A GENERAL EQUATION FOR THE RATIO OF THE AREAS BELOW THE BLOOD OR PLASMA CONCENTRATION TIME-CURVES FOLLOWING INTRAVENOUS AND ORAL DRUG ADMINISTRATION AND ITS APPLICATION TO INTER-SUBJECT VARIATIONS IN DRUG ELIMINATION

D.P. VAUGHAN

Department of Clinical Pharmacology, University of Birmingham, Birmingham B15 2TJ

A. TRAINOR

Centre of Material Science, University of Birmingham, Birmingham B15 2TJ

- 1 When a drug is metabolized in the liver the total area under the plasma or blood concentration-time curve following oral drug administration is less than the area obtained after intravenous drug administration. This difference has been termed the 'first-pass effect'.
- 2 General equations for the areas below the blood or plasma concentration-time curve of a drug following intravenous and oral drug administration are derived.
- 3 An explicit expression for the ratio of areas below the blood or plasma concentration-time curves following intravenous and oral drug administration is derived.
- 4 By the application of the derived equations it is shown that the relative contribution of hepatic drug metabolism and urinary excretion to inter-subject variation in drug elimination can be easily ascertained.

Introduction

Most pharmacokinetic analyses of drug distribution and elimination assume a compartmental model in which the site of drug elimination via metabolism and excretion is the central compartment. With these pharmacokinetic models a reduction in the area below the blood level-time curve following oral drug administration as compared with that obtained after intravenous drug administration necessitates the assumption that orally administered drug is either incompletely absorbed or metabolized in the gastrointestinal tract. However, after portal vein drug infusion (e.g. aspirin, Harris & Riegelman, 1969; lignocaine, Boyes, Adams & Duce, 1970; pentazocine, Pittman & Portman, 1974) a comparable reduction in the area below the plasma-time curve is observed. This phenomenon has been termed the 'first-pass' effect and is attributed to the fact that drugs are exposed to the liver before reaching the

vascular sampling site following oral administration (Gibaldi, Boyes & Feldman, 1971).

These facts can be incorporated into a linear mammillary model; this requires orally administered drug to be absorbed into a compartment, other than the central compartment in which drug elimination occurs, whereas intravenously administered drug is absorbed directly into the central compartment. When urinary excretion of drug occurs an elimination rate constant is also required in the central compartment (Vaughan, 1972; Vaughan & Beckett, 1974; Gibaldi *et al.*, 1971).

We have derived an explicit relationship for the ratio of the areas below the plasma concentration-time curves or the blood concentration-time curves of a drug following intravenous and oral drug administration and have used the expression to ascertain the relative contributions of urinary excretion and metabolism to inter-subject variation in drug elimination.

Theory

Integrated equation for the central compartment in a linear mammillary pharmacokinetic model

For any linear mammillary model (see Figure 1), consisting of $N - 1$ compartments of which $N - 2$ are reversibly connected to the central compartment (designated compartment 1) with first-order drug

Figure 1 A general linear mamillary drug disposition model consisting of $N - 1$ compartments of which $N - 2$ are reversibly connected to the central compartment. Drug absorption occur irreversibly via first order processes from compartment N into all other compartment. Elimination of drug is allowed from any compartment. In the diagram j is an integer ($j = 3$ to $N - 1$) and the dotted brackets indicate the multiplicity of these compartments.

$$\text{By definition } E_1 = K_{10} + \sum_{j=2}^{N-1} K_{1j} \cdot E_j = K_{1j} + K_{j0} \quad (j = 2 \text{ to } N-1)$$

$$\text{and } E_N = \sum_{j=1}^N K_{Nj}.$$

absorption from an irreversibly connected compartment (designated compartment N) into all the other compartments and in which drug elimination is allowed from all or any combination of compartments the following system of differential equations with constant co-efficients (Equations 1, 2 & 3) can be written

$$\dot{X}_1 = -E_1 X_1 + \sum_{j=2}^{N-1} K_{j1} X_j + K_{N1} X_N \quad (\text{Equation 1})$$

$$\dot{X}_j = K_{j1} X_1 - E_j X_j + K_{Nj} X_N \quad (\text{Equation 2})$$

($j = 2$ to $N - 1$)

$$\dot{X}_N = -E_N X_N \quad (\text{Equation 3})$$

where

X_1, X_j ($j = 2$ to $N - 1$) and X_N = amount of drug in compartments 1, j and N respectively.

$\dot{X}_1, \dot{X}_j$ ($j = 2$ to $N - 1$) and $\dot{X}_N$ = differential of X_1, X_j and X_N with respect to time.

N = number of compartments in the kinetic model.

K_{1j} and K_{j1} ($j = 2$ to $N - 1$) = first-order amount rate constant for drug transfer from compartment 1 to compartment j and from compartment j to compartment 1 respectively.

K_{Nj} ($j = 1$ to $N - 1$) = first-order amount rate constant for drug absorption from compartment N to compartment j .

K_{j0} ($j = 1$ to $N - 1$) = first-order amount rate constant for drug elimination from compartment j . (See Figure 1.)

E_1, E_j and E_N = Sum of first-order exit rate constants from compartment 1, j and N respectively.

The set of linear differential equation (Equations 1, 2 and 3) have the matrix form of

$$\begin{pmatrix} \dot{X}_1 \\ \dot{X}_2 \\ \dot{X}_3 \\ \vdots \\ \dot{X}_{N-1} \\ \dot{X}_N \end{pmatrix} = \begin{pmatrix} -E_1 & K_{21} & K_{31} & \dots & K_{N-1,1} & K_{N1} \\ K_{12} & -E_2 & 0 & \dots & 0 & K_{N2} \\ K_{13} & 0 & -E_3 & \dots & 0 & K_{N3} \\ \vdots & \vdots & \vdots & & \vdots & \vdots \\ K_{1,N-1} & 0 & 0 & \dots & -E_{N-1} & K_{N,N-1} \\ 0 & 0 & 0 & \dots & 0 & -E_N \end{pmatrix} \begin{pmatrix} X_1 \\ X_2 \\ X_3 \\ \vdots \\ X_{N-1} \\ X_N \end{pmatrix} \quad (\text{Equation 4})$$

Writing the matrix of constant co-efficients in Equation 4 as (a_{st}) then

$$\begin{pmatrix} \dot{X}_1 \\ \dot{X}_2 \\ \dot{X}_3 \\ \vdots \\ \dot{X}_{N-1} \\ \dot{X}_N \end{pmatrix} = (a_{st}) \begin{pmatrix} X_1 \\ X_2 \\ X_3 \\ \vdots \\ X_{N-1} \\ X_N \end{pmatrix} \quad \dots (\text{Equation 5})$$

Letting $(a_{st})^{-1}$ be the inverse matrix of (a_{st}) and multiplying Equation 5 by $(a_{st})^{-1}$ then

$$\begin{pmatrix} X_1 \\ X_2 \\ X_3 \\ \vdots \\ X_{N-1} \\ X_N \end{pmatrix} = (a_{st})^{-1} \begin{pmatrix} \dot{X}_1 \\ \dot{X}_2 \\ \dot{X}_3 \\ \vdots \\ \dot{X}_{N-1} \\ \dot{X}_N \end{pmatrix} \quad \dots (\text{Equation 6})$$

Integrating Equation 6 with respect to time from $t = 0$ to $t = \infty$ then

$$\begin{pmatrix} \int_0^\infty X_1(dt) \\ \int_0^\infty X_2(dt) \\ \int_0^\infty X_3(dt) \\ \vdots \\ \int_0^\infty X_{N-1}(dt) \\ \int_0^\infty X_N(dt) \end{pmatrix} = (a_{st})^{-1} \begin{pmatrix} \int_0^\infty \dot{X}_1(dt) \\ \int_0^\infty \dot{X}_2(dt) \\ \int_0^\infty \dot{X}_3(dt) \\ \vdots \\ \int_0^\infty \dot{X}_{N-1}(dt) \\ \int_0^\infty \dot{X}_N(dt) \end{pmatrix} \quad \dots (\text{Equation 7})$$

The boundary conditions for the pharmacokinetic model are; at $t = 0$ and $t = \infty$ the amount of drug in compartments 1 to $N - 1$ is zero; at $t = 0$ and $t = \infty$ the amount of drug in compartment N is equal to the dose of administered drug and zero respectively, whence

$$\int_0^{\infty} \dot{X}_j(dt) = 0 \quad \dots \text{(Equation 8)}$$

$$(j = 1 \text{ to } N-1)$$

$$\int_0^{\infty} \dot{X}_N(dt) = -D \quad \dots \text{(Equation 9)}$$

Where D is the dose of drug. Combining Equations 7, 8 and 9 then

$$\begin{pmatrix} \int_0^{\infty} X_1(dt) \\ \int_0^{\infty} X_2(dt) \\ \int_0^{\infty} X_3(dt) \\ \vdots \\ \int_0^{\infty} X_N(dt) \end{pmatrix} = (a_{st})^{-1} \begin{pmatrix} 0 \\ 0 \\ 0 \\ \vdots \\ -D \end{pmatrix} \quad \dots \text{(Equation 10)}$$

Describing the elements of the reciprocal matrix $(a_{st})^{-1}$ as $\bar{a}_{ij}$ then Equation 10 becomes

$$\begin{pmatrix} \int_0^{\infty} X_1(dt) \\ \int_0^{\infty} X_2(dt) \\ \int_0^{\infty} X_3(dt) \\ \vdots \\ \int_0^{\infty} X_{N-1}(dt) \\ \int_0^{\infty} X_N(dt) \end{pmatrix} = \begin{pmatrix} \bar{a}_{11} & \bar{a}_{21} & \bar{a}_{31} & \dots & \bar{a}_{N-1,1} & \bar{a}_{N1} \\ \bar{a}_{12} & \bar{a}_{22} & \bar{a}_{32} & \dots & \bar{a}_{N-1,2} & \bar{a}_{N2} \\ \bar{a}_{13} & \bar{a}_{23} & \bar{a}_{33} & \dots & \bar{a}_{N-1,3} & \bar{a}_{N3} \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ \bar{a}_{1,N-1} & \bar{a}_{2,N-1} & \bar{a}_{3,N-1} & \dots & \bar{a}_{N-1,N-1} & \bar{a}_{N,N-1} \\ \bar{a}_{1N} & \bar{a}_{2N} & \bar{a}_{3N} & \dots & \bar{a}_{N-1,N} & \bar{a}_{NN} \end{pmatrix} \begin{pmatrix} 0 \\ 0 \\ 0 \\ \vdots \\ 0 \\ -D \end{pmatrix} = \begin{pmatrix} -\bar{a}_{N1}D \\ -\bar{a}_{N2}D \\ -\bar{a}_{N3}D \\ \vdots \\ -\bar{a}_{N,N-1}D \\ -\bar{a}_{NN}D \end{pmatrix} \quad \dots \text{(Equation 11)}$$

The area below the curve of drug amount against time in compartment one is given from Equation 11 as

$$\int_0^{\infty} X_1(dt) = -\bar{a}_{N1}D \quad \dots \text{(Equation 12)}$$

where $\bar{a}_{N1}$ is the element in the reciprocal matrix of $(a_{st})^{-1}$. This can be evaluated by the application of Equation 13 (see Appendix 1).

$$\bar{a}_{st} = \frac{A_{ts}}{\Delta} \quad \dots \text{(Equation 13)}$$

where $\bar{a}_{st}$ is the element of a reciprocal matrix and A_{ts} is the co-factor in the corresponding adjugate matrix of (a_{st}) . Δ is the determinant of the matrix (a_{st}) .

This procedure gives

$$\text{Area}^1 = \int_0^{\infty} X_1(dt) = \frac{(-1)^N D \begin{vmatrix} K_{21} & K_{31} & \dots & K_{N-1,1} & K_{N1} \\ -E_2 & 0 & \dots & 0 & K_{N2} \\ 0 & -E_3 & \dots & 0 & K_{N3} \\ \vdots & \vdots & & \vdots & \vdots \\ 0 & 0 & \dots & -E_{N-1} & K_{N,N-1} \end{vmatrix}}{\begin{vmatrix} -E_1 & K_{21} & K_{31} & \dots & K_{N-1,1} & K_{N1} \\ K_{12} & -E_2 & 0 & \dots & 0 & K_{N2} \\ K_{13} & 0 & -E_3 & \dots & 0 & K_{N3} \\ \vdots & \vdots & \vdots & & \vdots & \vdots \\ K_{1,N-1} & 0 & 0 & \dots & -E_{N-1} & K_{N,N-1} \\ 0 & 0 & 0 & \dots & 0 & -E_N \end{vmatrix}} \quad \dots \text{(Equation 14)}$$

Δ can be simply evaluated by dividing each row except the first by the j th term (i.e. the diagonal element) whence

$$\Delta = \prod_{j=2}^N (-1)^{N-1} E_j \begin{vmatrix} -E_1 & K_{21} & K_{31} & K_{N-1,1} & K_N \\ K_{12}/-E_2 & 1 & 0 & \dots & 0 & K_{N2}/-E_2 \\ K_{13}/-E_3 & 0 & 1 & \dots & 0 & K_{N3}/-E_3 \\ \vdots & \vdots & \vdots & & \vdots & \vdots \\ K_{1,N-1}/-E_{N-1} & 0 & 0 & \dots & 1 & K_{N,N-1}/-E_{N-1} \\ 0 & 0 & 0 & \dots & 0 & 1 \end{vmatrix} \quad \dots \text{(Equation 15)}$$

The determinant of Equation 15 is in the form of

$$\prod_A \begin{vmatrix} a_{11} & a_{21} & a_{31} & \dots & a_{N1} \\ a_{12} & 1 & 0 & \dots & a_{N2} \\ a_{13} & 0 & 1 & \dots & a_{N3} \\ \vdots & \vdots & \vdots & & \vdots \\ a_{1N} & 0 & 0 & \dots & 1 \end{vmatrix} \quad \dots \text{(Equation 16)}$$

which has the general solution of

$$\prod A \left[a_{11} - \sum_{i=2}^N a_{1i}a_{i1} + a_{1N} \sum_{i=2}^N a_{i1}a_{Ni} \right] \quad \dots \text{(Equation 17)}$$

Since in the determinant, Δ , $a_{1N} = 0$ then

$$\Delta = \prod_{j=2}^N (-1)^{N-1} E_j \left[-E_1 + \sum_{j=2}^{N-1} \frac{K_{1j}K_{j1}}{E_j} \right] \quad \dots \text{(Equation 18)}$$

The determinant in the numerator of Equation 14 has the general solution of

$$K_{N1} \prod_{j=2}^{N-1} E_j + \sum_{j=2}^{N-1} K_{j1}K_{Nj} \frac{\prod_{j=2}^{N-1} E_j}{E_j} \quad \dots \text{(Equation 19)}$$

Combining Equations 14, 18 & 19 and dividing through by $(-1)^N$ then

$$\text{Area}^1 = \int_0^\infty X_1(dt) = \frac{D \left[K_{N1} \prod_{j=2}^{N-1} E_j + \sum_{j=2}^{N-1} K_{j1}K_{Nj} \frac{\prod_{j=2}^{N-1} E_j}{E_j} \right]}{\left[\prod_{j=1}^N E_j - \prod_{j=2}^N E_j \sum_{j=2}^{N-1} \frac{K_{1j}K_{j1}}{E_j} \right]} \quad \dots \text{(Equation 20)}$$

Total area under the amount of drug in the central compartment-time curves after intravenous and oral drug administration by the application of equation 20

Intravenous administration If the vascular system being sampled is a component of the central compartment and drug absorption, from compartment N , only occurs into compartment 1 then this situation is comparable to intravenous drug administration. In this particular case only K_{N1} is operative and $K_{Nj} = 0$ ($j = 2$ to $N - 1$) thus $E_N = K_{N1}$ and area^1 ($\equiv \text{area}^{\text{iv}}$) is given by Equation 20 as

$$\text{Area}^{\text{iv}} = \frac{DK_{N1} \prod_{j=2}^{N-1} E_j}{\left[K_{N1} \prod_{j=1}^{N-1} E_j - K_{N1} \prod_{j=2}^{N-1} E_j \sum_{j=2}^{N-1} \frac{K_{1j}K_{j1}}{E_j} \right]} = \frac{D}{\left[E_1 - \sum_{j=2}^{N-1} \frac{K_{1j}K_{j1}}{E_j} \right]} \quad \dots \text{(Equation 21)}$$

Oral drug administration When drug absorption occurs into a compartment other than the central compartment (e.g. compartment 2) from which drug elimination occurs the situation is comparable to oral drug administration. In this particular case only E_{N2} is operative and $K_{Nj} = 0$ ($j = 1$ to $N - 1$, $j \neq 2$). Thus $E_N = K_{N2}$ and area^1 ($\equiv \text{area}^{\text{oral}}$) is given by Equation 20 as

$$\text{Area}^{\text{oral}} = \frac{DK_{21}K_{N2} \prod_{j=2}^{N-1} E_j}{\left[K_{N2} \prod_{j=1}^{N-1} E_j - K_{N2} \prod_{j=2}^{N-1} E_j \sum_{j=2}^{N-1} \frac{K_{1j}K_{j1}}{E_j} \right]} = \frac{DK_{21}}{E_2 \left[E_1 - \sum_{j=2}^{N-1} \frac{K_{1j}K_{j1}}{E_j} \right]} \quad \dots \text{(Equation 22)}$$

Equations 21 and 22 provide solutions for the total area (i.e. from $t = 0$ to $t = \infty$) below the amount of drug in the central compartment-time curve when the drug is absorbed into the central compartment (designated compartment 1) and into a compartment (designated compartment 2) other than the central one respectively.

At this stage in the derivation of an expression for the ratio of the total areas below the plasma or blood concentration-time curves following intravenous and oral drug administration (see Equations 27a and b) some relevant information can be obtained by inspection of Equations 21 and 22 viz (a) the absorption rate constant K_{Nj} ($j = 1$ and 2 for absorption into the central compartment and compartment 2 respectively) from compartment N is eliminated in the process of derivation. Consequently, the total areas as defined by Equations 21 and 22 are independent of the input rate constant; (b) the total area for a particular route of administration is proportional to the dose (D); (c) the area obtained after oral drug administration (Equation 22) is less than that obtained after intravenous drug administration (Equation 21). The latter results from the fact that Equation 22 differs from Equation 21 by the scalar K_{21}/E_2 and since $E_2 = K_{21} + K_{20}$ the scalar is less than unity.

Experimental observations after intravenous and hepatic portal drug administration (e.g. aspirin, Harris & Riegelman, 1969) support the above statements.

Relationship between the total area under the plasma or blood concentration-time curve after intravenous and oral drug administration by the application of equations 21 and 22

In equations 21 and 22 the total area below the amount of drug in the central compartment-time curves in a linear mammillary system consisting of $N - 1$ equilibrating compartments ($N =$ an unspecified interger) following intravenous and oral drug administration are expressed as a function of all the rate constants. However, the denominators of Equations 21 and 22 contain a common factor

$$\text{i.e., } E_1 - \sum_{j=2}^{N-1} \frac{K_{1j}K_{j1}}{E_j}$$

Consequently, division of Equation 21 and by Equation 22 eliminates the majority of transference rate constants (K_{1j} 's and K_{j1} 's) and exit rate constants (K_{j0} 's) which are composites of the E_j 's. Division of Equation 21 by Equation 22 yields for any linear mammillary system:

$$\frac{\text{Area under the amount of drug-time curve for the central compartment when drug absorption occurs into the central compartment}}{\text{Area under the amount of drug-time curve for the central compartment when drug absorption occurs into a compartment other than the central from which drug elimination occurs (designated compartment 2)}} = \frac{\text{Area}^{\text{iv}}}{\text{Area}^{\text{oral}}} = \frac{E_2}{K_{21}} = \frac{K_{21} + K_{20}}{K_{21}} \quad \dots (\text{Equation 23})$$

Inspection of Equation 23 demonstrates that the ratio $\text{Area}^{\text{iv}}/\text{Area}^{\text{oral}}$ is independent of all exit rate constants (i.e., K_{j0} , $j = 1$ to $N - 1$, $j \neq 2$; see Figure 1) excepting the one associated with the particular compartment into which orally administered drug was considered to be absorbed. Equation 23 is also independent of all transference rate constants excepting K_{21} . Since in the derivation of Equation 23 the compartment into which oral drug absorption occurred was designated compartment 2, for numerical convenience, Equation 23 can be expressed in a general form whilst retaining the numerical notation of 1 for the central compartment, thus

$$\frac{\text{Area}^{\text{iv}}}{\text{Area}^{\text{oral}}} = \frac{E_q}{K_{q1}} = \frac{K_{q1} + K_{q0}}{K_{q1}} = 1 + \frac{K_{q0}}{K_{q1}} \quad \dots (\text{Equation 24})$$

where $q =$ any interger other than 1.

In the derivation of Equation 24 the amount of drug in the central compartment has been used exclusively. However, in most pharmacokinetic experiments drug concentrations in either blood or plasma are obtained. These latter values are directly proportional to the amount of drug in the central compartment by the central compartment volume (amount of drug in the central compartment $\equiv VC_{p,b}$; where V is the volume of the central compartment and $C_{p,b}$ is either the plasma or blood concentrations of the drug). The central compartment volume is a kinetic parameter of the pharmacokinetic model (Riegelman, Loo & Rowland, 1968) and is defined as that volume which appears to be in spontaneous equilibrium with the vascular sampling site. When blood concentrations of a drug are measured the central compartment volume is defined by reference to blood. If plasma is used as the representative fluid of the central compartment the erythrocytes are not, by definition, a component of this compartment.

Since

$$\text{Area}^{\text{iv}} = V_p \int_0^\infty C_p^{\text{iv}} = V_b \int_0^\infty C_b^{\text{iv}} \quad \dots (\text{Equation 25})$$

and

$$\text{Area}^{\text{oral}} = V_p \int_0^\infty C_p^{\text{oral}} = V_b \int_0^\infty C_b^{\text{oral}} \quad \dots (\text{Equation 26})$$

where, V_p and V_b = the volume of the central compartment defined in reference to plasma and blood respectively. C_p and C_b = the plasma and blood drug concentrations respectively. Substitution of Equations 25 and 26 into Equation 24 gives:

$$\frac{\text{Area}^{\text{iv}}}{\text{Area}^{\text{oral}}} = \frac{V_p \int_0^\infty C_p^{\text{iv}}}{V_p \int_0^\infty C_p^{\text{oral}}} = \frac{\text{Total area under the plasma concentration-time curve after intravenous drug administration}}{\text{Total area under the plasma concentration-time curve after oral drug administration}} = 1 + \frac{K_{q0}}{K_{q1}} \quad \dots (\text{Equation 27a})$$

$$\frac{\text{Area}^{\text{iv}}}{\text{Area}^{\text{oral}}} = \frac{V_b \int_0^\infty C_b^{\text{iv}}}{V_b \int_0^\infty C_b^{\text{oral}}} = \frac{\text{Total area under the blood concentration-time curve after intravenous drug administration}}{\text{Total area under the blood concentration-time curve after oral drug administration}} = 1 + \frac{K_{q0}}{K_{q1}} \quad \dots (\text{Equation 27b})$$

When the urinary excretion of unchanged drug is related to the plasma or blood concentration of a drug the cumulative urinary excretion of unchanged drug following intravenous and oral drug administration can replace the total areas under the plasma or blood concentration-time curves as used in Equations 27a and b. This is possible in a linear system since for any route of drug administration

$$\frac{dU}{dt} = K_e \times \begin{matrix} \text{amount of drug in the} \\ \text{central compartment} \end{matrix} = K_e V_p C_p = K_e V_b C_b \quad \dots (\text{Equation 28})$$

where, dU/dt = the rate of urinary excretion of unchanged drug and K_e = the urinary excretion rate constant.

Integrating Equation 28 with respect to time then

$$\int_0^\infty \frac{dU}{dt} = K_e V_p \int_0^\infty C_p = K_e V_b \int_0^\infty C_b = \begin{matrix} \text{cumulative urinary excretion of unchanged} \\ \text{drug from } t = 0 \text{ to } t = \infty \end{matrix} \quad \dots (\text{Equation 29})$$

Substituting the cumulative urinary excretion of unchanged drug (see Equation 29) obtained after intravenous and oral drug administration into either Equation 27a or 27b gives

$$\frac{\text{Total amount of unchanged drug excreted in urine after intravenous drug administration}}{\text{Total amount of unchanged drug excreted in urine after oral drug administration}} = 1 + \frac{K_{q0}}{K_{q1}} \quad \dots (\text{Equation 30})$$

If different doses are used by the two routes of administration the ratio of areas as used in Equations 27a and b and the ratio of cumulative urinary excretion of unchanged drug (Equation 30) are multiplied by $D^{\text{iv}}/D^{\text{oral}}$, where D^{iv} and D^{oral} are the respective drug doses administered by the intravenous and oral route. The latter assumes that within the context of a single route of administration the area is directly proportional to the dose; the validity of which has already been demonstrated (see Equations 21 and 22).

Throughout the derivation of Equations 27a, 27b and 30 the liver has been regarded as an integral part of a compartment other than the central compartment (i.e. compartment 2, subsequently generalized to compartment q). In physiological terms K_{q0} represents drug metabolism in the liver and K_{q1} represents the ratio of liver blood or plasma flow to the volume of the liver compartment. K_{10} as depicted in the

general pharmacokinetic model (see Figure 1) can be regarded as being the rate constant for urinary excretion of drug (K_e).

It should be noted that the derived relationships (Equations 27a, 27b and 30) are entirely independent of drug exit rate constants from any compartment in the pharmacokinetic model other than the compartment which contains the liver and that when the liver is not regarded as an integral part of the central compartment the ratio of the total areas below the blood or plasma concentration-time curve will only be unity when no drug metabolism occurs in the liver. Also the relationships (Equations 27a, 27b and 30) are independent of the number of compartments in the pharmacokinetic model and drug elimination can occur from any compartment or combination of compartments.

Application of equations 27a, 27b and 30 to the assessment of inter-subject variations in drug metabolism by the liver

With some drugs (e.g. pentazocine, Vaughan & Beckett, 1974; nortriptyline, Alexanderson, Sjoqvist & Price Evans, 1969) considerable inter-subject variations in blood concentrations achieved with a single dose or multiple doses of drug are observed. These differences can be ascribed to either individual variations in drug metabolism by the liver or other tissues or to variations in drug excretion via the urine. Since the derived equations (Equations, 27a, 27b and 30) are independent of the urinary excretion rate constant for unchanged drug, extra hepatic drug metabolism and the absorption mode of a drug, it is relatively simple to obtain a numerical solution of K_{q0}/K_{q1} . These latter two rate constants govern the percentage of drug eliminated by metabolism in the liver regardless of the route of administration.

The relative contribution of hepatic metabolism to the inter-subject variations in pentazocine elimination is now calculated to illustrate the use of the derived equations. After intravenous and oral administration of pentazocine, as aqueous solutions, a three-fold inter-subject variation in the blood concentrations and the cumulative urinary excretion of unchanged drug has been observed (Beckett *et al.*, 1970; see Table 1). The distribution of pentazocine has been described by a three compartmental linear pharmacokinetic model (i.e. $N - 1 \equiv 3$) consisting of a central compartment in equilibrium with a metabolic compartment and a deep tissue compartment (Vaughan & Beckett, 1974). However, the distribution characteristics of the drug are not required for the application of the derived equations (Equations 27a or 27b or 30).

Table 1 Cumulative urinary excretion of pentazocine after intravenous administration in four subjects and the calculated values of K_{q0}/K_{q1}

Subject	Cumulative urinary excretion of pentazocine (% dose in 36 h) after intravenous administration*	Ratio of cumulative urinary excretion after intravenous and oral administration	K_{q0}/K_{q1}
III	23.2	1.7	0.7
II	15.6	1.8	0.8
I	12.6	3.1	2.1
IV	8.0	3.1	2.1

* Experimental data from Beckett *et al.* (1970) and Vaughan (1972).

Under conditions of an acidic urinary pH, the urinary excretion of pentazocine is completed in 24 h and the urinary excretion of drug is directly proportional to the blood concentrations of the drug (Beckett *et al.*, 1970; Vaughan, 1972; Vaughan & Beckett, 1974). Consequently, Equation 30 is applicable for the calculation of K_{q0}/K_{q1} (see Table 1). Comparison of the calculated values of K_{q0}/K_{q1} obtained from the ratio of cumulative urinary excretions of pentazocine following intravenous and oral administration (Table 1) substantiate that the overall three-fold variation in urinary excretion is caused by a variation in the amount of drug metabolized in the liver. However, the 1.5 variation observed between subjects I and IV can be ascribed to a variation in the elimination rate via the urine since the ratio of K_{q0}/K_{q1} is identical for these two subjects.

Discussion

Often when considering inter-subject variations in drug elimination the plasma drug half-life ($T_{1/2}$) is used as an index of drug elimination. When applying this method the tacit assumption is made that the body behaves as a single homogenous compartment. However, the half-life is a hybrid rate constant and its use can result in erroneous conclusions (Vaughan, 1972).

Alternatively, complicate pharmacokinetic models can be proposed to describe drug distribution and elimination which provide numerical solutions for the rates of urinary excretion (K_e) and metabolism (K_{q0}). This involves using either non-linear least squares digital programs or analogue computers. Unfortunately, even the latter methods do not give unique solutions for the rate constants. Furthermore, the method is erroneous unless the correct model is ascribed to the experimental data.

When a drug is subjected to 'first-pass' metabolism in the liver there is little point in obtaining an exact numerical value for the metabolic rate constant since this parameter alone does not determine the amount of drug metabolized. The amount of drug eliminated by metabolism is determined by both K_{q0} and K_{q1} (see Equation 24).

Since Equations 27a and 27b are general and independent of both the number of compartments in the pharmacokinetic model (Figure 1) and the rate of urinary excretion (K_e) their use obviates the necessity to ascribe a detailed pharmacokinetic model for drug disposition and the subsequent use of computers. Their use provides a direct solution for the ratio of rate constants which govern the amount of drug eliminated by metabolism in the liver.

When the urinary excretion rate of unchanged drug is directly proportional to blood or plasma concentrations of drug the data required for

Equations 27a and 27b is simply obtained by measuring the cumulative urinary excretion of drug (see Equation 30). This latter simplification is important when investigating inter-subject variations in drug metabolism since blood concentrations of drug are not required.

Application of Equations 27a, 27b and 30 can be extended to the influence of one drug on the pharmacokinetics of another drug. For example if a drug is thought to induce the metabolism of another drug the hypothesis can be verified or contradicted by obtaining values for K_{q0}/K_{q1} prior to and during treatment with the suspected inducing agent. No change in the ratio K_{q0}/K_{q1} indicates the absence of liver enzyme induction. In the absence of a change in K_{q0}/K_{q1} changes in the amount of drug and its metabolites excreted in urine are likely to have been produced by either a variation in drug metabolism in some tissue other than liver or by a change in the urinary excretion of unchanged drug.

It is also possible to use the intravenous/oral ratio (Equations 27a, 27b and 30) to estimate changes in liver metabolism in conditions involving liver and kidney failure.

Drug interactions in the gastro-intestinal tract which reduce the fraction of an oral dose actually absorbed invalidate the application of Equations 27a, 27b and 30. However, the amount of drug absorbed can be calculated from the data obtained following oral and intravenous drug administration (see Appendix II). In this case the oral dose is multiplied by the fraction of dose actually absorbed prior to applying Equations 27a, 27b and 30.

D.P.V. is supported by a grant from Roussel Laboratories Ltd. We thank Professor O.L. Wade and Dr M. Mitchard for their interest.

Appendix I

The following example is used to illustrate the evaluation of an element in an inverse matrix.

Let (a_{st}) be a matrix and $(a_{st})^{-1}$ its inverse so that

$$(a_{st}) = \begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix} \text{ and } (a_{st})^{-1} = \begin{pmatrix} \bar{a}_{11} & \bar{a}_{12} & \bar{a}_{13} \\ \bar{a}_{21} & \bar{a}_{22} & \bar{a}_{23} \\ \bar{a}_{31} & \bar{a}_{32} & \bar{a}_{33} \end{pmatrix}$$

A submatrix of (a_{st}) can be obtained by omitting rows and column t from the original matrix. The determinant of this submatrix is the minor of a_{st} . The signed minor A_{st} , i.e., the co-factor, is obtained by

$$A_{st} = [(-1)^{s+t}] \times [\text{minor of } a_{st}]$$

whence

$$A_{11} = (-1)^{1+1} \begin{vmatrix} a_{22} & a_{23} \\ a_{32} & a_{33} \end{vmatrix} \quad A_{12} = (-1)^{1+2} \begin{vmatrix} a_{21} & a_{23} \\ a_{31} & a_{33} \end{vmatrix} \quad \text{and} \quad A_{13} = (-1)^{1+3} \begin{vmatrix} a_{21} & a_{22} \\ a_{31} & a_{32} \end{vmatrix}$$

in a similar manner all the other co-factors can be obtained. The matrix of co-factors (A_{st}) is given by

$$(A_{st}) = \begin{pmatrix} A_{11} & A_{12} & A_{13} \\ A_{21} & A_{22} & A_{23} \\ A_{31} & A_{32} & A_{33} \end{pmatrix}$$

From (A_{st}) another matrix (A_{ts}) can be obtained by changing the rows into columns and columns into rows, this transposition gives the adjugate matrix (A_{ts}) whence

$$\text{adjugate matrix} = (A_{ts}) = \begin{pmatrix} A_{11} & A_{21} & A_{31} \\ A_{12} & A_{22} & A_{32} \\ A_{13} & A_{23} & A_{33} \end{pmatrix}$$

The product of a matrix and adjugate matrix is the determinant, Δ , of the original matrix multiplied by a unit matrix of the same order.

Whence

$$(a_{st})^{-1} = \frac{(A_{ts})}{\Delta} = \begin{pmatrix} A_{11} & A_{21} & A_{31} \\ A_{12} & A_{22} & A_{32} \\ A_{13} & A_{23} & A_{33} \end{pmatrix} / \Delta \quad \dots (\text{Equation 1a})$$

Suppose we wish to evaluate the element a_{13} in the inverse matrix then from 1a

$$\bar{a}_{13} = \frac{\text{the co-factor of the third row in column 1 of the adjugate matrix}}{\Delta}$$

by inspection of 1a we find $\bar{a}_{13} = A_{13}/\Delta$ where A_{13} is a co-factor of the original matrix as described previously.

Appendix 2

When a drug is eliminated from the body by urinary excretion and hepatic metabolism the following equation (Vaughan, unpublished observations) can be used to obtain the fraction of an oral dose actually absorbed

$$\frac{D^{\text{oral}} \text{ area}^{\text{oral}}}{D^{\text{iv}} \text{ area}^{\text{iv}}} = \left(\frac{f \cdot HP}{HP + \frac{f \cdot D^{\text{oral}}}{\text{area}^{\text{oral}}}} \right) \left(1 + \frac{RC}{HP} \right)$$

where $\text{area}^{\text{oral}}$ and area^{iv} = the total area under the blood concentration-time curve after oral and intravenous drug administration respectively; HP = hepatic blood flow; RC = renal clearance and f = the fraction of the oral dose actually absorbed.

The equation presented is an extension of the work of Gibaldi, Boyes & Feldman (1971) in which a detail account of the operation and applications of a similar equation are given.

References

- ALEXANDERSON, B., SJOQVIST, F. & PRICE EVANS, D.A. (1969). Steady-plasma levels of nortriptyline in twins: Influence of genetic factors and drug therapy. *Br. med. J.*, **4**, 764-768.
- BECKETT, A.H., KOUROUNAKIS, P., VAUGHAN, D.P. & MITCHARD, M. (1970). The absorption, blood concentrations and excretion of pentazocine after oral, intramuscular or rectal administration to man. *J. Pharm. Pharmac.*, **22**, 1695-1745.
- BOYES, R.N., ADAMS, H.J. & DUCE, B.R. (1970). Oral

- absorption and disposition kinetics of lignocaine hydrochloride in dogs. *J. Pharmac. exp. Ther.*, **174**, 1-8.
- GIBALDI, M., BOYES, R.N. & FELDMAN, S. (1971). Influence of first-pass effect on availability of drugs on oral administration. *J. Pharm. Sci.*, **60**, 1338-1340.
- HARRIS, P.A. & RIEGELMAN, S. (1969). Influence of the route of administration on the area under the plasma concentration time curve. *J. Pharm. Sci.*, **58**, 71-75.
- PITTMAN, K.A. & PORTMAN, G.A. (1974). Pharmacokinetics of pentazocine in the rhesus monkey. *J. Pharm. Sci.*, **63**, 84-89.
- RIEGELMAN, S., LOO, J. & ROWLAND, M. (1968). Concept of a volume of distribution and possible errors in evaluation of this parameter. *J. Pharm. Sci.*, **57**, 128-133.
- VAUGHAN, D.P. (1972). *Biopharmaceutical and biochemical studies on some analgesics*. Ph.D. Thesis, University of London.
- VAUGHAN, D.P. & BECKETT, A.H. (1974). An analysis of the inter-subject variation in the metabolism of pentazocine. *J. Pharm. Pharmac.*, **26**, 789-798.

(Revised October 15, 1974)