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SCIENTIFIC COMMENTARY

Rapid Method of Obtaining Area Under Curve for Any Compartment of Any Linear Pharmacokinetic Model in Terms of Rate Constants[1]

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INTRODUCTION

The classical method of obtaining areas in terms of kinetic constants involves the following steps: (a) writing the differential equations for the model; (b) obtaining the Laplace transform (a_i) for the amount in a given compartment at time t (A_i); (c) taking the antitransform which provides the expression for A_i which is a polyexponential equation; (d) integrating the polyexponential equation between the limits of $t = 0$ and $t = \infty$; and (e) simplifying the result. The last step in this sequence often involves horrendous algebra.

THEORETICAL

The Laplace transform of a function, $F(t)$, is obtained as indicated by

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[1] *Editorial Note:* Dr. Wagner's article is published as a Scientific Commentary for the sake of the reader uninformed in basic properties of the LaPlace transform. It represents a reiteration of a basic theorem of LaPlace transforms. The final value theorem can be found in P. A. McCollum and B. F. Brown, *LaPlace Transform Tables and Theorems*, Holt, Rinehart and Winston, New York, pp. 73–74, 1965. It may also be found in H. S. Carslow and J. C. Jaeger, *Operational Methods in Applied Mathematics*, Dover Publications, New York, pp. 255–256, 1963.

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$$L[F(t)] = a_i = \int_0^\infty F(t)\, e^{-st}\, dt \tag{1}$$

When $s = 0$, then $e^{-st} = 1$, and

$$(a_i)_{s=0} = \int_0^\infty F(t)\, dt \tag{2}$$

In linear pharmacokinetics, $F(t)$ is given by

$$F(t) = V_p \int_0^\infty C_i\, e^{-\lambda_i t} = \int_0^\infty A_i\, e^{-\lambda_i t} \tag{3}$$

for the plasma or reference compartment, where V_p is the volume of that compartment, the C_i's and A_i's are coefficients with dimensions of concentration and mass, respectively, and the λ_i's are either eigenvalues or microscopic rate constants of the particular model.

Dost's "law of corresponding areas" (1) may be stated as follows: the ratio of the area beneath the blood level–time curve after oral administration to that following intravenous administration of the same dose is a measure of the absorption of the drug administered. This may be expressed mathematically as

$$F = \int_0^\infty C_p^{\text{p.o.}}\, dt \Big/ \int_0^\infty C_p^{\text{i.v.}}\, dt \tag{4}$$

In equation 4, F symbolizes the fraction of the dose which is absorbed (hence is the bioavailability factor due to incomplete absorption), $C_p^{\text{p.o.}}$ is the plasma concentration at time t after oral administration, and $C_p^{\text{i.v.}}$ is the plasma concentration at time t after intravenous administration.

Now, Dost's law should be replaced by

$$FF^* = D_{\text{i.v.}} \int_0^\infty C_p^{\text{p.o.}}\, dt \Big/ D_{\text{p.o.}} \int_0^\infty C_p^{\text{i.v.}}\, dt \tag{5}$$

In equation 5, $D_{\text{i.v.}}$ represents the dose given intravenously, $D_{\text{p.o.}}$ represents the dose given orally and F^* is the bioavailability factor due to the so-called first-pass effect. When dealing with linear pharmacokinetic models, the value of F^* is obtained by assuming $F = 1$ and $D_{\text{i.v.}} = D_{\text{p.o.}}$ and then substituting the appropriate values for the two areas into equation 5 and simplifying, if necessary.

EXPERIMENTAL

Figure 1 shows the schematic diagrams of 6 linear pharmacokinetic models. Table I lists the Laplace transforms for the amounts in the designated plasma compartment (signified by V_p being written below that compartment) after both oral, $a_p^{p,o}$, and intravenous, $a_p^{i,v}$, administration, the corresponding areas, and the value of F^* for the model. The areas obtained by the application of equation 2 were all checked by the classical method of integrating the polyexponential equation for the amount in the plasma compartment as a function of time and agreement was obtained in each case.

Since the products of the λ_i's appearing in the area expressions cancel when the ratio of the oral to the intravenous area is made to obtain F^*, it is not necessary to know what the λ_i's mean in terms of the microscopic rate

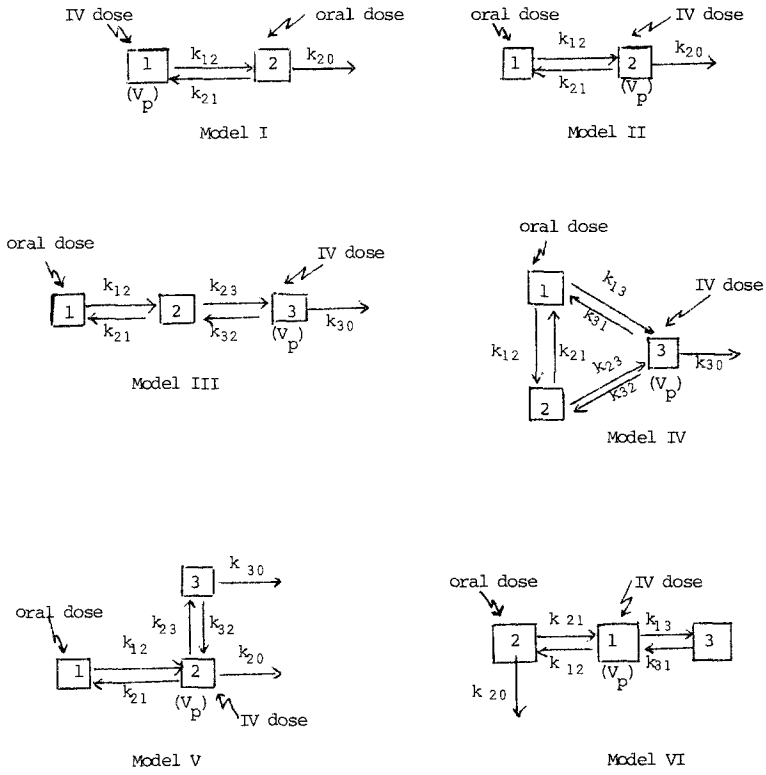

Fig. 1. Schematic diagrams of six linear pharmacokinetic models.

Table I. Laplace Transforms for Amounts in the Plasma Compartment (Designated by V_p) Following Oral Administration, $a_p^{p.o.}$, and Intravenous Administration, $a_p^{i.v.}$, the Corresponding Areas, and the Value of F^* for Six Different Linear Pharmacokinetic Models

Model	Laplace transforms		Areas		
	$a_p^{p.o.}$	$a_p^{i.v.}$	Oral	Intravenous	F^*
I	$\frac{k_{21}FD_{p.o.}}{(s+\lambda_1)(s+\lambda_2)}$	$\frac{(s+E_2)D_{i.v.}}{(s+\lambda_1)(s+\lambda_2)}$	$\frac{k_{21}FD_{p.o.}}{\lambda_1\lambda_2}$	$\frac{E_2D_{i.v.}}{\lambda_1\lambda_2}$	$\frac{k_{21}}{k_{20}+k_{21}}$
II	$\frac{k_{12}FD_{p.o.}}{(s+\lambda_1)(s+\lambda_2)}$	$\frac{(s+k_{12})D_{i.v.}}{(s+\lambda_1)(s+\lambda_2)}$	$\frac{FD_{p.o.}}{k_{20}}$[a]	$\frac{D_{i.v.}}{k_{20}}$[a]	1
III	$\frac{k_{12}k_{23}FD_{p.o.}}{(s+\lambda_1)(s+\lambda_2)(s+\lambda_3)}$	$\frac{[(s+k_{12})(s+E)-k_{12}k_{21}]D_{i.v.}}{(s+\lambda_1)(s+\lambda_2)(s+\lambda_3)}$	$\frac{k_{12}k_{23}FD_{p.o.}}{\lambda_1\lambda_2\lambda_3}$	$\frac{k_{12}k_{23}D_{i.v.}}{\lambda_1\lambda_2\lambda_3}$	1
IV	$\frac{[k_{13}(s+E_2)+k_{12}k_{23}]FD_{p.o.}}{(s+\lambda_1)(s+\lambda_2)(s+\lambda_3)}$	$\frac{[(s+E_1)(s+E_2)-k_{12}k_{21}]D_{i.v.}}{(s+\lambda_1)(s+\lambda_2)(s+\lambda_3)}$	$\frac{[k_{13}E_2+k_{12}k_{23}]FD_{p.o.}}{\lambda_1\lambda_2\lambda_3}$	$\frac{[E_1E_2-k_{12}k_{21}]D_{i.v.}}{\lambda_1\lambda_2\lambda_3}$	1[b]
V	$\frac{k_{12}(s+E_3)FD_{p.o.}}{(s+\lambda_1)(s+\lambda_2)(s+\lambda_3)}$	$\frac{(s+k_{12})(s+E_3)D_{i.v.}}{(s+\lambda_1)(s+\lambda_2)(s+\lambda_3)}$	$\frac{k_{12}E_3FD_{p.o.}}{\lambda_1\lambda_2\lambda_3}$	$\frac{k_{12}E_3D_{i.v.}}{\lambda_1\lambda_2\lambda_3}$	1
VI	$\frac{k_{21}(s+k_{31})FD_{p.o.}}{(s+\lambda_1)(s+\lambda_2)(s+\lambda_3)}$	$\frac{(s+k_{31})(s+E)D_{i.v.}}{(s+\lambda_1)(s+\lambda_2)(s+\lambda_3)}$	$\frac{k_{21}k_{31}FD_{p.o.}}{\lambda_1\lambda_2\lambda_3}$	$\frac{k_{31}E_2D_{i.v.}}{\lambda_1\lambda_2\lambda_3}$	$\frac{k_{21}}{k_{20}+k_{21}}$

[a]Result obtained after use of equation 2 and the k_{12}'s have been canceled.
[b]This result is obtained since the numerators of the area expressions are equivalent when $F = 1$ and $D_{p.o.} = D_{i.v.}$.

constants to obtain the value of F^* for any particular model. However, for the models shown in Fig. 1, the products are as follows:

$$\text{Models I and II:} \quad \lambda_1\lambda_2 = k_{12}k_{20} \tag{6}$$

$$\text{Model III:} \quad \lambda_1\lambda_2\lambda_3 = k_{12}E_2E_3 - k_{12}k_{23}k_{32} - k_{12}k_{21}E_3 \tag{7}$$

where $E_2 = k_{21} + k_{23}$ and $E_3 = k_{32} + k_{30}$.

$$\text{Model IV:} \quad \lambda_1\lambda_2\lambda_3 = E_1E_2E_3 - k_{23}k_{32}E_1 - k_{12}k_{21}E_3 - k_{13}k_{21}k_{32} - k_{12}k_{23}k_{31} - k_{13}k_{31}E_2 \tag{8}$$

where $E_1 = k_{12} + k_{13}$, $E_2 = k_{21} + k_{23}$, and $E_3 = k_{30} + k_{31} + k_{32}$.

$$\text{Model V:} \quad \lambda_1\lambda_2\lambda_3 = k_{12}E_2E_3 - k_{12}k_{23}k_{32} - k_{12}k_{21}E_3 \tag{9}$$

where $E_2 = k_{20} + k_{23} + k_{21}$ and $E_3 = k_{30} + k_{32}$.

$$\text{Model VI:} \quad \lambda_1\lambda_2\lambda_3 = E_1E_3k_{31} - k_{12}k_{21}k_{31} - k_{13}k_{31}E_2 \tag{10}$$

where $E_1 = k_{12} + k_{13}$ and $E_2 = k_{20} + k_{21}$.

DISCUSSION

The above method is clearer and more in keeping with acceptable pharmacokinetic theory than the method proposed by Nüesch (2) to make the correction (i.e., find F^*) that makes Dost's law valid for a given compartment model.

However, in the real world (as contrasted to the abstract world of models) the only way to prove that Dost's law is applicable to a particular drug is to show that, with some type of dosage form, $FF^* = 1$ when one measures the drug in plasma after both oral and intravenous administration and applies equation 5. Such a result implies that the oral dose was completely absorbed (i.e., $F = 1$) and that for conditions existing in the body $F^* = 1$. If the oral area is less than the intravenous area, one really cannot determine whether this was caused by $F < 1$ or $F^* < 1$ or both being less than unity. This is because the bioavailability factors are confounded (i.e., appear as a product, FF^*, in equation 5). It has been recognized for some time that the value of F^* can be so close to unity (e.g., when $k_{21} \gg k_{20}$ in models I and VI of Fig. 1) that, with the errors involved in plasma assays and in estimating the areas, one cannot distinguish the value from unity.

REFERENCES

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