore be considered to give model-dependent estimates of V_{ss}.

When the plasma concentration–time profile following an i.v. bolus is described by Eqn. 1

$$C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} + C_3 e^{-\lambda_3 t} \quad (1)$$

there are many different three-compartment open models that will fit the data

equally well. The four methods of determining V_{ss} mentioned above will give the value appropriate to the three-compartment mammillary model shown in Fig. 1 which was stated by Collier (1983) to be the minimum possible value of V_{ss}. The maximum possible value of V_{ss} is given by

$$V_{ss} = CL\left[\frac{1}{\lambda_1} + \frac{1}{\lambda_2} + \frac{1}{\lambda_3}\right] \tag{2}$$

and applies to the three-compartment catenary model shown in Fig. 2.

Minimum value of V_{ss}

Consider the model shown in Fig. 1. Gibaldi and Perrier (1975) have shown that

$$\lambda_1\lambda_2 + \lambda_2\lambda_3 + \lambda_1\lambda_3 = k_{10}k_{21} + k_{13}k_{21} + k_{10}k_{31} + k_{21}k_{31} + k_{31}k_{12} \tag{3}$$

and

$$\lambda_1\lambda_2\lambda_3 = k_{10}k_{21}k_{31} \tag{4}$$

At steady-state

$$k_{21}V_2 = k_{12}V_1 \tag{5}$$

and

$$k_{31}V_3 = k_{13}V_1 \tag{6}$$

Therefore

$$V_{ss} = V_1\left[1 + \frac{k_{12}}{k_{21}} + \frac{k_{13}}{k_{31}}\right] \tag{7}$$

This may be rearranged to give

$$V_{ss} = V_1\left[\frac{k_{21}k_{31} + k_{12}k_{31} + k_{21}k_{13}}{k_{21}k_{31}}\right] \tag{8}$$

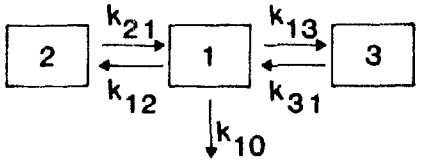

Fig. 1. A three-compartment open mammillary model.

Multiplying top and bottom by k_{10} gives

$$V_{ss} = k_{10}V_1\left[\frac{k_{21}k_{31} + k_{12}k_{31} + k_{21}k_{13}}{k_{10}k_{21}k_{31}}\right] \tag{9}$$

This may also be written as

$$V_{ss} = CL\left[\frac{\lambda_1\lambda_2 + \lambda_2\lambda_3 + \lambda_1\lambda_3 - k_{10}k_{21} - k_{10}k_{31}}{\lambda_1\lambda_2\lambda_3}\right] \tag{10}$$

which further simplifies to

$$V_{ss} = CL\left[\frac{1}{\lambda_1} + \frac{1}{\lambda_2} + \frac{1}{\lambda_3} - \frac{1}{k_{31}} - \frac{1}{k_{21}}\right] \tag{11}$$

Eqn. 10 gives a value for V_{ss} which is identical to that given by the four methods mentioned previously which assume drug to be eliminated from the central compartment but do not require estimation of micro-rate constants.

Maximum value of V_{ss}

Consider the model shown in Fig. 2. The application of the method of Laplace transforms gives

$$\begin{aligned}\bar{A}_1 = D[&(k_{21} + k_{23} + s)(k_{30} + k_{32} + s) - k_{32}k_{23}] \\ &\times [s^3 + s^2(k_{12} + k_{23} + k_{21} + k_{30} + k_{32}) \\ &+ s(k_{32}k_{21} + k_{32}k_{12} + k_{30}k_{21} + k_{30}k_{12} + k_{30}k_{23} + k_{23}k_{12}) \\ &+ k_{30}k_{23}k_{12}]^{-1}\end{aligned} \tag{12}$$

where $\bar{A}_1$ is the Laplace transform of the amount of drug in compartment 1, D is the dose of drug administered and S is the Laplace operator.

Eqn. 12 can be simplified further to give

$$\bar{A}_1 = \frac{D(k_{21} + k_{23} + s)(k_{30} + k_{32} + s) - k_{32}k_{23}}{(s + \lambda_1)(s + \lambda_2)(s + \lambda_3)} \tag{13}$$

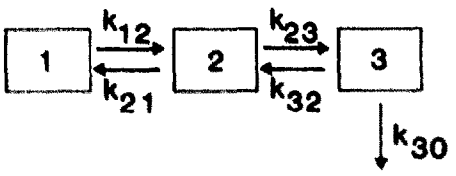

Fig. 2. A three-compartment open catenary model.

where

$$\lambda_1\lambda_2 + \lambda_2\lambda_3 + \lambda_1\lambda_3 = k_{32}k_{21} + k_{32}k_{12} + k_{30}k_{21} + k_{30}k_{23} + k_{30}k_{12} + k_{23}k_{12} \quad (14)$$

and

$$\lambda_1\lambda_2\lambda_3 = k_{30}k_{23}k_{12} \quad (15)$$

At steady-state

$$k_{12}V_1 + k_{32}V_3 = (k_{21} + k_{23})V_2 \quad (16)$$

and

$$k_{23}V_2 = (k_{30} + k_{32})V_3 \quad (17)$$

Therefore

$$V_{ss} = V_1\left[1 + \frac{k_{12}}{(k_{21} + k_{23}) - \dfrac{k_{32}k_{23}}{(k_{32} + k_{30})}} + \frac{k_{23}k_{12}}{(k_{32} + k_{30})(k_{21} + k_{23}) - k_{32}k_{23}}\right] \quad (18)$$

This can be rearranged as follows

$$V_{ss} = V_1\left[\frac{(k_{32} + k_{30})(k_{21} + k_{23}) - k_{32}k_{23} + k_{12}(k_{32} + k_{30}) + k_{23}k_{12}}{(k_{32} + k_{30})(k_{21} + k_{23}) - k_{32}k_{23}}\right] \quad (19)$$

Multiplying top and bottom by $\lambda_1\lambda_2\lambda_3$ gives

$$V_{ss} = \frac{V_1k_{30}k_{23}k_{12}}{(k_{32} + k_{30})(k_{21} + k_{23}) - k_{32}k_{23}} \times \left[\frac{k_{32}k_{21} + k_{30}k_{21} + k_{30}k_{23} + k_{12}k_{32} + k_{30}k_{12} + k_{23}k_{12}}{\lambda_1\lambda_2\lambda_3}\right] \quad (20)$$

This may also be written as

$$V_{ss} = k_{30}V_3\left[\frac{\lambda_1\lambda_2 + \lambda_2\lambda_3 + \lambda_1\lambda_3}{\lambda_1\lambda_2\lambda_3}\right] \quad (21)$$

Clearance may be defined either for a single bolus dose when $CL = D/AUC_\infty$ or for a system at steady-state when

$$CL = \text{rate of elimination}/Cp_{ss} = \text{rate of infusion}/Cp_{ss} \quad (22)$$

both clearance values being identical. For a system at steady-state the use of the term "apparent volume of distribution" assumes the concentration of drug to be identical in each compartment. Therefore not only will rate of elimination from compartment 1 = rate of elimination from compartment 3 for the model described in Fig. 2 but

$$\text{Clearance (compartment 1)} = \text{Clearance (compartment 3)} \tag{23}$$

Therefore

$$\frac{D}{AUC_{\infty}} = \text{Clearance} = k_{30}V_3 \tag{24}$$

(This can be shown to be the case for solving Eqn. 1 as shown in Appendix 2.)
Eqn. 21 may therefore be expressed as

$$V_{ss} = CL\left[\frac{1}{\lambda_1} + \frac{1}{\lambda_2} + \frac{1}{\lambda_3}\right] \tag{25}$$

(An alternative proof is given in Appendix 1.)

By comparing Eqns. 25 and 11 it can be seen that V_{ss} for the model represented in Fig. 2 will be in excess of V_{ss} for the model represented in Fig. 1.

Using similar algebraic techniques to those above it can be shown that the value of V_{ss} for all other possible three-compartment models is intermediate between the values of V_{ss} for the models shown in Figs. 1 and 2. However, in performing such algebraic manipulation it should be remembered that the values of micro-rate constants will vary according to the model which is fitted although the exponents will remain the same in each case.

Discussion

It is not possible to be definitive regarding which three-compartment model correctly describes the disposition of an i.v. bolus dose of drug which can be represented by an equation of the type shown in Eqn. 1. Therefore one cannot be definitive regarding the correct value of V_{ss}. However, following an i.v. bolus dose the use of the methods described by Wagner (1976) or Benet and Galeazzi (1979) will permit the minimum possible value of V_{ss} to be estimated while the use of Eqn. 25 will permit the maximum possible value of V_{ss} to be determined.

Appendix 1

Alternative proof of Eqn. 2

An alternative approach to the proof of Eqn. 2 is as follows: consider the model shown in Fig. 2 where drug is infused to steady-state. The application of the method

of Laplace transforms gives

$$\bar{A}_1 = \frac{k_0(1-e^{st})(k_{21}+k_{23}+s)(k_{32}+k_{30}+s)-k_{32}k_{23}}{s(s+\lambda_1)(s+\lambda_2)(s+\lambda_3)} \quad (A1)$$

$$\bar{A}_2 = \frac{k_0 k_{12}(1-e^{st})(k_{32}+k_{30}+s)}{s(s+\lambda_1)(s+\lambda_2)(s+\lambda_3)} \quad (A2)$$

$$\bar{A}_3 = \frac{k_0 k_{12} k_{23}(1-e^{st})}{s(s+\lambda_1)(s+\lambda_2)(s+\lambda_3)} \quad (A3)$$

where $\bar{A}_1$, $\bar{A}_2$ and $\bar{A}_3$ are the Laplace transforms of the amount of drug in compartments 1, 2 and 3, respectively.

Converting to the time domain, at steady-state:

$$A_1^{ss} = \frac{k_0[(k_{21}+k_{23})(k_{32}+k_{30})-k_{32}k_{23}]}{\lambda_1\lambda_2\lambda_3} \quad (A4)$$

$$A_2^{ss} = \frac{k_0 k_{12}(k_{32}+k_{30})}{\lambda_1\lambda_2\lambda_3} \quad (A5)$$

$$A_3^{ss} = \frac{k_0 k_{12} k_{23}}{\lambda_1\lambda_2\lambda_3} \quad (A6)$$

The apparent volume of distribution at steady-state can be obtained from:

$$V_{ss} = \frac{\text{amount of drug in the body at steady-state}}{\text{concentration in compartment 1 at steady-state}} \quad (A7)$$

$$V_{ss} = \frac{A_1^{ss}+A_2^{ss}+A_3^{ss}}{A_1^{ss}/V_1} \quad (A8)$$

Substituting into Eqn. A8 from Eqns. A4–A6 gives:

$$V_{ss} = V_1\left[1+\frac{k_{12}(k_{32}+k_{30})+k_{23}k_{12}}{(k_{32}+k_{30})(k_{21}+k_{23})-k_{32}k_{23}}\right] \quad (A9)$$

This in turn simplifies to Eqn. 18 which further simplifies to give Eqn. 25.

Appendix 2

Solving Eqn. 1 in terms of the rate constants for a three-compartment open catenary model (Fig. 2)

Converting Eqn. 12 into the time domain and expressing in terms of concentra-

tion gives:

$$C = \frac{D[(k_{21}+k_{23}-\lambda_1)(k_{30}+k_{32}-\lambda_1)-k_{32}k_{23}]\,e^{-\lambda_1 t}}{V_1(\lambda_2-\lambda_1)(\lambda_3-\lambda_1)}$$

$$+\frac{D[(k_{21}+k_{23}-\lambda_2)(k_{30}+k_{32}-\lambda_2)-k_{32}k_{23}]\,e^{-\lambda_2 t}}{V_1(\lambda_1-\lambda_2)(\lambda_3-\lambda_2)}$$

$$+\frac{D[(k_{21}+k_{23}-\lambda_3)(k_{30}+k_{32}-\lambda_3)-k_{32}k_{23}]\,e^{-\lambda_3 t}}{V_1(\lambda_1-\lambda_3)(\lambda_2-\lambda_3)} \qquad \text{(A10)}$$

In view of the relationships expressed in Eqns. 14 and 15 and that

$$\lambda_1+\lambda_2+\lambda_3 = k_{12}+k_{21}+k_{23}+k_{32}+k_{30} \qquad \text{(A11)}$$

the term C_2 in Eqn. 1 may be written as:

$$C_2 = [(C_1+C_2+C_3)k_{21}k_{30}+k_{21}k_{32}+k_{23}k_{30}+k_{23}k_{32}+\lambda_2^2$$

$$-\lambda_2(k_{21}+k_{23}+k_{30}+k_{32})-k_{32}k_{23}][(\lambda_1-\lambda_2)(\lambda_3-\lambda_2)]^{-1} \qquad \text{(A12)}$$

This simplifies to give:

$$\frac{C_2}{C_1+C_2+C_3} = \frac{\lambda_3\lambda_1-k_{12}(\lambda_1+\lambda_3)+k_{12}^2+k_{12}k_{21}}{(\lambda_1-\lambda_2)(\lambda_3-\lambda_2)} \qquad \text{(A13)}$$

Similarly,

$$\frac{C_1}{C_1+C_2+C_3} = \frac{\lambda_2\lambda_3-k_{12}(\lambda_2+\lambda_3)+k_{12}^2+k_{12}k_{21}}{(\lambda_2-\lambda_1)(\lambda_3-\lambda_1)} \qquad \text{(A14)}$$

Combining Eqns. A13 and A14 and solving for k_{12} gives:

$$k_{12} = \frac{\dfrac{\lambda_3\lambda_1-\lambda_2\lambda_3+C_1(\lambda_2-\lambda_1)(\lambda_3-\lambda_1)-C_2(\lambda_1-\lambda_2)(\lambda_3-\lambda_2)}{C_1+C_2+C_3}}{(\lambda_1-\lambda_2)} \qquad \text{(A15)}$$

Substituting for k_{12} in Eqn. A13 or A14 allows k_{21} to be determined. Rearrangement of Eqn. 14 gives:

$$\lambda_1\lambda_2+\lambda_2\lambda_3+\lambda_1\lambda_3-k_{30}k_{23}-k_{12}(k_{32}+k_{30}+k_{23}) = k_{21}(k_{32}+k_{30}) \qquad \text{(A16)}$$

Using the relationships shown in Eqn. 15 and Eqn. A11, this may be written as:

$$\lambda_1\lambda_2 + \lambda_2\lambda_3 + \lambda_1\lambda_3 - \frac{\lambda_1\lambda_2\lambda_3}{k_{12}} - k_{12}(\lambda_1 + \lambda_2 + \lambda_3 - k_{12} - k_{21})$$

$$= k_{12}(\lambda_1 + \lambda_2 + \lambda_3 - k_{12} - k_{21} - k_{23}) \tag{A17}$$

This may be rearranged to give an expression for k_{23}

$$k_{23} = -\left[\frac{\lambda_1\lambda_2 + \lambda_2\lambda_3 + \lambda_1\lambda_3 - \frac{\lambda_1\lambda_2\lambda_3}{k_{12}} - k_{12}(\lambda_1 + \lambda_2 + \lambda_3 - k_{12} - k_{21})}{k_{21}}\right.$$

$$\left. - (\lambda_1 + \lambda_2 + \lambda_3 - k_{21} - k_{12})\right] \tag{A18}$$

The remaining two rate constants may be determined as follows:

$$k_{30} = \frac{\lambda_1\lambda_2\lambda_3}{k_{23}k_{12}} \tag{A19}$$

$$k_{32} = \lambda_1 + \lambda_2 + \lambda_3 - k_{12} - k_{21} - k_{30} - k_{23} \tag{A20}$$

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