International Journal of Pharmaceutics, 18 (1984) 353–359
Elsevier

IJP 00631

Short Communication

Theoretical justification for the midpoint back-extrapolation method of estimating apparent volume of distribution of drugs after a short intravenous infusion

M. Barzegar-Jalali

Pharmaceutics Division, School of Pharmacy, Tabriz University, Tabriz (Iran)

(Received May 24th, 1983)
(Modified version received September 19th, 1983)
(Accepted October 1st, 1983)

The apparent volume of distribution, V_d, of drugs is a very important parameter which is used for dosage regimen calculations. Chiou et al. (1978, 1980) have developed a rapid and very simple approach named as the midpoint back-extrapolation method for estimating V_d of drugs following a short constant-rate intravenous infusion. According to the method the value of V_d is estimated by Eqn. 1

$$V_d = \frac{D}{C_b} \tag{1}$$

in which D is the dose of drug administered via infusion over a short period of time (T) and C_b is a hypothetical drug concentration on the back-extrapolated semilogarithmic plot of post-infusion blood level vs time corresponding to midpoint of the infusion period. This method has been developed intuitively without any theoretical justification (Chiou, 1983).

In this report theoretical justifications for the method as well as a general equation based on the back-extrapolation technique are presented using the one- and two-compartment open models. The method has been tested using simulated and experimental data.

(1) The post-infusion blood level, C, for the one-compartment model is described

Correspondence: M. Barzegar-Jalali, Pharmaceutics Division, School of Pharmacy, Tabriz University, Tabriz, Iran.

0378-5173/84/$03.00 © 1984 Elsevier Science Publishers B.V.

by the following equation (Gibaldi and Perrier, 1975)

$$C = \frac{D}{KV_dT}(1 - e^{-KT})e^{-K(t-T)} = \frac{D}{V_d}\left(\frac{e^{KT} - 1}{KT}\right)e^{-Kt} \tag{2}$$

where K is a first-order elimination rate-constant of drug and t is time taken from the beginning of the infusion. Re-arrangement of Eqn. 2 will result in Eqn. 3

$$V_d = \frac{D}{C}\left(\frac{e^{KT} - 1}{KT}\right)e^{-Kt} \tag{3}$$

In order to calculate the value of V_d from Eqn. 1 the following condition should be met in Eqn. 3 i.e.,

$$\left(\frac{e^{KT} - 1}{KT}\right)e^{-Kt_b} = 1 \tag{4}$$

or

$$t_b = \frac{\ln\left(\frac{e^{KT} - 1}{KT}\right)}{K} \tag{5}$$

where t_b is a time at which the right-hand side of Eqn. 3 will be equal to D/C_b or the time corresponding to C_b. The proof given below indicates that the Eqns. 4 and 5 hold when only $t_b \simeq T/2$.

The expansion of e^{KT} results in the following series

$$e^{KT} = 1 + KT + \frac{K^2T^2}{2} + \frac{K^3T^3}{6} + \frac{K^4T^4}{24} + \frac{K^5T^5}{120} + \cdots \tag{6}$$

For the cases where $KT \leqslant 1.5$ the values of the terms having the powers higher than 3 in this series are negligible and can be omitted. Eqn. 5 can therefore be written as

$$t_b = \frac{\ln\left[\frac{\left(1 + KT + \frac{K^2T^2}{2} + \frac{K^3T^3}{6}\right) - 1}{KT}\right]}{K} = \frac{\ln\left(1 + \frac{KT}{2} + \frac{K^2T^2}{6}\right)}{K} \tag{7}$$

But, the term inside the parenthesis on the far right-hand side of Eqn. 7 is approximately equal to $e^{KT/2}$ (because $e^{KT/2} \simeq 1 + (KT)/2 + (K^2T^2)/8$). Thus,

Eqn. 7 becomes Eqn. 8

$$t_b = \frac{\ln(e^{KT/2})}{K} = \frac{KT}{2K} = \frac{T}{2} \tag{8}$$

(2) Eqn. 1 can also be derived as follows. Substituting T/2 for t into Eqn. 3 and simplification would yield Eqn. 9

$$V_d = \frac{D}{C_b}\left(\frac{e^{KT/2} - e^{-KT/2}}{KT}\right) \tag{9}$$

The values of $e^{KT/2}$ and $e^{-KT/2}$ are given by

$$e^{KT/2} = 1 + \frac{KT}{2} + \frac{K^2T^2}{8} + \frac{K^3T^3}{48} + \cdots \tag{10}$$

$$e^{-KT/2} = 1 - \frac{KT}{2} + \frac{K^2T^2}{8} - \frac{K^3T^3}{48} + \cdots \tag{11}$$

When $KT \leqslant 1.5$, the terms with powers higher than 2 can be omitted. Substitution of the values of $e^{KT/2}$ and $e^{-KT/2}$ from Eqns. 10 and 11 into Eqn. 9 and subsequent simplification would give Eqn. 1.

(3) Based on the back-extrapolation method a general equation for estimating V_d can also be derived for any T/n value provided that $n \geqslant 2$. Substituting C'_b for C and the corresponding time, T/n for t into Eqn. 3 would yield Eqn. 12

$$V_d = \frac{D}{C'_b}\left[\frac{e^{KT(1-(1)/n)} - e^{-KT/n}}{KT}\right] \tag{12}$$

Expanding the terms $e^{KT(1-(1)/n)}$ and $e^{-KT/n}$ in Eqn. 12 and omitting the terms with powers higher than 2 (for cases when $KT \leqslant 1.5$) would lead to

$$V_d = \frac{D}{C'_b} \cdot \frac{\left[1 + KT\left(1 - \frac{1}{n}\right) + \frac{K^2T^2}{2}\left(1 - \frac{1}{n}\right)^2\right] - \left[1 - \frac{KT}{n} + \frac{K^2T^2}{2n^2}\right]}{KT} \tag{13}$$

which can be simplified to

$$V_d = \frac{D}{C'_b}\left(1 + \frac{KT}{2} - \frac{KT}{n}\right) = \frac{D}{C'_b}\left[1 + KT\left(\frac{1}{2} - \frac{1}{n}\right)\right] \tag{14}$$

Eqn. 14 is applicable to any time T/n. When n = 2, C'_b becomes C_b and Eqn. 14 simplifies to Eqn. 1.

(4) In the cases where before the infusion, there is a measurable blood level, C_0,

from previous administrations, the midpoint back-extrapolation method can also be applied successfully. In these situations the post-infusion blood level is given by

$$C = \left[\frac{D}{KV_dT}(1 - e^{-KT}) + C_0\, e^{-KT}\right] e^{-K(t-T)} \tag{15}$$

Substitution of C_b and T/2 for C and t, simplification and rearrangement would yield

$$V_d = \frac{D}{C_b - C_0\, e^{-KT/2}}\left(\frac{e^{KT/2} - e^{-KT/2}}{KT}\right) \tag{16}$$

Applying a similar method of derivation given in section (2) to the term inside the parenthesis in Eqn. 16 will result in Eqn. 17 for estimation of V_d.

$$V_d = \frac{D}{C_b - C_0\, e^{-KT/2}} \tag{17}$$

The general back-extrapolation equation for these situations is

$$V_d = \frac{D}{C'_b - C_0\, e^{-KT/n}}\left[1 + KT\left(\frac{1}{2} - \frac{1}{n}\right)\right] \tag{18}$$

(5) The terminal linear β-phase of post-infusion blood level plot for the 2-compartment open model is described by Eqn. 19

$$C = \left[\frac{D(K_{21} - \beta)(1 - e^{-\beta T})}{V_1 T\beta(\alpha - \beta)}\right] e^{-\beta(t-T)} \tag{19}$$

in which V_1 is the volume of the central compartment, t is time measured from the start of the infusion, α, β and K_{21} have their usual meanings (Gibaldi and Perrier, 1975; Wagner, 1975). Substitution of T/2 for t, C_b(a concentration corresponding to T/2 on the back-extrapolated plot) for C, simplification and re-arrangement would yield

$$V_1 = \frac{D}{C_b}\left[\frac{(K_{21} - \beta)(e^{\beta T/2} - e^{-\beta T/2})}{\beta T(\alpha - \beta)}\right] \tag{20}$$

Expansion of $e^{\beta T/2}$ and $e^{-\beta T/2}$ in Eqn. 20 and simplification will result in Eqn. 21

$$V_1 = \frac{D}{C_b}\left(\frac{K_{21} - \beta}{\alpha - \beta}\right) \tag{21}$$

It is obvious from Eqn. 21 that in the cases where the term $(K_{21} - \beta)/(\alpha - \beta)$ is not

equal to 1, the value of V_1 estimated by the midpoint back-extrapolation method (Eqn. 1) will not be accurate.

Re-arrangement of Eqn. 21 would lead to Eqn. 22

$$\left(\frac{\alpha-\beta}{K_{21}-\beta}\right)V_1=\frac{D}{C_b} \tag{22}$$

But, the term on the left-hand side of Eqn. 22 is equal to V_{dext} (V_d extrapolated or the extrapolated volume of distribution and is defined by $V_{dext} = D/B$ in which B is the zero-time intercept of terminal linear β-phase following bolus intravenous administration of the dose D (Wagner, 1975)). Therefore, Eqn. 22 can be written as

$$V_{dext}=\frac{D}{C_b} \tag{23}$$

Thus, for drugs with the 2-compartment open model the midpoint back-extrapolation method would give the accurate value of V_{dext} rather than V_1.

The general equation for the 2-compartment model would be similar to Eqn. 14 in which β replaces K.

In deriving Eqns. 1, 14, 17, 18 and 23 it has been assumed that the product KT or βT should be less than 1.5. In other words, the infusion time T should not exceed $2.16t_{1/2}$ (biological half-life) of the drug. Eqn. 2 was employed to simulate C_b values for different hypothetical infusion times assuming D = 100 mg, K = 0.693 h^{-1}, V_d = 10.1, and t = T/2 h. The values of C_b were then inserted in Eqn. 1 to calculate the values of V_d. The result of the calculations together with KT values and error associated with the values of calculated V_d are given in Table 1.

It is seen from Table 1 that for the error free blood level data, the midpoint back-extrapolation method always underestimates the V_d value. The extent of underestimation depends on the product KT or the relative magnitude of infusion time and the biological half-life of the drug. In the cases where the product KT is less than 1.5 (or the infusion time is shorter than $2.16t_{1/2}$ of the drug) the error associated with V_d would be less than 8.7% and the smaller the product the more accurate V_d value. When the product KT exceeds 1.5 (or T exceeds $2.16t_{1/2}$), the

TABLE 1

EFFECT OF INFUSION TIME ON THE VALUE OF V_d CALCULATED FROM EQN. 1

T (h)	C_b (mg/ml)	V_d (l)	KT	% error in V_d
0.5	10.05	9.95	0.347	−0.5
1.00	10.20	9.80	0.693	−2.0
2.00	10.82	9.24	1.386	−7.6
2.15	10.95	9.13	1.490	−8.7
3.00	11.90	8.40	2.079	−16.0
4.00	13.52	7.40	2.772	−26.0

TABLE 2

THE VALUES OF V_d CALCULATED FROM EQNS. 17 AND 18 USING GENTAMICIN DATA

Patient	Eqn. 17	Eqn. 18 (n = 4)	Eqn. 18 (n = 8)
M.B.	0.1860 (−2.10)	0.1850 (−2.63)	0.1838 (−3.26)
D.L.	0.2489 (−0.44)	0.2479 (−0.84)	0.2467 (−1.30)
G.D.	0.4534 (−7.47)	0.4527 (−7.61)	0.4518 (−7.79)

The figures inside the parentheses are percent errors relative to the V_d values reported in Table III of the paper of Sawchuk and Zaske (1976). These authors have used a non-linear regression analysis to calculate the V_d values.

error in V_d would be greater than 8.7% which is usually unacceptable from a practical point of view.

Eqns. 17 and 18 (with n values of 4 and 8) have been applied to some experimental data on gentamicin given by Sawchuk and Zaske (1976) and the calculated V_d values expressed as l/kg are presented in Table 2.

In order to apply Eqns. 17 and 18 to the experimental data, it was necessary to know the values of D, C_0, K, T, C_b and C'_b. The value of D for each patient has been taken from Table II and the C_0 values in Eqns. 17 and 18 which are equal to C_{p_0} (blood level remaining from previous infusions) have been taken from Table III of that paper. The values of K have been calculated from $t_{1/2}$ (biological half-life) reported in the Table III using the equation $K = 0.693/t_{1/2}$. The infusion time (T) for all patients was 1h. For the calculation of C_b and C'_b it was necessary to calculate the value of zero-time intercept, C_{t_0}, of post-infusion data from Eqn. 24 using the values of $C_{P_{max}}$ (given in column a of the Table III) and K and T.

$$C_{P_{max}} = C_{t_0} e^{-KT} \tag{24}$$

After estimating C_{t_0} from Eqn. 24, C_b and C'_b were calculated from

$$C_b = C_{t_0} e^{-KT/2} \tag{25}$$

and

$$C'_b = C_{t_0} e^{-KT/n} \tag{26}$$

The values of C_b, C'_b, $C_0 e^{-KT/2}$, and $C_0 e^{-KT/n}$ can also be read directly from a semilogarithmic blood level plot (Chiou et al., 1978).

In conclusion, the midpoint back-extrapolation and general back-extrapolation methods can be employed for estimating the V_d value provided the conditions mentioned above are met.

References

Chiou, W.L., Peng, G.W. and Nation, R.L., Rapid estimation of volume of distribution after a short intravenous infusion and its application to dosing adjustments. J. Clin. Pharmacol., 18 (1978) 266–272.

Chiou, W.L., Huang, S.M. and Huang, Y.C., Midpoint back-extrapolation method for the rapid estimation of drugs' volume of distribution and dosage adjustment exhibiting multicompartmental characteristics. Int. J. Clin. Pharmacol. Ther. Toxicol., 18 (1980) 1–4.

Chiou, W.L., Personal communication, April, 1983.

Gibaldi, M. and Perrier, D., In Swarbrick, J. (Ed.) Pharmacokinetics, Marcel Dekker, New York, 1975, Ch. 1 and 2.

Sawchuk, R.J. and Zaske, D.E., Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: gentamicin in burn patients. J. Pharmacokin. Biopharm., 4 (1976) 183–195.

Wagner, J.G., Fundamentals of clinical pharmacokinetics, Drug Intell. Publ., Hamilton, IL, 1975, Ch. 2.