New Calculation Method of Mean Total Body Clearance of Drugs and Its Application to Dosage Regimens

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Abstract □ A new method for calculating the mean total body drug clearance is proposed for determining the mean dosing rate for patients. In this method, the mean clearance can be calculated from the individual clearance values by the harmonic mean method, or it can be determined by dividing the same absorbed dose by the arithmetic mean of the areas under the plasma level–time curve from time zero to infinity from all of the subjects or patients studied. In this method, the arithmetic mean method is assumed to have been used for calculation of literature mean plasma levels. Various methods for calculating mean clearances also are evaluated. These methods yield different mean clearance values from the same set of individual data, resulting in different dosage regimen recommendations.

Keyphrases □ Total body clearance—mean calculation, harmonic mean method, dosage rate □ Pharmacokinetics—mean total body clearance, calculation, harmonic mean method □ Dosage regimens—mean total body clearance, calculation, harmonic mean method

The total body clearance, Cl_p, of drugs is an important clinical pharmacokinetic parameter since, in linear pharmacokinetics, the intravenous dosing rate for maintaining the desired steady-state plasma level in an ith patient, C_{pi}^{ss}, is theoretically equal to the product of C_{pi}^{ss} and the total body drug clearance of the patient, Cl_{pi} (1). This principle also should be applied to the mean dosing rate for achieving a certain mean plasma level in multiple dosing after correction for the dose fraction absorbed.

BACKGROUND

Although it occasionally is feasible to individualize a patient's dosage regimen by studying or predicting the patient's Cl_p of the drug (1), the mean total body clearance obtained from group studies of normal subjects or patients often is used as a guide for initiating drug therapy (1–8). Therefore, proper calculation of the mean total body clearance might be important in pharmacokinetic studies.

There appear to be no serious questions in the literature regarding the validity of methods for calculating the individual Cl_p from plasma data obtained after intravenous administration. For example, the individual Cl_p can be calculated by any of the following three equations, which should yield the same result in linear pharmacokinetics (6, 7):

$$Cl_p = \frac{\text{intravenous dose}}{AUC} \qquad \text{(Eq. 1)}$$

$$Cl_p = V_{d,\text{area}}\beta \qquad \text{(Eq. 2)}$$

$$Cl_p = V_p K_{el} \qquad \text{(Eq. 3)}$$

where AUC is the area under the plasma level–time curve from time zero to infinity, $V_{d,\text{area}}$ is the apparent volume of distribution determined by the area method, β is the terminal exponential rate constant in the plasma level decay profile, V_p is the apparent volume of distribution of the central compartment, and K_{el} is the first-order elimination rate constant from the central compartment in a multicompartmental open model (7, 9). In a one-compartment open model system, Cl_p can be calculated by Eq. 1 or as the product of the apparent volume of distribution, V_d, and the apparent first-order elimination rate constant, K. Such methods will be referred to as the product-of-means method.

The arithmetic mean method is commonly used for calculating the mean Cl_p from a group of subjects (8, 10–19). In this method, all of the individual clearance values ($Cl_{p1}, Cl_{p2}, \ldots, Cl_{pn}$) are added and the sum is divided by the total number of subjects, n. In another commonly used method, apparently based on Eq. 3, the arithmetic mean V_p is multiplied by the arithmetic mean K_{el} (10). A recent study (10) on theophylline clinical pharmacokinetics reported that, depending on which of the two methods was used for calculation of the mean Cl_p, a 25–30% difference could occur. Therefore, depending on the method used, the recommended intravenous theophylline infusion rate can vary similarly (10). This inconsistency was considered to be unfortunate by the authors (10). Undoubtedly, different mean Cl_p values also will result for other drugs when these two methods are employed.

The purpose of this note is to propose a new method for calculation of the mean total body clearance that might be useful for the determination of mean dosage regimens in patients. In addition, several existing methods will be evaluated.

THEORETICAL

There are many ways to calculate the mean value of a data set. For example, the mean can be determined by the arithmetic mean, geometric mean, and harmonic mean methods (20). In pharmacokinetic studies, the arithmetic mean method has been used almost exclusively to calculate the means of the steady-state trough, peak, or averaged plasma drug levels after multiple or constant-rate dosing. This method also is used most often in calculation of the mean plasma levels of many endogenous substances such as creatinine and urea. Therefore, it is logical to propose that when a mean dosage regimen is recommended to obtain a targeted mean steady-state plasma level, $\overline{C_p^{ss}}$, for a group of patients, the arithmetic mean of the individual steady-state plasma levels achieved should be used to evaluate the recommended dosage regimen. Based on this assumption, it will be shown that the harmonic mean method should be used for calculating the mean total body clearance to achieve the desired arithmetically averaged steady-state blood, plasma, or serum level.

Since:

$$C_{pi}^{ss} = \frac{K_{0i}}{Cl_{pi}} \qquad \text{(Eq. 4)}$$

where K_{0i} is the zero-order dosing rate for the ith patient, therefore:

$$\overline{C_p^{ss}} = \frac{1}{n}\sum_{i=1}^{n} C_{pi}^{ss} \qquad \text{(Eq. 5)}$$

$$\overline{C_p^{ss}} = \frac{1}{n}\sum_{i=1}^{n} \frac{K_{0i}}{Cl_{pi}} \qquad \text{(Eq. 6)}$$

If $K_{01} = K_{02} = \ldots = K_{0n} = K_0$, then:

$$\overline{C_p^{ss}} = \frac{K_0}{n}\sum_{i=1}^{n} \frac{1}{Cl_{pi}} \qquad \text{(Eq. 7)}$$

$$\overline{C_p^{ss}} = \frac{K_0}{\overline{Cl_p}} \qquad \text{(Eq. 8)}$$

where:

$$\frac{1}{\overline{Cl_p}} = \frac{1}{\text{harmonic mean } Cl_p} = \frac{1}{n}\sum_{i=1}^{n} \frac{1}{Cl_{pi}} \qquad \text{(Eq. 9)}$$

Since for each individual the Cl_p also is related to the dose and to the AUC according to Eq. 1, Eq. 9 becomes:

$$\frac{1}{\overline{Cl_p}} = \frac{1}{n}\left(\frac{AUC_1}{\text{dose}_1} + \frac{AUC_2}{\text{dose}_2} + \ldots + \frac{AUC_n}{\text{dose}_n}\right) \qquad \text{(Eq. 10)}$$

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Table I—Relevant Pharmacokinetic Parameters[a] Based on Blood Theophylline Levels in Seven Asthmatic Subjects after Intravenous Study and the Resulting Steady-State Blood Levels after Different Infusion Rates Calculated from Different Mean Cl_p Values (Mean × 10 mg/liter) for Achieving the Targeted Mean Steady-State Blood Level of 10 mg/liter

Subject	β, hr^{-1}	K_{el}, hr^{-1}	V_p, liter/kg	Total Body Clearance, $K_{el}V_p$, liter/kg/hr	$V_d\beta$[b], liter/kg	C_p^{ssc}, mg/liter	C_p^{ssd}, mg/liter	C_p^{sse}, mg/liter	C_p^{ssf}, mg/liter
HW	0.130	0.149	0.464	0.0691	0.5315	9.20	9.78	12.50	9.82
VW	0.114	0.119	0.336	0.0400	0.3509	15.90	16.90	21.60	17.05
AG	0.171	0.359	0.225	0.0808	0.4725	7.88	8.38	10.71	8.45
AE	0.141	0.267	0.212	0.0566	0.4014	11.24	11.94	15.27	12.05
VM	0.241	0.750	0.119	0.0893	0.3705	7.12	7.57	9.68	7.64
JL	0.168	0.181	0.407	0.0737	0.4387	8.63	9.17	11.72	9.25
TS	0.166	0.361	0.176	0.0635	0.3825	10.02	10.65	13.61	10.74
Arithmetic mean	0.162	0.312	0.277	0.0676	0.4209	10.00	10.63	13.58	10.72

[a] Data from Ref. 18. [b] Determined by $(K_{el}V_p)/\beta$. [c] Based on the mean Cl_p calculated by the harmonic mean method (0.0636 liter/kg/hr). [d] Based on the mean Cl_p calculated by the arithmetic mean method (0.0676 liter/kg/hr). [e] Based on the mean Cl_p calculated by the $\overline{K}_{el}\overline{V}$ method (0.0864 liter/kg/hr). [f] Based on the mean Cl_p calculated by the $\overline{V}_{d,area}\overline{\beta}$ method (0.0682 liter/kg/hr).

When all of the doses used are the same or all of the obtained AUC values are corrected for the same dose when different doses are used, Eq. 10 can be simplified and rearranged to:

$$\overline{Cl}_p = \frac{\text{dose}}{(AUC_1 + AUC_2 + \ldots + AUC_n)/n} \qquad \text{(Eq. 11)}$$

$$\overline{Cl}_p = \frac{\text{dose}}{\text{arithmetic mean } AUC} \qquad \text{(Eq. 12)}$$

The method employing Eq. 12 for calculating the mean Cl_p will be referred to as the mean area method. This method and the harmonic mean (Eq. 9) method theoretically should yield the same mean Cl_p.

DISCUSSION

An example based on reported theophylline data (18) illustrates the consequence of employing different methods for the calculation of the mean total body clearance when the targeted mean blood level is set at 10 mg/liter. Relevant pharmacokinetic data in seven asthmatic subjects and analytical results are summarized in Table I. The mean Cl_p values determined by the harmonic mean, arithmetic mean, and two product-of-means ($\overline{K}_{el}\overline{V}_p$ and $\overline{V}_{d,area}\overline{\beta}$) methods are 0.0636, 0.0676, 0.0864, and 0.0682 liter/kg/hr, respectively. The largest difference among these methods is 35.8%.

Only the newly proposed harmonic method results in a correct arithmetic mean of 10 mg/liter of the steady-state blood level. The $\overline{K}_{el}\overline{V}_p$ method yields a mean blood level of 13.5 mg/liter. These results are based on the assumption that the dosing rate for all patients is equal to 10 mg/liter times the mean Cl_p. The difference in the mean Cl_p of propranolol in three subjects (14) estimated by the harmonic and arithmetic mean methods is 41.8%. In all of the methods studied, the harmonic mean method yields the lowest mean clearance values in the discussed and other simulated examples.

When employing the mean AUC method (Eqs. 11 and 12), the dose used for the entire test population should be the same. If not, the AUC for each individual should be corrected to the same dose in terms of the total dose or dose per unit of body weight or body surface area. The potential error of using the linear trapezoidal rule method for the estimation of the AUC was discussed recently (21). In estimating the individual total body drug clearance after oral dosing, the potential first-pass effect in the liver and lungs was ignored in many pharmacokinetic studies. Appropriate equations for such corrections are available (22–24).

It was pointed out recently (24) that the conventional concept for obtaining the initial plasma level at time zero after intravenous bolus dosing by the summation of the exponential coefficients (*i.e.*, $\Sigma_{i=1}^{n} A_i$ in $\Sigma_{i=1}^{n} A_i e^{-K_i t}$) and also for obtaining the AUC by $\Sigma_{i=1}^{n} (A_i)/(K_i)$ is not correct in terms of absolutes and could result in serious errors under certain circumstances. However, such conventional methods of pharmacokinetic analysis might be adequate as a reasonable approximation for most studies (24).

This discussion is based on the assumption that the arithmetic mean method is used for averaging the steady-state blood or plasma level data. Statistically speaking, if other methods such as the harmonic or geometric mean methods could be shown to be superior for averaging these blood or plasma data, a different conclusion regarding the best approach for estimating the mean Cl_p could be reached. Based on the rationale discussed under *Theoretical*, it also was concluded recently that the harmonic mean method is best for calculating the mean volumes of distribution for designing a rational dosage regimen (25). For general purposes, the conventional arithmetic mean method is acceptable for averaging the apparent volumes of distribution and the total body clearances of drugs. The harmonic mean method has been recommended for calculation of the mean biological half-life of drugs (12).

REFERENCES

(1) W. L. Chiou, M. A. F. Gadalla, and G. W. Peng, *J. Pharmacokinet. Biopharm.*, **6**, 135 (1978).

(2) W. L. Chiou, G. W. Peng, and R. L. Nation, *J. Clin. Pharmacol.*, **18**, 266 (1978).

(3) W. L. Chiou, S. M. Huang, and Y. C. Huang, *Int. J. Clin. Pharmacol. Biopharm.*, in press.

(4) W. L. Chiou, *J. Pharm. Sci.*, **67**, 1776 (1978).

(5) M. Gibaldi and G. Levy, *J. Am. Med. Assoc.*, **235**, 1987 (1976).

(6) J. G. Wagner, "Fundamentals of Clinical Pharmacokinetics," Drug Intelligence Publications, Hamilton, Ill., 1976.

(7) M. Gibaldi and D. Perrier, "Pharmacokinetics," Dekker, New York, N.Y., 1975.

(8) J. R. Powell, J. F. Thiercelin, S. Vozeh, L. Sansom, and S. Riegelman, *Am. Rev. Respir. Dis.*, **116**, 17 (1977).

(9) W. L. Chiou, *J. Pharm. Pharmacol.*, **24**, 342 (1972).

(10) F. A. Chrzanowski, P. J. Niebergall, R. L. Mayock, J. M. Taubin, and E. T. Sugita, *Clin. Pharmacol. Ther.*, **22**, 188 (1977).

(11) F. A. Chrzanowski and P. J. Niebergall, *ibid.*, **22**, 936 (1977).

(12) F. B. Eatman, W. A. Colburn, H. G. Boxenbaum, H. N. Posmanter, R. E. Weinfeld, R. Ronfeld, L. Weissman, J. D. Moore, M. Gibaldi, and S. A. Kaplan, *J. Pharmacokinet. Biopharm.*, **5**, 481 (1977).

(13) P. Gal, W. J. Jusko, A. M. Yurchak, and B. A. Franklin, *Clin. Pharmacol. Ther.*, **23**, 438 (1978).

(14) R. Gomeni, G. Bianchetti, R. Sega, and P. L. Morselli, *J. Pharmacokinet. Biopharm.*, **5**, 183 (1977).

(15) J. R. Koup, W. J. Jusko, C. M. Elwood, and R. K. Kohli, *Clin. Pharmacol. Ther.*, **18**, 9 (1975).

(16) P. M. Loughnan, D. S. Sitar, R. I. Ogilivie, A. Eisen, Z. Fox, and A. H. Heims, *J. Pediatr.*, **88**, 874 (1976).

(17) A. Mangione, T. E. Imhoff, R. V. Lee, L. Y. Hum, and W. J. Jusko, *Chest*, **73**, 616 (1978).

(18) P. A. Mitenko and R. I. Ogilivie, *Clin. Pharmacol. Ther.*, **14**, 509 (1973).

(19) K. M. Piafsky, D. S. Sitar, R. E. Rangno, and R. I. Ogilivie, *N. Engl. J. Med.*, **296**, 1495 (1977).

(20) E. B. Mode, "Elements of Statistics," 3rd ed., Prentice-Hall, Englewood Cliffs, N.J., 1961.

(21) W. L. Chiou, *J. Pharmacokinet. Biopharm.*, **6**, 539 (1978).

(22) *Ibid.*, **3**, 193 (1975).

(23) W. L. Chiou, *J. Pharm. Sci.*, **67**, 260 (1978).

(24) W. L. Chiou, *J. Pharmacokinet. Biopharm.*, in press.

(25) W. L. Chiou, *J. Pharm. Sci.*, **68**, 1067 (1979).

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