Fraction of the Bioavailable Dose Remaining in the Body at the Time of Peak Plasma Concentration in a Linear, Open, One-Compartment Model

To the Editor:

Recently, Kaltenbach et al.[1] developed a simple method to determine the percent of dose absorbed at the time of peak plasma concentration (t_{max}) in an open, one-compartment model with linear kinetics. It was shown that the percentage of drug absorbed at t_{max} depends only on the value of the ratio k_a/k_e, where k_a and k_e are the first-order rate constants for absorption and elimination, respectively. The knowledge of the extent of drug absorption at t_{max} is indeed of great significance for the practicing clinician in guiding drug therapy.[1] However, it is at least of equal importance for the practitioner to know how much of the fraction of dose absorbed at t_{max} remains actually in the body (i.e., excluding the unabsorbed drug in the gastrointestinal tract). The knowledge of both the fraction absorbed at t_{max} and the fraction remaining in the body at t_{max} is certainly of great value for the appropriate design of dosage forms and dosage regimens, as well as for the understanding of dose–effect relationship. The purpose of this communication is to report a method to determine the fraction of the fraction of dose absorbed at t_{max} which remains in the body at this time in a linear, open, one-compartment body model.

Let $X_{sys,\ t_{max}}$ be the amount of drug remaining in the system at t_{max} and $f_{abs,\ t_{max}}$ be the fraction of the bioavailable dose (FD) absorbed between the time zero and t_{max}. The material balance leads to eq 1:

$$X_{sys,\ t_{max}} = (f_{abs,\ t_{max}})(FD) - (f_{el,\ t_{max}})(f_{abs,\ t_{max}})(FD) \quad (1)$$

where F is the fraction absorbed of the dose (D) and $f_{el,\ t_{max}}$ denotes the fraction of the fraction of dose absorbed $[f_{abs,\ t_{max}}(FD)]$ which is eliminated (excreted and metabolized) between time zero and t_{max}. Rearrangement of eq 1 yields:

$$F_{sys,\ t_{max}} = \frac{X_{sys,\ t_{max}}}{FD} = (f_{abs,\ t_{max}})(1 - f_{el,\ t_{max}}) \quad (2)$$

where $F_{sys,\ t_{max}}$ denotes the fraction of the bioavailable dose which remains in the system at t_{max}.

As it is shown in the *Appendix* for the most common case where $k_a \neq k_e$, the fraction eliminated ($f_{el,\ t_{max}}$) is given by:

$$f_{el,\ t_{max}} = \frac{(AUC)_0^{t_{max}}}{(f_{abs,\ t_{max}})(AUC)_0^{\infty}} \quad (3)$$

where $(AUC)_0^{t_{max}}$ and $(AUC)_0^{\infty}$ are the areas under the curve for the specified time limits of the plasma concentration–time plot. Therefore, substitution of eq 3 into eq 2 gives:

$$F_{sys,\ t_{max}} = (f_{abs,\ t_{max}}) - \frac{(AUC)_0^{t_{max}}}{(AUC)_0^{\infty}} \quad (4)$$

According to Kaltenbach et al.,[1] $f_{abs,\ t_{max}}$ can be expressed by eq 5 (their eq 3) for the general case with $k_a \neq k_e$:

$$f_{abs,\ t_{max}} = 1 - (k_a/k_e)^{-k_a/(k_a - k_e)} \quad (5)$$

It is also shown in the *Appendix* that the ratio $(AUC)_0^{t_{max}}/(AUC)_0^{\infty}$ can be expressed solely as a function of k_a/k_e:

$$\frac{(AUC)_0^{t_{max}}}{(AUC)_0^{\infty}} = 1 - \frac{1}{(k_a/k_e) - 1}$$

$$\left[(k_a/k_e)^{[(k_a/k_e) - 2]/[(k_a/k_e) - 1]} - (k_a/k_e)^{-(k_a/k_e)/[(k_a/k_e) - 1]}\right] \quad (6)$$

Substitution of eqs 5 and 6 into eq 4 results in:

$$F_{sys,\ t_{max}} = (k_a/k_e)^{1/[1 - (k_a/k_e)]} \quad (7)$$

In the special case of equivalent rate constants ($k_a = k_e = k$), Kaltenbach et al.[1] have shown that:

$$f_{abs,\ t_{max}} = 0.632 \quad (8)$$

It is shown in the *Appendix* that under these conditions, the ratio $(AUC)_0^{t_{max}}/(AUC)_0^{\infty}$ is also independent of the magnitude of ratio k_a/k_e; that is:

$$\frac{(AUC)_0^{t_{max}}}{(AUC)_0^{\infty}} = 0.264 \quad (9)$$

Substituting the values for $f_{abs,\ t_{max}}$ and $(AUC)_0^{t_{max}}/(AUC)_0^{\infty}$ from eqs 8 and 9 into eqs 2 and 3, respectively, the following is obtained:

$$F_{sys,\ t_{max}} = 0.368 \quad (10)$$

In other words, when $k_a = k_e$, 36.8% of the bioavailable dose of a drug remains in the body at t_{max}, while the percentage of the bioavailable dose at t_{max} is, according to eq 8, 63.2%.

In the general case where $k_a \neq k_e$, eq 7 reveals that the fraction of the bioavailable dose remaining in the body at t_{max} ($F_{sys,\ t_{max}}$) depends solely on the ratio k_a/k_e. In Figure 1, the $F_{sys,\ t_{max}}$ is expressed as percent ($100 \times F_{sys,\ t_{max}}$) and plotted against the ratio of rate constants (k_a/k_e). For comparative purposes, the percentage of drug absorbed at t_{max}, $100 \times f_{abs,\ t_{max}}$, given by Kaltenbach et al.[1] is also plotted as a function of k_a/k_e. As can be seen when $k_a/k_e = 2$, 75% of the bioavailable dose is absorbed at t_{max}, whereas 50% of the bioavailable dose remains in the system. The largest difference (26.4%) between the percentage of the bioavailable dose absorbed at t_{max} and the percentage of the bioavailable dose remaining in the body at t_{max} is observed when $k_a = k_e = k$. This difference diminishes progressively as the ratio k_a/k_e becomes larger or smaller.

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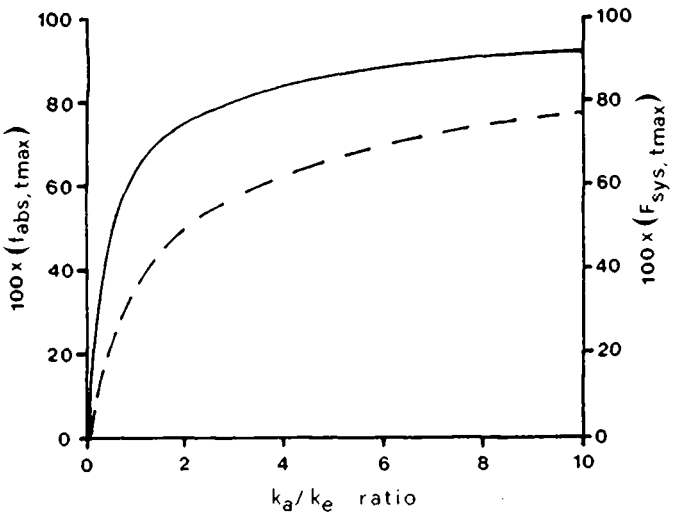

Figure 1—Percentage of (——) the bioavailable dose absorbed [100 × ($f_{abs,\ t_{max}}$)] and (– – –) that remaining in the body [100 × ($F_{sys,\ t_{max}}$)] at the time of peak plasma concentration as a function of the k_a/k_e ratio.

Appendix

Derivation of Equation 3—In the course of the construction of the percent absorbed–time plots,[2] the following fundamental equation is used for the fraction absorbed:

$$\frac{X_t}{FD} = \frac{C_t + k_e\int_0^t C\,dt}{k_e\int_0^\infty C\,dt} \qquad \text{(A1)}$$

where X_t is the amount of drug which has entered the system between time zero and time t, C_t is the plasma concentration at time t and the other symbols are as defined in the text. Applying eq A1 for $t = t_{max}$ and expressing the left-hand side of eq A1 as the fraction absorbed at t_{max}, the following can be written:

$$f_{abs,\ t_{max}} = \frac{C_{t_{max}} + k_e(\mathrm{AUC})_0^{t_{max}}}{k_e(\mathrm{AUC})_0^\infty} \qquad \text{(A2)}$$

Solving in terms of $(\mathrm{AUC})_0^{t_{max}}/(\mathrm{AUC})_0^\infty$:

$$\frac{(\mathrm{AUC})_0^{t_{max}}}{(\mathrm{AUC})_0^\infty} = (f_{abs,\ t_{max}}) - \frac{C_{t_{max}}}{k_e(\mathrm{AUC})_0^\infty} \qquad \text{(A3)}$$

Substitution[2] of FD/Vk_e for $(\mathrm{AUC})_0^\infty$ into eq A3 results in:

$$\frac{(\mathrm{AUC})_0^{t_{max}}}{(\mathrm{AUC})_0^\infty} = (f_{abs,\ t_{max}}) - \frac{C_{t_{max}}\,Vd}{FD} \qquad \text{(A4)}$$

where Vd is the volume of distribution. The term ($C_{t_{max}}Vd$) corresponds to the amount of drug in the system at t_{max} ($X_{sys,\ t_{max}}$) and therefore, in accord with eq 2, eq A4 can be written as:

$$\frac{(\mathrm{AUC})_0^{t_{max}}}{(\mathrm{AUC})_0^\infty} = (f_{abs,\ t_{max}}) - (F_{sys,\ t_{max}}) \qquad \text{(A5)}$$

By combining and rearranging eqs 2 and A5, eq 3 can be readily obtained.

Derivation of Equation 6—The equation describing the concentration (C) of drug in plasma for the one-compartment model is given[3] by:

$$C = \frac{FDk_a}{Vd(k_a - k_e)}[\exp(-k_e t) - \exp(-k_a t)] =$$

$$\frac{\Lambda k_a}{k_a - k_e}[\exp(-k_e t) - \exp(-k_a t)] \qquad \text{(A6)}$$

where $\Lambda = FD/Vd$. Integration of eq A6 between the limits $t = 0$ and $t = t_{max}$ gives:

$$(\mathrm{AUC})_0^{t_{max}} = \frac{\Lambda k_a}{k_a - k_e}\int_0^{t_{max}}[\exp(-k_e t) - \exp(-k_a t)]dt$$

$$(\mathrm{AUC})_0^{t_{max}} = \frac{\Lambda k_a}{k_a - k_e}\left[-\frac{1}{k_e}\exp(-k_e t)\Big|_0^{t_{max}} + \frac{1}{k_a}\exp(-k_a t)\Big|_0^{t_{max}}\right]$$

$$(\mathrm{AUC})_0^{t_{max}} =$$

$$\frac{\Lambda k_a}{k_a - k_e}\left[\frac{1}{k_e} - \frac{1}{k_a} - \frac{\exp(-k_e t_{max})}{k_e} + \frac{\exp(-k_a t_{max})}{k_a}\right] \qquad \text{(A7)}$$

Substituting[3] $[\ln(k_a/k_e)]/(k_a - k_e)$ for t_{max} in eq A7 results in:

$$(\mathrm{AUC})_0^{t_{max}} = \frac{\Lambda k_a}{k_a - k_e}\left[\frac{1}{k_e} - \frac{1}{k_a} - \frac{\exp[-k_e \ln(k_a/k_e)/(k_a - k_e)]}{k_e} + \frac{\exp[-k_a \ln(k_a/k_e)/(k_a - k_e)]}{k_a}\right] \qquad \text{(A8)}$$

Equation A8 simplifies to:

$$(\mathrm{AUC})_0^{t_{max}} = \frac{\Lambda}{k_e} - \frac{\Lambda}{k_a - k_e}\left[(k_a/k_e)^{[(k_a/k_e) - 2]/[(k_a/k_e) - 1]} - (k_a/k_e)^{-(k_a/k_e)/[(k_a/k_e) - 1]}\right] \qquad \text{(A9)}$$

Using[3] the fundamental eq A10, eq 6 is obtained by dividing eqs A9 and A10:

$$(\mathrm{AUC})_0^\infty = \frac{FD}{Vdk_e} = \frac{\Lambda}{k_e} \qquad \text{(A10)}$$

Derivation of Equation 9—The equation describing the concentration (C) of drug in plasma for the linear one-compartment model with equal rate constants ($k_a = k_e = k$) is given[3] by:

$$C = \frac{FD}{Vd}kt\exp(-kt) = \Lambda kt\exp(-kt) \qquad \text{(A11)}$$

Integration of eq A11 between the limits $t = 0$ and $t = t_{max} = 1/k$[3] gives:

$$(\mathrm{AUC})_0^{t_{max}} = \Lambda \int_0^{1/k} kt \exp(-kt)dt =$$

$$-\frac{\Lambda}{k}(kt+1)\exp(-kt)\Big|_0^{1/k} = \frac{\Lambda}{k}\left(1-\frac{2}{e}\right) \qquad \text{(A12)}$$

Equation A10 is written as follows for the model with equal rate constants:

$$(\mathrm{AUC})_0^{\infty} = \Lambda/k \qquad \text{(A13)}$$

By dividing eqs A12 and A13, eq 9 is obtained.

References and Notes

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BOOK REVIEWS

Bioorganic Photochemistry, Volume 1: Photochemistry and the Nucleic Acids. Edited by H. Morrison, Wiley-Interscience: New York. 1990. ix + 437 pp. 25 × 17 cm. ISBN 0-471-62987-1. $59.95.

This monograph is the first of a series dealing with phenomena and processes at the interface between biochemistry and organic photochemistry; it contains five chapters each written by a group of authors who are specialists in the areas covered.

The opening chapter, a small textbook in itself, discusses the photochemistry of nucleic acids. It covers the history of the subject, photophysics and photochemistry of nucleic acids, the conventional physical methods of study such as fluorometry and electron spin resonance spectroscopy, as well as the more modern methods such as synchrotron-radiation excitation and picosecond time-resolved fluorometry. In addition, the areas of far ultraviolet, near ultraviolet, and vacuum ultraviolet irradiation of nucleic acids and their components; photooxidation reactions; anoxic, photosensitized photoreactions; and triplet sensitized photoreactions are covered. This chapter alone is worth the price of the book.

The remaining chapters deal with more specialized subjects. The second chapter discusses DNA binding of photosensitizers, endogenous and exogenous photosensitizers, and mechanisms of photodynamic action. Also discussed is photoaffinity labeling of DNA.

The third chapter covers photoreactions of alcohols, alcohol-derived amino acids, sulfhydryl compounds, carboxylic acids, and amines with nucleic acid bases of 5-bromouracil with amino acids, and the photoreactions of the nucleic acids andpolynucleotides with amino acids and proteins.

The fourth chapter details the rationale and use of psoralens as light-activated cross-linking agents for pyrimidine bases in double-stranded nucleic acids. Although the treatment here is primarily concerned with the use of psoralens as probes of nucleic acid structure and function, the reactivity described is virtually identical to that in which psoralens are used as therapeutic agents for a variety of skin diseases. This should make the chapter of particular interest to pharmaceutical scientists.

The fifth chapter deals with the photochemistry of 4-thiouracil derivatives. The photochemistry of 4-thiouracil in oxidation, reduction, addition, and dimerization reactions is treated before going on to the related photochemistry of its nucleoside, 4-thiouridine. The role of photoactivation of the nucleoside as a cross-linker of tRNA, as well as its incorporation into cellular nucleic acids, is discussed at length. A discussion of the chemical incorporation of 4-thiouridine into polynucleotides is also presented.

All the chapters in volume 1 of *Bioorganic Photochemistry* are uniformly well-written; the book will be a welcome addition to the library of anyone involved in photochemistry and/or chemotherapy. This reviewer looks forward to subsequent volumes in the series.

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Current Books

Quality Control of Packaging Materials in the Pharmaceutical Industry. By Kenneth Harburn. Marcel Dekker: New York. 1991. 183 pp. 24 × 16 cm. ISBN 0-8247-8243-7. $69.75.

Drug Testing Issues & Options. Edited by R. H. Coombs and L. J. West. Oxford University Press: New York. 1991. 243 pp. 25 × 17 cm. ISBN 0-19-505414-8. $39.95.

Protective Groups in Organic Synthesis. By T. W. Greene and P. G. M. Wuts. John Wiley: New York. 1991. 473 pp. 25 × 16 cm. ISBN 0-471-62301-6. $59.95.

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