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DRUG ABSORPTION:
SOME MATHEMATICAL CONSIDERATIONS

by

Frederick R. Sidell, M.D.

May 1972

DEPARTMENT OF THE ARMY
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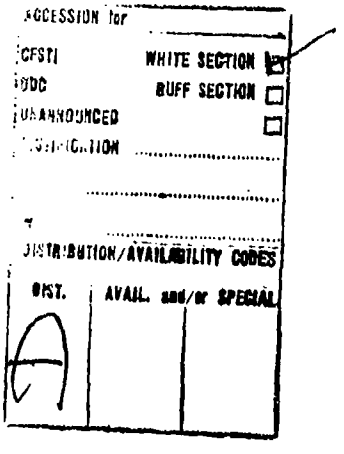

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13. ABSTRACT

Using the absorption equation of Wagner and Nelson and the integrated form of the equation describing the plot of plasma concentration versus time, formulas were derived which may be helpful in comparing rates of drug absorption. The percentage absorbed over a specified time period and the time required for absorption to be 25%, 50%, 75%, or 99% complete can be readily calculated if it is assumed the basic equations are valid.

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Medical Research Division

May 1972

Task 1T061102B71A02

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FOREWORD

The work described in this report was authorized under Task 1T061102B71A02, Life Sciences Basic Research in Support of Materiel. This work was started in May 1971 and completed in August 1971.

DIGEST

Using the absorption equation of Wagner and Nelson and the integrated form of the equation describing the plot of plasma concentration versus time, formulas were derived which may be helpful in comparing rates of drug absorption. The percentage absorbed over a specified time period and the time required for absorption to be 25%, 50%, 75%, or 99% complete can be readily calculated if it is assumed the basic equations are valid.

DRUG ABSORPTION: SOME MATHEMATICAL CONSIDERATIONS

The rate and amount of absorption of a drug is of interest in comparing different pharmaceutical preparations of the same drug or in comparing the absorption efficiency of similar drugs.

Assuming a one-compartment open model, the equation of Wagner and Nelson[1] states that the amount of drug absorbed by time, t, is equal to

$$Q_t = C_t V + VK \int_o^t (C)dt \qquad (1)$$

where Q_t = the amount absorbed by time, t; C_t = plasma concentration at time, t; K = first-order rate constant for elimination of the drug from the volume of distribution, V; and the term under the integral is the area under the curve of a plot of plasma concentration versus time to time, t. This states that the amount absorbed by time, t, is the amount in the body at time, t, plus that which has entered but has already been eliminated from the body.

This model and equation assume that the volume of distribution, V, remains constant throughout the period t = 0 to t = ∞, and that the plasma concentration is the same as the concentration throughout the volume of distribution.

The total amount absorbed is

$$Q_t = VK \int_o^\infty (C)dt \qquad (2)$$

since $C_t = 0$ at $t = \infty$.

The percentage of drug absorbed at time, t, is therefore

$$\frac{Q_t}{Q_a} = \frac{VC_t + VK \int_o^t (C)dt}{VK \int_o^\infty (C)dt} \times 100 = \frac{C_t + K \int_o^t (C)dt}{K \int_o^\infty (C)dt} \times 100. \qquad (3)$$

If the absorption rate process is unknown, the area under the integral can be estimated by the trapezoid rule or other means. However,

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[1] Wagner, J. G., and Nelson, E. J. Pharm. Sci. 53, 1392 (1964).

absorption frequently follows a first-order process, and in this case the plot of concentration versus time will fit the equation*

$$C_t = Be^{-Kt} - Ae^{-kt} \tag{4}$$

where k = the first-order rate constant for absorption, and A and B are the intercepts at t = 0 of the lines whose slopes are k and K.

When this is the case, the total amount absorbed is

$$Q_\infty = VK \int_o^\infty \left(Be^{-Kt} - Ae^{-kt}\right)dt \tag{5}$$

or

$$VK\left(\frac{B}{K} - \frac{A}{k}\right) \tag{6}$$

or

$$V\left(B - \frac{KA}{k}\right) \tag{7}$$

By a similar integration, the amount absorbed by time, t, is

$$Q_t = VC_t + KV \int_o^t \left(Be^{-Kt} - Ae^{-kt}\right)dt \tag{8}$$

or

$$V\left[Ae^{-kt}\left(\frac{K}{k} - 1\right) + B - \frac{KA}{k}\right] \tag{9}$$

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* This equation is basically the same as the equation

$$C_t = \frac{Dk}{V(k-K)}\left(e^{-kt} - e^{-Kt}\right)$$

described elsewhere (D = dose).[2] If there is no "lag time" in the absorption process, i.e., when $C = 0$ at $t = 0$, $A = B = \frac{Dk}{V(k-K)}$. When there is a "lag time," i.e., when $C \neq 0$ at $t = 0$, $A \neq B \neq \frac{Dk}{V(k-K)}$, but $A = \frac{Dke^{kt_1}}{V(k-K)}$ and $B = \frac{Dke^{Kt_1}}{V(k-K)}$ where t_1 is the "lag time."

A and B (also k and K) can also be determined graphically by the method of residuals. A and B have no biological meaning as they do in the similar equation describing blood concentrations after intravenous administration; they are merely mathematical conveniences.

[2] Teorell, T. Arch. Int. Pharmacodyn. Ther. 57, 205 (1937).

Comparisons between drugs or between different preparations of the same drug can be made by calculating the percentage of the total amount absorbed within a certain time or by calculating the time necessary for a certain percentage of absorption. The former calculation can be made by substituting the time into the equation

$$\frac{Q_t}{Q_\infty} = \frac{Ae^{-kt}\left(\frac{K}{k} - 1\right) + B - \frac{KA}{k}}{\left(B - \frac{KA}{k}\right)} \tag{10}$$

Equations to estimate the time necessary to absorb a given percentage of drug that is eventually absorbed can also be developed. For example, the time for absorption to be 50% complete is given by setting

$$Q_t = \frac{Q_\infty}{2}$$

or (11)

$$B - \frac{KA}{k} = 2x\left[C - \frac{B}{e^{Kt}} + \frac{KA}{ke^{kt}} + B' - \frac{KA}{k}\right]$$

wherein

$$t_{50} = \frac{\left(\ln\left[\frac{(2A(k-K))}{kB-KA}\right]\right)}{k} \tag{12}$$

The time for absorption to be 25% complete is

$$t_{25} = \frac{\left(\ln\left[\frac{4A(k-K)}{3(Bk-AK)}\right]\right)}{k} \tag{13}$$

The time for 75% absorption is

$$t_{75} = \frac{\left(\ln\left[\frac{(4A(k-K))}{Bk-KA}\right]\right)}{k} \tag{14}$$

and for 99% absorption

$$t_{99} = \frac{\left(\ln\left[\frac{(A(k-K))}{.01(kB-KA)}\right]\right)}{k} \tag{15}$$

One further application of this integration would be to calculate the volume of distribution under circumstances when the fraction of the dose that is absorbed is known. Since Q = FD, where F = the fraction of the dose absorbed,

$$Q = FD = V\left(B - \frac{KA}{k}\right), \tag{16}$$

and

$$V = \frac{FD}{\left(B - \frac{KA}{k}\right)} \tag{17}$$

After intramuscular administration, absorption is usually assumed to be 100% and F = 1. Therefore,

$$V = \frac{D\ *}{\left(B - \frac{KA}{k}\right)} \tag{18}$$

On the other hand, the volume of distribution may be known and the fraction absorbed may be the unknown. Such a case may arise when the drug is given by a route by which absorption is assumed to be 100%, e.g., intravenously or intramuscularly, and at another time when the drug is given by another route, e.g., orally. This assumes the drug is in the same volume of distribution by each route. In this case

$$F = \frac{V\left(B - \frac{KA}{k}\right)}{D} \tag{19}$$

Application of these equations will be shown in forthcoming reports.

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* By a similar integration and rearrangement of terms, this can be shown to be $V = \frac{D}{\left(B + \frac{KA}{k}\right)}$ when the drug is given by rapid intravenous injection. This is the same, with different notation as equation 16 in a recent report by Cucinell and Perl.[3]

[3] Cucinell, S. A., and Perl, W., J. Pharm. Sci. 59, 1423 (1970).