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SCIENTIFIC COMMENTARY

Some Considerations on the Estimation of Steady State Apparent Volume of Distribution and the Relationships Between Volume Terms

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Application of statistical moment theory to four methods which do not involve detailed compartmental analysis for the determination of V_{ss} *shows them to be equal. Assuming drug to be eliminated exclusively from the central compartment results in the minimum value of* V_{ss} *being determined. A method for determining the maximum possible value of* V_{ss} *is shown which uses* AUC, *dose (iv), and the exponents which describe the plasma-concentration time curve. The relationships between the volume terms* V_{extrap}, V_{area} *and* V_{ss} *are discussed in terms of moment theory.*

KEY WORDS: V_{ss}; V_{area}; V_{extrap}; moment theory; two-compartment model.

METHODS FOR DETERMINATION OF V_{ss}

The apparent volume of distribution at steady state (V_{ss}) can be defined as the amount of drug in the body divided by the plasma concentration at steady state

$$V_{ss} = A_{ss}/C_{ss} \tag{1}$$

Several methods for determining V_{ss} which do not require detailed compartmental analysis have been published. Benet and Galeazzi (1) have described a method which requires the measurement of the area under the plasma concentration curve from zero to infinity (AUC) and also the measurement of the area under the first moment of the plasma curve from zero time to

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infinity ($AUMC$) following an intravenous bolus dose of drug. (This approach can also be used for other methods of drug administration provided the input function is known; see ref. 2). Thus

$$V_{ss} = \text{dose}\left[\int_0^\infty tC\,dt\right]\Big/\left[\int_0^\infty C\,dt\right]^2 = \text{dose}\,[AUMC]/[AUC]^2$$

$$= \text{dose}\,[MRT_{iv}]/AUC \qquad (2)$$

Earlier Wagner (3) described a method for determination of V_{ss}, where it is necessary first to describe the plasma concentration curve in terms of a polyexponential equation of a type similar to that shown in Eq. (3):

$$C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} \cdots + C_n e^{-\lambda_n t} \qquad (3)$$

Then V_{ss} may be defined as follows:

$$V_{ss} = \text{dose}\left[\sum_{i=1}^{i=n} \frac{C_i}{\lambda_i^2}\right]\Big/\left[\sum_{i=1}^{i=n} \frac{C_i}{\lambda_i}\right]^2 \qquad (4)$$

Both methods require the drug to obey linear kinetics and are invalid if there is an absorption phase (e.g., enterohepatic recycling). Yamaoka *et al* (4) demonstrated the following relationship:

$$\int_0^\infty tC\,dt\Big/\int_0^\infty C\,dt = \sum_{i=1}^{i=n} \frac{C_i}{\lambda_i^2}\Big/\sum_{i=1}^{i=n} \frac{C_i}{\lambda_i} \qquad (5)$$

Thus the equivalence of the V_{ss} terms described by Benet and Galeazzi (Eq. 2) and by Wagner (Eq. 4) can be seen. The obvious advantage of the method described by Benet and Galeazzi is that it is not necessary to define the plasma concentration curve in terms of an equation. However, both methods are based on the assumption that elimination of drug occurs exclusively from the central compartment, and in that sense both methods are model dependent.

A third method independent of compartmental analysis has been described by Riegelman *et al.* (5). This method requires the drug to be administered by intravenous infusion from zero time to time T when steady state has been achieved:

$$V_{ss} = \frac{\text{total infused dose}}{C_{ss}}\left[1 - \int_0^T C\,dt\Big/\int_0^\infty C\,dt\right]$$

$$= \frac{\text{total infused dose}}{C_{ss}}[1 - AUC_{0-T}/AUC] \qquad (6)$$

Again the assumption is made that elimination occurs exclusively from the central compartment. On the basis of a two-compartment body model

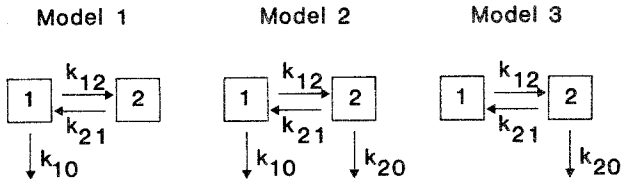

Fig. 1. The three possible linear two-compartment open models. In each case the concentration in compartment 1 (the central compartment) represents the measurable concentration of drug.

where this assumption is true (Fig. 1, model 1) Gibaldi (6) has shown that the amount of drug in the body at steady state (A_{ss}) is given as follows:

$$A_{ss} = \text{total infused dose}\left[1 - \int_0^T C\,dt \Big/ \int_0^\infty C\,dt\right] = \frac{ko(k_{12}+k_{21})}{\lambda_1\lambda_2} \tag{7}$$

where *ko* represents the infusion rate of the drug. At steady state the clearance of the drug (*CL*) will be given as follows:

$$CL = \frac{ko}{C_{ss}} \tag{8}$$

Therefore Eq. (7) can be written as follows:

$$\frac{A_{ss}}{C_{ss}} = \frac{CL(k_{12}+k_{21})}{\lambda_1\lambda_2} = V_{ss} \tag{9}$$

Using the following relationships,

$$\lambda_1\lambda_2 = k_{10}k_{21} \tag{10}$$

$$\lambda_1 + \lambda_2 = k_{10} + k_{21} + k_{12} \tag{11}$$

Eq. (9) may be rewritten as follows:

$$V_{ss} = CL\left[\frac{1}{\lambda_1} + \frac{1}{\lambda_2} - \frac{1}{k_{21}}\right] \tag{12}$$

For a drug following two-compartment body model kinetics with elimination occurring exclusively from the central compartment, Riegelman and Collier (7) demonstrated that the mean residence time (*MRT*) of the drug administered as an i.v. bolus is described as follows:

$$MRT_{iv} = \frac{1}{\lambda_1} + \frac{1}{\lambda_2} - \frac{1}{k_{21}} \tag{13}$$

Therefore Eq. (12) is equivalent to that of Benet and Galeazzi (Eq. 2), who also expressed V_{ss} as follows:

$$V_{ss} = CL \cdot MRT_{iv} = \frac{\text{dose}}{AUC}\left[\frac{AUMC}{AUC}\right] \tag{14}$$

There are, however, numerical problems associated with the use of Eq. (6) to estimate V_{ss}. If the infusion is many (>10) half-lives, AUC_{0-T} will approach the value of AUC. Small errors in estimating AUC will therefore result in large errors in determining V_{ss}. A more robust approach (M. Rowland, personal communication) is to infuse the drug until steady state is achieved and to measure the area under the fall-off curve:

$$V_{ss} = \frac{A_{ss}}{C_{ss}} = CL\int_{T}^{\infty} C\,dt/C_{ss} = \frac{ko \cdot AUC_{T-\infty}}{C_{ss}^2} \tag{15}$$

It can be shown by the method of Benet (8) that

$$A_{ss} = \frac{k_{21}ko}{\lambda_1\lambda_2} + \frac{k_{12}ko}{\lambda_1\lambda_2} \tag{16}$$

Therefore

$$V_{ss} = ko\left[\frac{1}{\lambda_1} + \frac{1}{\lambda_2} - \frac{1}{k_{21}}\right] \Big/ C_{ss} = \frac{koMRT_{iv}}{C_{ss}} = CL \cdot MRT_{iv} \tag{17}$$

Thus it is possible on the basis of moment theory to demonstrate the equivalence of the four methods for V_{ss} determination, mentioned above.

MODELS WHERE ELIMINATION DOES NOT OCCUR EXCLUSIVELY FROM THE CENTRAL COMPARTMENT

If the MRT is calculated from plasma level data using the following relationships,

$$MRT = \frac{AUMC}{AUC} \tag{18}$$

one is measuring the mean residence time of the drug in the central compartment. Consider a plasma concentration-time curve that may be described by Eq. (19):

$$C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} \tag{19}$$

Each of the three possible two-compartment open models shown in Fig. 1 will describe the data equally well, i.e., there is no unique solution. This point has been discussed by Wagner (3), who suggested that because of

the dilemma of not knowing from which compartment there are exit rate constants to outside the body, the assumption that elimination occurs solely from the central compartment will at least make all authors homogeneous in their approach. This, however, results in problems in determining the correct loading dose of drug for a patient if the "true" value of V_{ss} is unknown.

The definition of V_{ss} given by Riggs (9) for model 1 (Fig. 1) is

$$V_{ss} = \left[1 + \frac{k_{12}}{k_{21}}\right] V_1 \tag{20}$$

It is also possible to define V_{ss} for models 2 and 3 at the time when the rate of drug entry equals the rate of drug exit from the second compartment, so that

$$V_{ss} = \left[1 + \frac{k_{12}}{k_{20} + k_{21}}\right] V_1 \tag{21}$$

Equation (21) holds true for both models 2 and 3, but the value of the rate constants and hence the value of V_{ss} will be different for each model.

V_{ss} can also be defined for models 2 and 3 in terms of moment theory. First it is necessary to calculate the MRT for drug in the peripheral compartment. Yamaoka *et al.* (4) defined MRT as follows:

$$MRT = \frac{AUMC}{AUC} = \lim_{s \to 0}\left[\frac{d\bar{C}}{ds}\right] \Big/ \lim_{s \to 0}[\bar{C}] \tag{22}$$

where $\bar{C}$ is the Laplace transform of the drug concentration and s is the Laplace operator.

If $\bar{C}$ is considered to relate to the peripheral compartment, then (ref. 7)

$$\begin{aligned} AUC(2) &= \lim_{s \to 0}[\bar{C}] \\ &= \frac{k_{12}\,\text{dose}}{V_2 \lambda_1 \lambda_2} \end{aligned} \tag{23}$$

Similarly,

$$\begin{aligned} AUMC(2) &= \lim_{s \to 0}\left[\frac{d\bar{C}}{ds}\right] \\ &= \frac{k_{12}\,\text{dose}}{V_2 \lambda_1 \lambda_2}\left[\frac{1}{\lambda_1} + \frac{1}{\lambda_2}\right] \end{aligned} \tag{24}$$

Therefore the MRT of drug in the peripheral compartment is given by

$$MRT(2) = \frac{1}{\lambda_1} + \frac{1}{\lambda_2} \tag{25}$$

In the experimental situation, V_2 will of course be an apparent volume, not an absolute volume, as it is determined by reference only to the central compartment. The corresponding equations relating to drug in the central compartment were shown by Riegelman and Collier (7) to be

$$AUC(1) = \frac{\text{dose}\, E_2}{V_1 \lambda_1 \lambda_2} \tag{26}$$

$$AUMC(1) = \frac{\text{dose}\, E_2}{V_1 \lambda_1 \lambda_2}\left[\frac{1}{\lambda_1} + \frac{1}{\lambda_2} - \frac{1}{E_2}\right] \tag{27}$$

$$MRT(1) = \frac{1}{\lambda_1} + \frac{1}{\lambda_2} - \frac{1}{E_2} \tag{28}$$

where E_2 represents the sum of the exit rate constants from the peripheral compartment.

Table I lists three sets of parameters each of which describes the following equation:

$$C = 64.131\, e^{-2.2346t} + 35.869\, e^{-0.4654t} \tag{29}$$

If these parameters are used to calculate AUC for each model using either Eq. (23) (peripheral compartment) or Eq. (26) (central compartment), the estimates of AUC are identical regardless of the model or the compartment. Also if $AUMC$ is calculated for each model using Eq. (24) (peripheral compartment) or Eq. (27) (central compartment), the estimates are identical for each model (Table I), but in this case differ between compartments.

As expected. V_{ss} for model 1 is given by

$$V_{ss} = \frac{\text{dose}}{AUC}\left[\frac{AUMC(1)}{AUC}\right] = \frac{\text{dose}\,[MRT(1)]}{AUC} = \frac{\text{dose}}{AUC}\left[\frac{1}{\lambda_1} + \frac{1}{\lambda_2} - \frac{1}{E_2}\right] \tag{30}$$

A similar equation defines V_{ss} for model 3, but in this case, it is necessary to use $AUMC$ for drug in the peripheral compartment:

$$V_{ss} = \frac{\text{dose}}{AUC}\left[\frac{AUMC(2)}{AUC}\right] = \frac{\text{dose}\,[MRT(2)]}{AUC} = \frac{\text{dose}}{AUC}\left[\frac{1}{\lambda_1} + \frac{1}{\lambda_2}\right] \tag{31}$$

The method of using $AUMC$ to obtain V_{ss} for model 2 is not immediately obvious. It is necessary to know the fraction of the administered dose that is eliminated from each compartment. Then

$$V_{ss} = \frac{\text{dose}}{AUC}[f_1 MRT(1) + f_2 MRT(2)] \tag{32}$$

Table I. Parameter Values for Each of Models 1, 2, and 3 (Fig. 1) Which Describe Eq. (29).

Parameter	Model 1	Model 2	Model 3
Dose	1000.00	1000.00	1000.00
k_{12}	0.6545	1.20	1.6
k_{21}	1.10	0.60	0.45
k_{10}	0.9455	0.40	
k_{20}		0.50	0.65
V_1	10.00	10.00	10.00
V_{ss}	15.95	20.91	24.55
CL	9.4545	9.4545	9.4545
$AUC(1)$	105.76	105.76	105.76
$AUC(2)$	105.76	105.76	105.76
$AUMC(1)$	178.41	178.41	178.41
$AUMC(2)$	274.56	274.56	274.56

where f_1 and f_2 represent the fractions of the administered dose eliminated from the central and peripheral compartments, respectively.[2,3]

Comparing Eqs. (30) and (31) it can be seen that to calculate V_{ss} it is necessary to use the MRT value for drug molecules in the compartment from which they are directly eliminated from the body. With model 2, where V_{ss} is represented by Eq. (32), drug is eliminated directly from each of the two compartments. In this case the appropriate MRT value to use is the sum of the weighted MRT values of the two compartments, the weighting factor in each case being the fraction of the administered dose that is eliminated directly from that compartment.

With each model discussed, the $MRT(1)$ and $MRT(2)$ values represent the MRT of the drug in the relevant compartment, which is not necessarily the MRT of drug in the body. When the plasma level of drug administered as an i.v. bolus undergoes monoexponential decline, the $MRT(1)$ corresponds to the time for 63.2% of the drug to be eliminated from the body, the value 63.2% being equivalent to the mean of a log normally distributed cumulative curve. However, Riegelman and Collier (7) were wrong in saying that this was also the case for more complex pharmacokinetic models. When it is necessary to use a bi- or polyexponential function to describe drug disposition, the residence times of the individual drug molecules are no longer log normally distributed; instead the distribution is a skewed log distribution. In the case of model 1 $MRT(1)$ will normally correspond to greater than 63.2% elimination and for model 3, to less than 63.2% elimination.

[2]For model 2 using the parameters listed in Table I, $f_1 = 0.4231$ and $f_2 = 0.5769$.
[3]The derivations of Eqs. (31) and (32) are shown in the appendix.

However, a less abstract interpretation of $MRT(1)$ and $MRT(2)$ in Eqs. (30), (31), and (32) is possible. For systems at strady state the mean residence time of drug in the body (MRT) has been shown (10) to be equal to the time to infuse a dose equal to the amount of drug in the body under steady state conditions:

$$MRT = \frac{A_{ss}}{k_0} \tag{33}$$

For model 1 the MRT is equal to $MRT(1)$ obtained with an i.v. bolus, while for model 3, MRT is equal to $MRT(2)$. In the case of model 2, MRT is equal to the term $(f_1 MRT(1) + f_2 MRT(2))$.

As stated previously the correct model describing Eq. (29) cannot be known. However, assuming model 1 applies, V_{ss} can be estimated using the method of Benet and Galeazzi (1). This will represent the minimum possible value of V_{ss}. The maximum possible value of V_{ss} can be estimated by assuming model 3 applies, and evaluating Eq. (31), where λ_1 and λ_2 can be obtained by graphical means or by nonlinear regression, without the need for compartmental analysis. Thus the possible limits of V_{ss} can be obtained.

When the plasma concentration curve following an i.v. bolus dose can be described by an equation containing three exponential terms a similar situation applies. The minimum value for V_{ss} is given by the method of Benet and Galeazzi (1) and relates to a three compartment mammillary model where elimination occurs exclusively from the central compartment. It can also be shown that the maximum possible value for V_{ss} is given by Eq. (34) and relates to a three compartment catenary model where elimination occurs exclusively from the third compartment. Thus

$$V_{ss} = \frac{\text{dose}}{AUC}\left[\frac{1}{\lambda_1} + \frac{1}{\lambda_2} + \frac{1}{\lambda_3}\right] \tag{34}$$

RELATIONSHIP BETWEEN V_{ss}, V_{area} AND V_{extrap}

In terms of a two-compartment open model (model 1, Fig. 1), the apparent volume of distribution obtained by back extrapolation of the terminal log-linear phase of elimination has been shown to be equal to the following (ref. 5):

$$V_{extrap} = \frac{(\lambda_1 - \lambda_2)V_1}{(k_{21} - \lambda_2)} \tag{35}$$

while

$$V_{area} = \frac{(\lambda_1 - k_{10})V_1}{(k_{21} - \lambda_2)} = \frac{\lambda_1 V_1}{k_{21}} \tag{36}$$

Because λ_2 will always be less than k_{10},

$$V_{extrap} > V_{area}$$

Similarly, it has been shown (11) that

$$V_{ss} = \left[\frac{\lambda_1 + (\lambda_2 - k_{10})}{k_{21}}\right] V_1 \tag{37}$$

and because $(\lambda_2 - k_{10})$ will always be negative,

$$V_{extrap} > V_{area} > V_{ss}$$

Such a relationship can also be demonstrated in terms of moment theory. Given that the "true" apparent volume of distribution (V_{ss}) is defined by

$$V_{ss} = \frac{\text{dose}}{AUC}[MRT(1)] \tag{38}$$

V_{extrap} will overestimate V_{ss} first by underestimating AUC by use of the term (C_2/λ_2) [this is in place of the correct term $(C_1/\lambda_1 + C_2/\lambda_2)$, which is equivalent to AUC], and second by overestimating $MRT(1)$ through the use of the term $(1/\lambda_2)$ in place of the correct term $(1/\lambda_1 + 1/\lambda_2 - 1/E_2)$. That is,

$$V_{extrap} = \frac{\text{dose}\ (1/\lambda_2)}{(C_2/\lambda_2)} = \frac{\text{dose}}{C_2} \tag{39}$$

Likewise V_{area} will overestimate V_{ss} by use of the same incorrect term for $MRT(1)$:

$$V_{area} = \frac{\text{dose}\ (1/\lambda_2)}{AUC} \tag{40}$$

However, if models 2 and 3 are considered, then V_{ss} msy be larger than V_{area}, and in some instances, larger than V_{extrap}. The latter two volume terms will remain unchanged regardless of the model, but MRT for the peripheral compartment will be larger than MRT for the central compartment, i.e.,

$$(1/\lambda_1 + 1/\lambda_2) > (1/\lambda_1 + 1/\lambda_2 - 1/E_2)$$

Comparing Eqs. (40) and (31), it can be seen that V_{ss} for model 3 will exceed the value of V_{area}.

The MRT value required to calculate V_{ss} for model $2(f_1 MRT(1) + f_2 MRT(2))$ will vary from the minimum value obtained with model 1 to

the maximum value obtained with model 3 according to the fraction of drug eliminated from each compartment. Therefore, with model 2 there will be occasions when V_{ss} will exceed V_{area}, and other instances when the reverse will be true. Also, with models 2 and 3 one cannot be definitive regarding the relationship between V_{ss} and V_{extrap}. Whether or not V_{ss} will be the larger of the two volume terms will depend upon the relative contributions of $1/\lambda_1$ to the numerator (MRT) and C_1/λ_1 to the denomenator (AUC) of Eqs. (31) and (32).

MODEL DEPENDENCY OF V_{ss}

Benet and Ronfeld (12) pointed out that V_{ss} is only "model independent" (that is independent of the rate of elimination and hence clearance of the drug) when elimination occurs exclusively from the central compartment. However, V_{ss} is dependent upon which model (e.g., Fig. 1) correctly describes the disposition of the drug in the body. Clearance (CL) is dependent on the rate of elimination, but may be considered a model independent parameter in that regardless of which two-compartment open model one chooses to represent the plasma-concentration profile, the estimate of CL is the same.[4] With model 2 a decrease in CL caused by a decrease in k_{10} will not affect V_{ss}. However, a decrease in k_{20} in either model 2 or 3 will cause an increase in V_{ss}, while an increase in k_{20} will have the reverse effect. This is analogous to the situation where V_{area} decreases with an increase in CL (5).

CONCLUSIONS

Using the approach of moment theory to the calculation of V_{ss}, the equivalence of the methods described by Riegelman *et al.* (5) and Wagner (3) to that described by Benet and Galeazzi (1) has been demonstrated. When calculation of V_{ss} is required for model 3 (where elimination occurs exclusively from the peripheral compartment), this may be done by measuring AUC and the exponents defining the plasma-concentration profile following an intravenous bolus dose of drug. The value of V_{ss} for model 2 will be intermediate between that of models 1 and 3, but cannot be determined without rigorous compartmental modelling. The use of V_{ss} determined by the method of Benet and Galeazzi (1) will result in an

[4]Using the parameters listed in table I, CL may be calculated as the product of the elimination rate constant and the volume of distribution of the compartment from which elimination occurs. For model 2, CL_{total} is equal to the sum of the individual CL values for each compartment.

underestimate of the amount of drug in the body at steady state and hence also an underestimate of the necessary loading dose, if elimination occurs partly or exclusively from the peripheral compartment. Whereas CL is a model independent parameter, V_{ss} is model dependent and will increase with a decrease in CL of drug from a peripheral compartment.

APPENDIX

Derivation of Eq. (31)

Assuming model 3 (Fig. 1) applies,

$$\lambda_1\lambda_2 = k_{12}k_{20} \tag{A1}$$

$$\lambda_1+\lambda_2 = k_{12}+k_{21}+k_{20} \tag{A2}$$

Equation (21) can be written as

$$V_{ss} = \frac{(k_{12}+k_{21}+k_{20})V_1}{(k_{21}+k_{20})} \tag{A3}$$

Multiplying top and bottom by $k_{12}k_{20}$ and simplifying,

$$V_{ss} = \frac{(\lambda_1+\lambda_2)k_{20}V_2}{\lambda_1\lambda_2} \tag{A4}$$

But $k_{20}V_2 = CL$, so Eq. (A4) can be simplified further to give

$$V_{ss} = CL\left[\frac{1}{\lambda_1}+\frac{1}{\lambda_2}\right] \tag{A5}$$

Derivation of Eq. (32)

Assuming model 2 (Fig. 1) applies,

$$\lambda_1\lambda_2 = k_{10}k_{20}+k_{10}k_{21}+k_{12}k_{20} \tag{A6}$$

$$\lambda_1+\lambda_2 = k_{10}+k_{12}+k_{21}+k_{20} \tag{A7}$$

Equation (21) can be written as follows:

$$V_{ss} = \frac{(\lambda_1+\lambda_2-k_{10})V_1}{(k_{20}+k_{21})} \tag{A8}$$

Multiplying top and bottom by $\lambda_1\lambda_2$ and expanding gives:

$$V_{ss} = V_1\left[\frac{(\lambda_1+\lambda_2)(k_{10}(k_{20}+k_{21})+k_{20}k_{12})-k_{10}\lambda_1\lambda_2}{(k_{20}+k_{21})\lambda_1\lambda_2}\right] \tag{A9}$$

This can be rearranged to give:

$$V_{ss} = V_1\left[\frac{k_{10}(k_{20}+k_{21})[\lambda_1+\lambda_2-\lambda_1\lambda_2/(k_{20}+k_{21})]+k_{20}k_{12}(\lambda_1+\lambda_2)}{(k_{20}+k_{21})\lambda_1\lambda_2}\right] \tag{A10}$$

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

$$V_{ss} = \frac{V_1\lambda_1\lambda_2}{(k_{20}+k_{21})}\left[\frac{k_{10}(k_{20}+k_{21})}{\lambda_1\lambda_2}\,\frac{[\lambda_1+\lambda_2-\lambda_1\lambda_2/(k_{20}+k_{21})]}{\lambda_1\lambda_2} + \frac{k_{20}k_{12}}{\lambda_1\lambda_2}\,\frac{(\lambda_1+\lambda_2)}{\lambda_1\lambda_2}\right] \tag{A11}$$

However, using the method described by Benet (11), it can be shown that following an i.v. bolus dose, the total amounts eliminated from each of compartments 1 and 2 are $k_{10}(k_{20}+k_{21})D/\lambda_1\lambda_2$ and $k_{20}k_{12}D/\lambda_1\lambda_2$, respectively. Therefore, Eq. (A11) can be simplified further to give:

$$V_{ss} = \frac{V_1\lambda_1\lambda_2}{(k_{20}+k_{21})}\left[f_1\left(\frac{1}{\lambda_1}+\frac{1}{\lambda_2}-\frac{1}{E_2}\right)+f_2\left(\frac{1}{\lambda_1}+\frac{1}{\lambda_2}\right)\right] \tag{A12}$$

where f_1 and f_2 are the fractions of dose eliminated by compartments 1 and 2, respectively, and $E_2 = (k_{20}+k_{21})$. But

$$\frac{V_1\lambda_1\lambda_2}{(k_{20}+k_{21})} = V_1\left[k_{10}+\frac{k_{12}k_{20}}{(k_{20}+k_{21})}\right] = k_{10}V_1+k_{20}V_2 = CL \tag{A13}$$

Therefore, Eq. (A13) can be simplified to give:

$$V_{ss} = CL[f_1MRT(1)+f_2MRT(2)] \tag{A14}$$

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