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Critical Evaluation of the Potential Error in Pharmacokinetic Studies of Using the Linear Trapezoidal Rule Method for the Calculation of the Area Under the Plasma Level–Time Curve

Win L. Chiou[1]

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The linear trapezoidal rule method is commonly used for the estimation of the area under the plasma level–time curve. Error analyses are performed when the method is used in first-order absorption and first-order elimination kinetics in the one-compartment system. It is found that significant underestimations and overestimations in area during the absorption phase and postabsorption phase, respectively, can occur when the method is improperly used. During the exponential postabsorption phase the relative error is only a function of the ratio (n) *of the time interval over the half-life of the two plasma data points in the interval. The error from the linear trapezoidal rule method at* $n = 0.5$ *is about 1%. The error increases to 15.5% and 57.1% when* n *is increased to 2 and 4, respectively. It is recommended that for most absorption studies the linear trapezoidal method be used for prepeak and plateau plasma data and the logarithmic trapezoidal method for postpeak plasma data.*

KEY WORDS: trapezoidal rule; area under the curve; pharmacokinetics; clearance; bioavailability; integration method; sulfisoxazole.

INTRODUCTION

The linear trapezoidal rule method has been widely used as a means to estimate the area under the blood, plasma, or serum level–time curve, especially in studies using other than the rapid bolus intravenous injection or short-term intravenous infusion. Although it is commonly recognized that the more frequent the blood sampling schedule, the smaller the error in the calculation of area (1,2), it appears that very few systematic and quantitative studies have been made to critically evaluate the potential error of using this

[1]Clinical Pharmacokinetics Laboratory and Department of Pharmacy, College of Pharmacy, University of Illinois at the Medical Center, Chicago, Illinois 60612.

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method for area analysis in various pharmacokinetic settings. Limited error analyses have been reported in situations where the linear trapezoidal rule is used during the first-order elimination process (3), in the zero-order input–first-order elimination process (4), and also in the estimation of the total area under the curve obtained after a first-order absorption–first-order elimination (2). After the first submission of this article to the Journal, an extensive comparison of area analysis by the linear trapezoidal, logarithmic trapezoidal, Lagrange, and spline methods was reported by Yeh and Kwan (5). The last two methods, which require the use of a computer, were shown to be superior to the two trapezoidal methods. However, the trapezoidal methods were still concluded to be the logical choice in some cases because of their simplicity. In a related subject the geometric mean, rather than the arithmetic mean of the plasma concentrations as used in the linear trapezoidal rule, was suggested to be a better choice for estimating Michaelis–Menten kinetic parameters (5).

The purpose of this article is to critically evaluate potential sources of error when using the conventional linear trapezoidal rule method for various pharmacokinetic studies. A simple system of the one-compartment open model with first-order absorption and first-order elimination kinetics will be used for illustration.

THEORETICAL

Error Analyses During the Absorption and Postabsorption Phases

In a linear one-compartment open-model system, the plasma area in a given interval from t_1 to t_2, i.e., $AUC^{in}_{t_1-t_2}$, can be integrated to be equal to

$$AUC^{in}_{t_1-t_2} = \int_{t_1}^{t_2} C_p\, dt \tag{1}$$

$$= \frac{K_a F X_0}{V(K_a - K)} \left(\frac{e^{-K_a t}}{K_a} - \frac{e^{-Kt}}{K} \right)_{t_1}^{t_2} \tag{2}$$

$$= \frac{K_a F X_0}{V(K_a - K)} \left(\frac{e^{-K_a t_2}}{K_a} - \frac{e^{-Kt_2}}{K} - \frac{e^{-K_a t_1}}{K_a} + \frac{e^{-Kt_1}}{K} \right) \tag{3}$$

On the other hand, the area between t_1 and t_2 based on the linear trapezoidal rule method, $AUC^{tr}_{t_1-t_2}$, can be calculated by

$$AUC^{tr}_{t_1-t_2} = \frac{(C_{p1} + C_{p2})(t_2 - t_1)}{2} \tag{4}$$

where C_{p1} and C_{p2} are the theoretical plasma concentrations at times t_1 and t_2, respectively. They can be defined by the following:

$$C_{p1} = \frac{K_a F X_0}{V(K_a - K)}(e^{-Kt_1} - e^{-K_a t_1}) \tag{5}$$

$$C_{p2} = \frac{K_a F X_0}{V(K_a - K)}(e^{-Kt_2} - e^{-K_a t_2}) \tag{6}$$

The percent of error in using the linear trapezoidal rule relative to the exact equation 3 for the estimation of area between t_1 and t_2 should be equal to

$$\text{Percent error} = \frac{\text{AUC}^{\text{tr}}_{t_1-t_2} - \text{AUC}^{\text{in}}_{t_1-t_2}}{\text{AUC}^{\text{in}}_{t_1-t_2}} 100 \tag{7}$$

Substitution of equations 3 and 4 into equation 7 will result in

$$\text{Percent error} = \frac{A - B}{B} 100 \tag{8}$$

where

$$A = (e^{-Kt_1} - e^{-K_a t_1} + e^{-Kt_2} - e^{-K_a t_2})(t_2 - t_1) \tag{9}$$

and

$$B = 2\left(\frac{e^{-K_a t_2}}{K_a} - \frac{e^{-Kt_2}}{K} - \frac{e^{-K_a t_1}}{K_a} + \frac{e^{-Kt_1}}{K}\right) \tag{10}$$

Equations 8–10 clearly indicate that the relative error of using the linear trapezoidal rule in area analysis in this simple pharmacokinetic scheme is a complex function of K_a, K, t_1 and t_2. This especially is the case during the absorption phase.

During the postabsorption phase, equation 8 can be reduced to

$$\text{Percent error} = \frac{0.693n(1 + e^{-0.693n}) - 2(1 - e^{-0.693n})}{2(1 - e^{-0.693n})} 100 \tag{11}$$

where n is equal to $(t_2 - t_1)$ divided by the elimination half-life, $t_{0.5}$ (i.e., $0.693/K$). Therefore, the relative error in the area analysis by the linear trapezoidal rule during the postabsorption exponential phase is only a function of n, and not exclusively related to the time interval or the elimination half-life of the drug. Equation 11 can also be used in any postabsorption–postdistribution (exponential) phase for drugs showing multiple compartmental characteristics.

Integration Method for the Calculation of Area During the Exponential Postabsorption Phase

The area under the curve between any two points, C_{p1} and C_{p2}, during the exponential postabsorption phase can also be accurately calculated by the following integration method (3,5):

$$\mathrm{AUC}_{t_1-t_2}=\frac{(C_{p1}-C_{p2})(t_2-t_1)}{\ln C_{p1}-\ln C_{p_2}} \tag{12}$$

which has been referred to as the logarithmic trapezoidal method (3,5).

DISCUSSION

During the absorption phase the relative error in area estimated by the linear trapezoidal rule method can be illustrated using the data of two drugs, theophylline (6) and doxycycline hyclate (7). The average absorption and elimination rate constants in normal adults after oral administration of theophylline in solution were reported to be 2.31 hr^{-1} and 0.1174 hr^{-1}, respectively, which correspond to a half-life of 0.3 hr and 5.9 hr, respectively (6). For doxycycline hyclate in solution form the average absorption and elimination rate constants in normal adults after oral dosing were found to be 0.8153 hr^{-1} and 0.055 hr^{-1}, respectively, which correspond to a half-life of 0.85 hr and 12.6 hr, respectively. Based on the above data the theoretical times for reaching the peak plasma level can be calculated (2) to be equal to 1.359 hr and 3.546 hr for theophylline and doxycycline, respectively. Error analyses were performed using equations 8–11 for when the time interval is equal to one-third of the peak time for both drugs. The results are summarized in Table I. The area is 15.7% and 14.7% underestimated for theophylline and doxycycline, respectively, during the first sampling period. The degree of the underestimation decreases progressively during the next two sampling periods. It must be noted that sampling schedules similar to the ones described above are common practice in pharmacokinetic studies. Also, as shown in Table I, the relative error

Table I. Percent Errors[a] in the Estimation of Area Under the Curve During the Absorption Phase of Theophylline and Doxycycline by the Linear Trapezoidal Rule Method

Theophylline	Time interval (hr)	0–0.453	0.453–0.906	0.906–1.359	0–0.906	0–1.359[b]
	Percent error	−15.7	−2.74	−0.841	−26.8	−34.7
Doxycycline	Time interval (hr)	0–1.18	1.18–2.36	2.36–3.456	0–2.36	0–3.546[b]
	Percent error	−14.7	−2.78	−0.358	−25.8	−33.8

[a] Based on equations 8–11.
[b] Peak time for each drug.

increases markedly if the first blood sample is taken at a later time. The above quantitative error analyses appear not to have been reported in the literature. Their potential implications in pharmacokinetic studies will be discussed later.

The results of error analyses during the postabsorption phase are summarized in Table II. The relative error increases with the increase of the n value, the ratio of interval over the biological half-life. For example, the percents of error are 0.998, 3.95, 15.5, and 57.1 when the n is equal to 0.5, 1, 2, and 4, respectively. These results clearly show that a long sampling interval may not always result in a significant degree of error in area estimate so long as the biological half-life of the drug in the body is also long. It is further obvious that a significant error can occur even with short sampling interval for drugs with a short biological half-life.

Use of the linear trapezoidal rule for area analysis between two data points separated by a relatively long interval as compared with the half-life (i.e., higher n values) during the post absorption phase is not uncommon. For example, an interval of up to 12 hr was used in the area calculation for a drug with an elimination half-life of 8 hr in an absorption rate calculation study (2). In another pharmacokinetic study of sulfisoxazole in humans, an interval of up to 24 hr was employed in the area calculation (8). The average biological half-life of sulfisoxazole in these subjects was only about 6 hr. The shortest half-life in one subject was 4.33 hr, which would yield an average n value of 5.54 during the postabsorption phase. Based on Table II it can be estimated that overestimation in the 24-hr area by the linear trapezoidal rule is about 100%. It is of interest to note that in that study the areas under the

Table II. Percent Errors in the Estimation of Area Under the Curve During the Postabsorption Phase by the Linear Trapezoidal Rule Method (Based on Equation 11)

Value of n[a]	Percent error
0.1	+0.0371
0.25	+0.251
0.50	+0.998
0.75	+2.24
1	+3.95
1.5	+8.84
2	+15.5
3	+33.7
4	+57.1
5	+84.4

[a] $n = (t_2 - t_1)$/elimination half-life.

curve from time zero to infinity from both oral and intramuscular administration in all seven subjects were generally (except for one oral study) greater than those from the intravenous study using the same dose. On the average the areas from the oral and intramuscular study are 23% and 15% higher than from the intravenous study, respectively (8). Although an increase in the biological half-life could result in a higher area, it appears that this is not the major reason as the average half-life increased by only 3.7% in the intramuscular study and decreased by 1.0% in the oral study (calculated by this author). Area analyses for data between 6 and 12 hr, 12 and 24 hr, and 24 and 48 hr for each of the seven subjects after oral administration were carried out using the linear trapezoidal rule method (equation 4) as used in their original study (confirmed by C. W. Abruzzo) and the integration method (equation 12). Results of the comparison of these two methods are summarized in Table III. Since the area under the curve after intravenous study was calculated by the integration method, the larger area obtained after oral dosing could therefore be attributable in part to the use of the linear trapezoidal rule method.

Another example of using long interval plasma data relative to the biological half-life was reported recently in a quinidine study in humans (9). The terminal half-life was approximately 6–7 hr and the linear trapezoidal rule was used for areas between 12 and 24 hr after intravenous dosing (9). It must be noted that the result of this method of area calculation is inconsequential for the purpose of their study.

Based on the above theories and discussion, it is clear that the improper use of the linear trapezoidal rule in area calculations could result in considerable underestimations during the absorption phase and marked

Table III. Percentages of Overestimation in Area by the Linear Trapezoidal Rule Method as Compared to the Integration Method During the Postabsorption Phase of Oral Sulfisoxazole Studies in Seven Human Subjects

Subject	6–12 hr	12–24 hr	24–48 hr	6–48 hr	Overestimate in 6–48 hr area / intravenous area[a]
1	4.33	7.89	25.43	9.93	6.79
2	2.61	15.57	53.70	16.40	12.47
3	2.69	11.34	25.45	10.30	6.61
4	4.89	8.42	22.52	9.72	7.28
5	7.51	18.10	51.30	15.73	7.78
6	2.55	9.58	19.57	8.81	—[b]
7	5.94	9.17	28.30	11.16	6.85

[a] Infinite area under the curve ($AUC_{0-\infty}$) after intravenous dosing based on data obtained from Kaplan *et al.* (8).
[b] Complete intravenous data not available.

overestimations during the postabsorption phase. Its net effect on the calculation of the true total area would vary with their relative contribution. Since in most experimental designs two to four blood samples are usually collected before the expected peaking time, which would result in a relatively small percent of error, and the area during the absorption phase is usually only a small fraction of the total area, the use of the linear trapezoidal rule is therefore more likely to have a net effect of overestimation in the total area. If a substantial over- or underestimation occurs, then it might lead to significant errors in the calculation of other pharmacokinetic properties based on the area data such as the extent of absorption, volume of distribution (area method), total body clearance, and amount of drug absorbed into and eliminated from the body (10,11). A less obvious but perhaps most sensitive and serious consequence due to the inaccurate estimate of the area by the linear trapezoidal rule method is its effect on the calculation of the clearance of drug during each particular time interval. For example, the renal clearance of a drug is theoretically calculated by (2,10)

$$\text{Renal clearance} = \frac{\text{amount of intact drug excreted between } t_1 \text{ and } t_2}{\int_{t_1}^{t_2} C_p\, dt} \tag{13}$$

Error in the estimate of $\int_{t_1}^{t_2} C_p\, dt$ would therefore result in a similar degree of error in the calculation of renal clearance (2,10). This might be exemplified in the example shown in Table III. Based on clearance values obtained in these three intervals using the linear trapezoidal rule method for area calculation, one might be misled to conclude that different renal excretion mechanisms are operating at different times or plasma concentrations. It seems not unreasonable to speculate that some inconsistencies or poor correlation in clearance of drugs or endogenous substances reported in the literature might be caused by the improper use or the inherent property of the linear trapezoidal rule method.

In light of the above discussion and the complexity of absorption and disposition kinetics (other than the simple compartment model illustrated in this article) of most drugs, it is recommended that for most absorption studies the linear trapezoidal method be used for prepeak and plateau (5) plasma data and the integration or logarithmic trapezoidal method for postpeak plasma data.

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