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A general method of determining the first order input rate constant of a drug that is directly absorbed into the central compartment

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A simple equation by which the first order rate constant for the absorption of a drug into the central compartment of any linear mammillary pharmacokinetic model can be calculated is presented. No specific knowledge of the distribution or elimination characteristics of the drug is required.

An equation to describe the Laplace transform for the disposition function of the central compartment (Rescigno & Segre, 1966) in a N compartment linear mammillary model, in which elimination of the drug can occur from any compartment, has been empirically derived (Benet, 1972). After intravenous, intramuscular or oral administration, plasma concentration or rate of urinary excretion of drugs can usually be described by a series of exponential terms, $A_i e^{-x_i t}$. The number of exponential terms depends upon the number of discernible compartments and the distribution characteristics of each drug (Rescigno & Segre, 1966).

Most methods of calculating the apparent first order absorption rate constant of a drug require the assumption of some specific linear pharmacokinetic model and presume a knowledge of the drug's distribution and elimination characteristics (Loo & Riegelman, 1968).

Since the assumption of an incorrect kinetic model can result in inaccurate estimates of the absorption or input rate constant (Loo & Riegelman, 1968), we have derived an expression for calculating the first order input rate constant for a drug entering the central compartment which does not require knowledge of the distribution or elimination characteristics of the drug.

THEORY

General solutions for the amount of a drug in the central compartment (X_1) of a N compartment linear mammillary model, with drug elimination occurring from any compartment or combination of compartments, can be developed from the equations of Benet (1972) by obtaining the inverse Laplace transform of the amount of drug in the central compartment by means of partial fractions. Thus for intravenous administration

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$$X_1 = D_1 \sum_{r=\alpha,\beta,\ldots n}^{n} \left| \frac{\prod_{i=2}^{N} (E_1 - r)}{\prod_{\substack{q=\alpha,\beta,\ldots n \\ q \neq r}}^{n} (q - r)} \right| e^{-rt} \quad .. \quad .. \quad .. \quad (1)$$

and for first order input into the central compartment

$$X_1 = K_a D_2 \sum_{r=K_a,\alpha,\ldots n}^{n} \left| \frac{\prod_{i=2}^{N} (E_1 - r)}{\prod_{\substack{q=K_a,\alpha,\beta,\ldots n \\ q \neq r}}^{n} (q - r)} \right| e^{-rt} \quad .. \quad .. \quad .. \quad (2)$$

where Π = the continuous product in which any term is equal to 1 when the index assumes a forbidden value, i.e. when q = r in the denominator; N = the number of reversibly connected compartments of which N–1 are reversibly connected to the central compartment; E_1 = the sum of the exit rate constants from compartment i; K_a = the first order rate constant for absorption into the central compartment; $\alpha,\beta \ldots n$ = hybrid rate constants where the number of terms (n) is determined by N; D_1 and D_2 = dose of drug administered.

As an example of the use of equations 1 and 2, consider the three compartment model (Fig. 1) proposed by Vaughan (1972) to describe the pharmacokinetics of pentazocine.

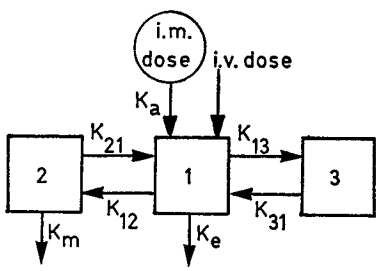

FIG. 1. A three-compartment model as proposed by Vaughan (1972) to describe the pharmacokinetic of pentazocine.

From this model (Fig. 1) N = 3, $E_1 = K_e + K_{13} + K_{12}$, $E_2 = K_m + K_{21}$ and $E_3 = K_{31}$ where K_e and K_m are the first order amount rate constants for urinary excretion and metabolism respectively. K_{ij} is the first order amount rate constant for drug transfer from compartment i to compartment j.

Substitution of these values into equations 1 and 2 yields:

(a) for intravenous administration,

$$X_{1iv} = \frac{D_1(E_2 - \alpha)(E_3 - \alpha)}{(\beta - \alpha)(\gamma - \alpha)} e^{-\alpha t} + \frac{D_1(E_2 - \beta)(E_3 - \beta)}{(\alpha - \beta)(\gamma - \beta)} e^{-\beta t}$$

$$+ \frac{D_1(E_2 - \gamma)(E_3 - \gamma)}{(\alpha - \gamma)(\beta - \gamma)} e^{-\gamma t}$$

(b) for intramuscular administration,

$$X_{1_{im}} = \frac{K_a D_2(E_2 - K_a)(E_3 - K_a)}{(\alpha - K_a)(\beta - K_a)(\gamma - K_a)} e^{-K_a t} + \frac{K_a D_2(E_2 - \alpha)(E_3 - \alpha)}{(K_a - \alpha)(\beta - \alpha)(\gamma - \alpha)} e^{-\alpha t}$$
$$+ \frac{K_a D_2(E_2 - \beta)(E_3 - \beta)}{(K_a - \beta)(\alpha - \beta)(\gamma - \beta)} e^{-\beta t} + \frac{K_a D_2(E_2 - \gamma)(E_3 - \gamma)}{(K_a - \gamma)(\alpha - \gamma)(\beta - \gamma)} e^{-\gamma t}$$

In the above example and in any other linear mammillary compartmental system (regardless of the value of N) with drug elimination (i.e. excretion and/or metabolism) occurring from any compartment, the plot of the logarithm of plasma drug concentration against time obtained after intravenous administration and after first order input into the central compartment will yield a final linear regression provided $\alpha, \beta \ldots n - 1 \gg n$. Thus for the three compartment model (Fig. 1) as t becomes large

$$X_{1_{iv}} = C_{p_{iv}} V_c \rightarrow \frac{D_1(E_2 - \gamma)(E_3 - \gamma)}{(\alpha - \gamma)(\beta - \gamma)} e^{-\gamma t} \quad .. \quad .. \quad .. \quad (3)$$

and similarly

$$X_{1_{im}} = C_{p_{im}} V_c \rightarrow \frac{K_a D_2(E_2 - \gamma)(E_3 - \gamma)}{(K_a - \gamma)(\alpha - \gamma)(\beta - \gamma)} e^{-\gamma t} \quad .. \quad .. \quad .. \quad (4)$$

where $C_{p_{iv}}$ and $C_{p_{im}}$ are the plasma concentrations of the drug after intravenous and intramuscular administration respectively and V_c is the volume of the central compartment*.

Writing $\frac{(E_2 - \gamma)(E_3 - \gamma)}{(\alpha - \gamma)(\beta - \gamma)V_c} = A^1$

and taking logarithms equations 3 and 4 become

$$\text{Ln } C_{p_{iv}} = \text{Ln } [D_1 A^1] - \gamma t \quad .. \quad .. \quad .. \quad (5)$$

and

$$\text{Ln } C_{p_{im}} = \text{Ln } \left[\frac{K_a D_2 A^1}{K_a - \gamma}\right] - \gamma t \quad .. \quad .. \quad .. \quad (6)$$

The final slopes of the logarithm of plasma drug concentration for both modes of drug administration (i.e. intravenous and intramuscular) thus give $-\gamma$. The ordinate intercepts of the ultimate regression lines at $t = 0$ give Ln $(A^1 D_1)$ and

Ln $\left[\frac{K_a A^1 D_2}{K_a - \gamma}\right]$ from which $A^1 D_1$ and $\frac{K_a A^1 D_2}{(K_a - \gamma)}$ may be evaluated.

The ratio of these quantities (R) is given by

$$R = \frac{D_1(K_a - \gamma)}{D_2 K_a} \quad .. \quad .. \quad .. \quad (7)$$

* When urinary excretion of a drug occurs from the central compartment, $\frac{dU_{iv}}{dt}\frac{1}{K_e}$ and $\frac{dU_{im}}{dt}\frac{1}{K_e}$ can replace $C_{p_{iv}} V_c$ and $C_{p_{im}} V_c$ in equations 3 and 4 respectively; where $\frac{dU}{dt}$ is the rate of urinary excretion of the drug and K_e is the first order rate constant for urinary excretion.

whence

$$K_a = \frac{-\gamma}{\left[R\frac{D_2}{D_1}\right]-1} \qquad .. \quad .. \quad .. \quad (8)$$

A general solution for K_a in any linear mammillary model can be expressed as follows:

$$K_a = \frac{-M_n}{\left[\frac{\text{intercept}_{1v}}{\text{intercept}_{1^0}}\frac{D_2}{D_1}\right]-1} \qquad .. \quad .. \quad .. \quad (9)$$

where M_n is the gradient of the terminal regression of either the logarithm of plasma concentrations or the logarithm of the urinary excretion rates of drug; intercept_{1v}, intercept_{1^0} are the antilogarithms of the respective ordinate intercepts at t = 0† after intravenous and first order input into the central compartment and D_1, D_2 are the doses of drug administered intravenously and by a first order input mode respectively.

The general expression (eqn 9) does not require any specific knowledge of the distribution kinetics (i.e. the number of compartments) or the elimination characteristics of the drug.

As an example of the use of equation 9 we have calculated the first order absorption rate constant for streptomycin after intramuscular administration. Using the plasma levels produced after both intravenous and intramuscular administration of streptomycin ($D_{1v} = D_{1m} = 0{\cdot}5$ g) as published by Wagner (1971), the following values were obtained: $\text{intercept}_{1v} = 44$; $\text{intercept}_{1m} = 58$ and the mean terminal regression (M_n) = 0·4105 h^{-1}. This gives a first order absorption rate constant (K_a) of 1·7 h^{-1}. A similar value ($K_a = 1{\cdot}48$ h^{-1}) was obtained by Wagner who assumed that the distribution of streptomycin in man is correctly described by a two compartment model in which drug elimination occurs solely from the central compartment.

In conclusion, the use of equation 9 provides a simple method for calculating the absolute value of the first order rate constant for the absorption of a drug into the central compartment without assuming a specific pharmacokinetic model.

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† The ratio (R) of the ordinate intercepts at t = 0 may be replaced by the ratio of any two perpendiculars drawn from any point on the terminal regressions to the abscissae provided that the two regression lines are parallel. In the case of non-parallelism the mean K_a should be estimated by using the ratios of $\overline{C}_{p_{iv}}$ to $\overline{C}_{p_1{}^0}$ at t = 0 and t = 24 h for the two values of the terminal regression and similarly by using the mean terminal regression. Provided the ratios of $\overline{C}_{p_{iv}}$ to $\overline{C}_{p_1{}^0}$ at t = 0 and t = 24 h are within 20% of each other then the mean K_a calculated as above, will be within ±5% of the value which would have been obtained with parallel regressions.

$\overline{C}_{p_{iv}}$ and $\overline{C}_{p_1{}^0}$ are the antilogs of the extrapolated values of the termined regression lines of Ln Cp *vs* time plots.