# Estimation of Absorption Rate Constant in a One-Compartment Model with the Profile of the Bioavailable Dose Eliminated as a Function of Multiples of Half-Life

*To the Editor:*

In a recent study, Chen and Pelsor[1] reevaluated the applicability of the half-life approach in the assessment of the relative extent of drug absorption for bioavailability/bioequivalence studies. This approach is based on the comparisons of the truncated areas under the curve (AUCs; that is, $AUC_{0-t}$) whenever the AUC of the plasma concentration versus time from zero to infinity ($AUC_{0-\infty}$) cannot be determined accurately. It was shown that the partial area comparisons can be used reliably for bioequivalence evaluation under certain conditions. This conclusion was derived[1] from simulation studies focusing on the calculation of the quotient $AUC_{0-t}/AUC_{0-\infty}$ at various times, expressed as multiples (n) of the elimination half-life ($t_{1/2}$) following oral administration. The aims of this communication are: (*1*) to provide a theoretical justification for the results of the previous study[1] concerning drugs with one-compartment model disposition, and (*2*) to develop a method for the estimation of absorption rate constant in a one-compartment model with the profile of the bioavailable dose eliminated as a function of multiples of half-life.

The conclusions of the previous study[1] for a drug following monoexponential disposition can be theoretically derived by considering eqs 1 and 2 (see *Appendix*) that relate the quotient $AUC_{0-nt_{1/2}}/AUC_{0-\infty}$ with the multiples of elimination half-life (n) and the ratio ($\Phi$) of the absorption rate constant ($k_a$) and elimination rate constant ($k_e$):

$$F_{el,nt_{1/2}} = \frac{(AUC)_{0-nt_{1/2}}}{(AUC)_{0-\infty}} = 1 - \frac{\phi(0.5)^n - (0.5)^{n\phi}}{\phi - 1}, \; k_a \neq k_e \tag{1}$$

$$F_{el,nt_{1/2}} = \frac{(AUC)_{0-nt_{1/2}}}{(AUC)_{0-\infty}} = 1 - [n(\ln 2) + 1](0.5)^n, k_a = k_e \tag{2}$$

In eqs 1 and 2 $F_{el,\,nt_{1/2}}$ is the fraction of the bioavailable dose eliminated from time zero to time $t = nt_{1/2}$ and $\Phi = k_a/k_e$. Equations 1 and 2 provide exact solutions for the simulations of Chen and Pelsor[1] and the empirical findings of Lovering et al.[2] In Table I, the exact values of the ratio $k_a/k_e$ for various pairs of $F_{el,\,nt_{1/2}}$ and n are presented. These values have been calculated with eq 1 by a numerical iterative technique (Newton–Raphson algorithm).

In Figure 1, $F_{el,\,nt_{1/2}}$ is plotted against multiples of elimination half-life with various $k_a/k_e$ ratios. Continuous lines in Figure 1 provide a clear view of the contribution of $AUC_{0-nt_{1/2}}$ to $AUC_{0-\infty}$ as a function of time expressed in multiples of half-life. The dotted line represents the upper limit of the master curves in Figure 1 and refers to the $F_{el,\,nt_{1/2}}$ after bolus intravenous administration according to the following equation:

$$F_{el,nt_{1/2}} = 1 - (0.5)^n \tag{3}$$

Equation 3 is easily derived in a similar manner to that followed for the derivation of eqs 1 and 2.

**Table I—Exact Values of the Ratio $k_a/k_e$ for Various Pairs of $F_{el,\,nt_{1/2}}$ and n**

| n[a] | $100 \times F_{el,\,nt_{1/2}}$ | | |
|---|---|---|---|
| | 80 | 85 | 90 |
| 3 | 2.61 | 6.00 | —[b] |
| 4 | 1.17 | 1.56 | 2.65 |
| 5 | 0.76 | 0.94 | 1.28 |
| 6 | 0.56 | 0.68 | 0.88 |

[a] Values of $k_a/k_e$ for n equal to 1 and 2 are not reported; according to eq 3, for intravenous administration and n equal to 1 and 2, $F_{el,\,nt_{1/2}}$ is 0.5 and 0.75, respectively; therefore, after oral administration for $n < 2$, $F_{el,\,nt_{1/2}}$ is <0.80, regardless of the value of the ratio $k_a/k_e$. [b] According to eq 1, at time equal to three elimination half-lives, the fraction of the bioavailable dose eliminated ($F_{el,\,nt_{1/2}}$) is <90%, regardless of the value of the ratio $k_a/k_e$.

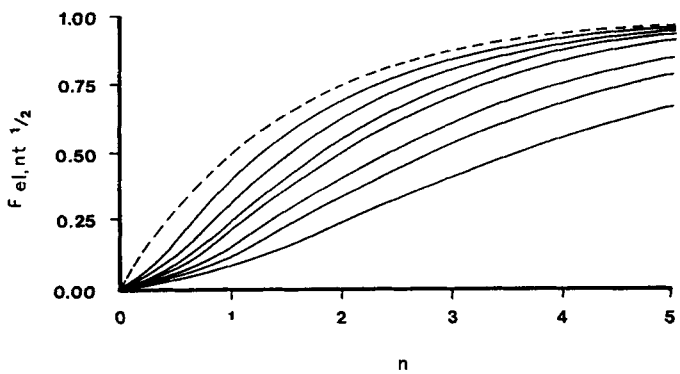


**Figure 1**—Fraction of the bioavailable dose eliminated from the body versus multiples of elimination half-life for drugs with monoexponential disposition kinetics following first-order absorption with the ratio $k_a/k_e$ equal to 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, and 6.0 (in ascending order). The dotted line refers to the profile for intravenous bolus administration.

An important characteristic of Figure 1 is its universal applicability for drugs following monoexponential disposition. In view of the simplicity of calculation of the parameter $AUC_{0-nt_{1/2}}/AUC_{0-\infty}$ from plasma concentration–time data, Figure 1 can be utilized as a nomogram to derive an initial estimate for the absorption rate constant by visual inspection. One simplistic example is shown in Figure 2. Data were taken from Wagner[3] (Table II) and plotted along with the theoretical lines for values of the ratio $k_a/k_e$ in the vicinity to that adhering to the experimental profile. Visual inspection reveals that the theoretical profile generated by assigning $k_a/k_e$ equal to 3.0 describes the experimental data adequately. Consequently, an estimate for the absorption rate constant can be directly derived: $3.0 \times k_e = 3.0 \times 0.119 = 0.357\ h^{-1}$ (see footnote b of Table II). Both, the routinely used Wagner–Nelson method[3] and the proposed method require estimates for $AUC_{0-\infty}$ and the elimination rate constant $k_e$. However, the proposed method is simpler



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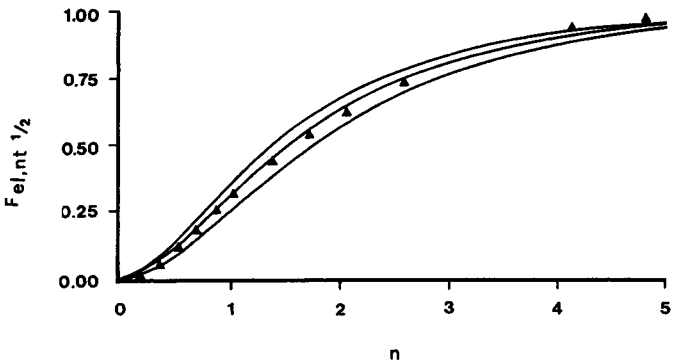


**Figure 2**—Fraction of the bioavailable dose eliminated from the body versus multiples of elimination half-life for the data taken from ref 3. Theoretical master curves for $k_a/k_e$ equal to 2.0, 3.0, and 4.0 (bottom to top) are also shown.

**Table II—Specific Example of the Application of Equation 1**

| $t$, h[a] | $C$, μg/mL[a] | n[b] | $AUC_{0-nt_{1/2}}/AUC_{0-\infty}$[c] |
|---|---|---|---|
| 1 | 2.28 | 0.172 | 0.015 |
| 2 | 3.69 | 0.343 | 0.054 |
| 3 | 5.52 | 0.515 | 0.114 |
| 4 | 5.52 | 0.687 | 0.186 |
| 5 | 5.08 | 0.858 | 0.256 |
| 6 | 4.91 | 1.030 | 0.321 |
| 8 | 4.10 | 1.373 | 0.439 |
| 10 | 3.38 | 1.717 | 0.536 |
| 12 | 3.33 | 2.060 | 0.624 |
| 15 | 2.66 | 2.575 | 0.742 |
| 24 | 0.80 | 4.120 | 0.945 |
| 28 | 0.49 | 4.807 | 0.979 |
| 32 | 0.31 | 5.494 | 1.000 |

[a] Data taken from Wagner.[3] [b] $n = t/t_{1/2}$; the value of $t_{1/2}$ was estimated from $t_{1/2} = \ln 2/k_e$ using the value $k_e = 0.119\ h^{-1}$ from Wagner.[3] [c] $AUC_{0-\infty}$ was approximated by $AUC_{0-32\ h}$; both $AUC_{0-nt_{1/2}}$ and $AUC_{0-32\ h}$ were estimated with the trapezoidal rule.

computationally and does not require supplementary calculations, such as regression analysis for the estimation of $k_a$. The simplicity of calculations for $AUC_{0-nt_{1/2}}/AUC_{0-\infty}$ based on the trapezoidal rule and the universal applicability of the master curves of Figure 1 offer an alternative approach for the initial estimation of $k_a$.

Apart from the profiles of $F_{el,nt_{1/2}}$ versus multiples of half-life used in Figures 1 and 2, the plot of $AUC_{0-t}/AUC_{0-\infty}$ as a function of time provides a useful picture of the output profile of drug from the body. The output profile can be used as a complement to the routinely used input profile of the fraction absorbed versus time plot.[3] Obviously, the difference in the two profiles (fraction absorbed minus fraction eliminated) for each time point represents the profile of the fraction of bioavailable dose remaining in the body.[4] Thus, an overall view of the entrance, residence, and exit of drug in the body can be drawn by co-plotting the three profiles. A simplistic example is given in Figure 3 for the data of Table II. This type of plot can be useful for pharmacokineticists working in research and for drug agencies for evaluation, comparison, and presentation of in vivo data of orally administered formulations.

In summary, the fractional area $AUC_{0-t}/AUC_{0-\infty}$ has an important physical meaning, expressing the fraction of the bioavailable dose eliminated from the body between time zero and time $t$. The plot of $AUC_{0-t}/AUC_{0-\infty}$ versus time provides a useful picture of the time course of the exit of a drug from the body. Finally, the use of the master curves of the output profile ($AUC_{0-nt_{1/2}}/AUC_{0-\infty}$ versus n) allows a simple derivation of an estimate for the absorption rate constant for drugs following monoexponential disposition.

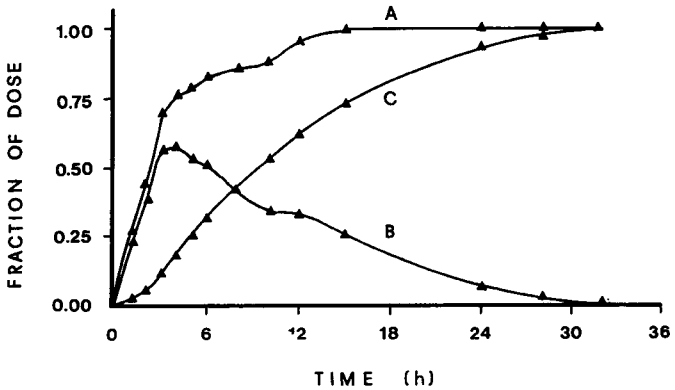


**Figure 3**—Curves for the fraction of dose absorbed (**A**), remaining in the body (**B**), and eliminated (**C**) as a function of time using the data of ref 3. The profile **A** was drawn as suggested.[3] Calculations for the profile **C** were based on the estimation of fractional area $AUC_{0-t}/AUC_{0-32}$ with the trapezoidal rule. Profile **B** represents the differences of profile **C** from profile **A** at the corresponding time points.

## Appendix

**Derivation of Equation 1**—In the one-compartment model with first-order kinetics, the concentration of drug versus time after oral administration is given by the following equation[5]:

$$C = \frac{FDk_a}{V(k_a - k_e)}(e^{-k_e t} - e^{-k_a t}) \quad \text{(A1)}$$

In eq A1, $F$ is the fraction of the dose ($D$) absorbed, $V$ is the distribution volume, $k_a$ is the absorption rate constant, and $k_e$ is the elimination rate constant. Let $A = (FDk_a)/[V(k_a - k_e)]$. Then, the integral from time zero to $nt_{1/2}$ is as shown in eqs A2 and A3:

$$AUC_{0-nt_{1/2}} = \int_0^{nt_{1/2}} A(e^{-k_e t} - e^{-k_a t})dt \quad \text{(A2)}$$

$$AUC_{0-nt_{1/2}} = -\frac{A}{k_e}e^{-k_e nt_{1/2}} + \frac{A}{k_e} + \frac{A}{k_a}e^{-k_a nt_{1/2}} - \frac{A}{k_a} \quad \text{(A3)}$$

Substitution of $t_{1/2}$ with $(\ln 2)/k_e$ and rearrangement of the resulting equation leads to the following:

$$AUC_{0-nt_{1/2}} = \frac{FD}{Vk_e}\left[1 - \frac{\phi(0.5)^n - (0.5)^{n\phi}}{\phi - 1}\right] \quad \text{(A4)}$$

In eq A4, $\Phi = k_a/k_e$. Equation 1 (see text) is obtained by dividing eq A4 with the following fundamental equation[5]:

$$AUC_{0-\infty} = \frac{FD}{Vk_e} \quad \text{(A5)}$$

**Derivation of Equation 2**—In the one-compartment model with oral administration, first-order kinetics, and $k_a = k_e = k$, the concentration of the drug versus time is given by the following equation[5]:

$$C = \frac{FD}{V}kte^{-kt} \quad \text{(A6)}$$

Therefore, the AUC between zero and $nt_{1/2}$ can be calculated as follows:

$$AUC_{0-nt_{1/2}} = FD/V\int_0^{nt_{1/2}} kte^{-kt}dt \quad \text{(A7)}$$

$$AUC_{0-nt_{1/2}} = -(FD/Vk)(knt_{1/2} + 1)e^{-knt_{1/2}} + (FD/Vk) \quad \text{(A8)}$$

Substituting $t_{1/2}$ with (ln 2)/$k$ and rearranging the resulting equation results in the following equation:

$$AUC_{0-nt_{1/2}} = (FD/Vk)[1 - (n \ln 2 + 1)(0.5)^n] \quad (A9)$$

Equation 2 (see text) is readily obtained by dividing eqs A9 and A5 (with $k_e = k$).

## References and Notes


1. Chen, M-L.; Pelsor, F. R. *J. Pharm. Sci.* **1991**, *80*, 406–408.
2. Lovering, E. G.; McGilveray, I. J.; McMillan, I.; Tostowaryk, W. *J. Pharm. Sci.* **1975**, *64*, 1521–1524.
3. Wagner, J. W. In *Biopharmaceutics and Relevant Pharmacokinetics*; Drug Intelligence: Hamilton, IL, 1971; chapter 36, p 281.
4. Macheras, P.; Symillides, M.; Reppas, C. *Biopharm. Drug Dispos.* **1992**, *13*, 229–232.
5. Gibaldi, M.; Perrier, D. In *Pharmacokinetics*, Marcel Dekker: New York, NY, 1982; pp 34, 38, 170.



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# CORRECTIONS AND ADDITIONS

**Proton Nuclear Magnetic Resonance Spectroscopy Studies of the Inclusion Complex of Piroxicam with β-Cyclodextrin.** Fronza, G.; Mele, A.; Redenti, E.; Ventura, P. *J. Pharm. Sci.* **1992**, *81*, 1162–1165.

On page 1162, column 2, **Results and Discussion,** line 12 should read: "In particular, the signal of the inner proton H-5′ of β-CD. . . ."

**In the Search for New Anticancer Drugs. XXIV: Synthesis and Anticancer Activity of Amino Acids and Dipeptides Containing the 2-Chloroethyl- and [*N*-(2-Chloroethyl)-*N*′-Nitroso]-aminocarbonyl Groups.** Sosnovsky, George; Prakash, Indra; Rao, Nuti Uma Maheswara. *J. Pharm. Sci.* **1993**, *82*, 1–10.

On page 6, column 1, the last sentence in the first paragraph should read: "The most abundant fragments . . . were attributed to the sequential loss of chlorine, $HNCH_2CH_2Cl$, and $OCHNCH_2CH_2Cl$ moieties, respectively (Table IX)."

On page 7, Table X, the last two columns (Survivors, On Day 30 and On Day 60) beginning with Compound MeCCNU, should read as follows:

| | |
|---|---|
| 3/6 | 1/6 |
| 6/6 | 6/6 |
| 2/6 | 2/6 |
| 0/6 | – |
| 0/6 | – |
| 0/5 | – |
| 5/6 | 1/6 |
| 5/6 | 2/6 |
| 6/6 | 3/6 |
| 5/5 | 5/5 |

On page 8, column 1, paragraph 1, the last six sentences should read: "For measuring $P$, 1-octanol and water layers were presaturated with each other prior to use. The values of $P$ ([compound in 1-octanol]/[compound in water]) and log $P$ are shown in Table XI."

**Logarithmic Transformation in Bioequivalence: Application with Two Formulations of Perphenazine.** Midha, K.K.; Ormsby, E.D.; Hubbard, J.W.; McKay, G.; Hawes, E.M.; Gavalas, L.; McGilveray, I.J. *J. Pharm. Sci.*, **1993**, *82*, 138–144.

On page 139, Table 1, the Expected Means Squares for Subject (SEQ) should read: "$\sigma^2_W + \sigma^2_B$".

On page 140, equation 3 should read:

$$MEAN_l = \exp^{\bar{X} + \frac{S^2}{2}}$$

and line 17 should read: "In eq 3, $S^2$ is the estimated variance of the Xs."

and line 22 should read: ". . . to account for the estimation of $\sigma^2$."

equation 5 should read:

$$STE_{diff} = \sqrt{\frac{1}{2}\left(\frac{1}{n_{TR}} + \frac{1}{n_{RT}}\right)S^2_W}$$

and line 28 should read: "In eq 5, $S^2_W$ is the residual from the crossover ANOVA."

line 36 should read: "Although the estimator consistently overestimates the true ratio of medians . . . ."

**Metabolism of 3-Indolylacetic Acid during Percutaneous Absorption in Human Skin.** Ademola, John, I.; Wester, Ronald C.; Maibach, Howard I. *J. Pharm. Sci.* **1993**, *82*, 150–154.

On page 150, column 2, line 4 in **Microsomal Preparations** should read: "The homogenates were centrifuged at 10 000 × *g* for 25 min. The clear supernatant collected was centrifuged again for 60 min at 108 000 × *g* to give cytosolic and microsomal fractions."

On page 150, column 2, line 2 in **Bioconversion of 3-Indolylacetic Acid by Human Skin Microsomes** should read: "Microsomal incubations were performed as follows: A sample (1.0 mg of protein) of the 108 000 × *g* precipitate was . . . ."

**Transdermal Iontophoretic Peptide Delivery: In Vitro and In Vivo Studies with Luteinizing Hormone Releasing Hormone.** Heit, Mark C.; Williams, Patrick L.; Jayes, Friederike L.; Chang, Shao K. *J. Pharm Sci.*, **1993**, *82*, 240–243. The CORRECTED ARTICLE appears on the pages following page 554.

**Determination of the Enantiomers of a New 1,4-Dihydropyridine Calcium Antagonist in Dog Plasma by Achiral/Chiral Coupled High-Performance Liquid Chromatography with Electrochemical Detection.** Fujitomo, Hiroyuki; Nishino, Ikuko; Ueno, Kyoji; Umeda, Tsuneji. *J. Pharm. Sci.* **1993**, 82, 319–322.

On page 319, column 2, line 4 in **Apparatus** should read: ". . . . ion-exchange column . . . ."

**Biliary Excretion and Pharmacokinetics of a Gadolinium Chelate Used as a Liver-Specific Contrast Agent for Magnetic Resonance Imaging in the Rat.** Schuhmann-Giampieri, Gabriele; Schmitt-Willich, Heribert; Frenzel, Thomas. *J. Pharm. Sci.* **1993**, *82*, 799–803. The contributor line has been corrected.