Department of Neurology,
Cornell Medical Center,
The New York Hospital, 525 East 68th Street,
New York, N.Y. 10021, U.S.A.

BENGT HINDFELT*
FRED PLUM

November 20, 1974

REFERENCES

BESSMAN, S. P. & BESSMAN, A. N. (1955). *J. clin. Invest.*, **34**, 622–632.

FOLBERGEROVA, J. (1964). *Physiol. Bohemoslov.* **13**, 21–31.

FOLBERGEROVA, J., PASSONEAU, J. V., LOWRY, O. H. & SCHULTZ, D. W. (1969). *J. Neurochem.*, **16**, 191–200.

GERSHOFF, S. N. (1956). *Am. J. Physiol.*, **184**, 43–50.

HINDFELT, B. (1973). *Scand. J. clin Lab. Invest.*, **31**, 289–299.

KARR, N. N. & HENDRICKS, E. L. (1949). *Am. J. med. Sci.*, **218**, 302–210.

PACE, J. & MCDERMOTT, E. E. (1952). *Nature*, **169**, 415–416.

RAO, S. L. N. & MEISTER, A. (1972). *Biochem.*, **11**, 1123–1131.

WARREN, K. S. & SCHENKER, S. (1964). *Lab. J. clin. Med.*, **64**, 442–449.

WEIL-MALHERBE, H. (1962). In *Neurochemistry* Editors: Elliott, K. A. C., Page, I. H. and Quastel, J. H., Springfield, Illinois: Charles C. Thomas.

WORCEL, A. & ERECINSKA, M. (1962). *Biochim. biophys. Acta*, **65**, 27–33.

*Present address and address for correspondence: Department of Neurology, University Hospital Lund, S–221 85 Lund, Sweden.

Estimation of biological availability after oral drug administration when the drug is eliminated by urinary excretion and metabolism

Most drugs undergo "first-pass" metabolism in the liver after oral administration and the reduction of the total area below the blood concentration-time curve, following oral drug administration, compared with that obtained after intravenous drug administration cannot be regarded as a correct estimate of biological availability.

Pharmacokinetic models (see Fig. 1) that account for the "first-pass" effect require orally administered drug to be absorbed into a peripheral compartment from which drug elimination occurs, whereas intravenously given drug is absorbed directly into the central compartment (Gibaldi, Boyes & Feldmann, 1971; Vaughan & Beckett, 1974). In these pharmacokinetic models the vascular site being sampled is regarded as an integral part of the central compartment and the liver as an integral part of the peripheral compartment.

Gibaldi & others (1971) have derived an expression (eqn 1) by which the fraction of an orally administered dose absorbed into the hepatic portal system and the extent of "first-pass" metabolism can be calculated.

$$\frac{\text{Area}^{\text{oral}}}{\text{Area}^{\text{iv}}} = \frac{\text{F (flow rate)}}{\text{flow rate} + \text{F dose/area}^{\text{oral}}} \qquad (1)$$

In equation 1, flow rate is the hepatic blood flow, $\text{area}^{\text{oral}}$ and area^{iv} are the total areas below the blood level-time curve obtained after oral and intravenous drug administration respectively, dose is the oral drug dose and F is the fraction of the oral dose absorbed. When applying equation 1 the mean hepatic blood flow of 1·53 litre min^{-1} (Bradley, Ingelfinger & Bradley, 1952) is used.

Equation 1 has been extensively used in biopharmaceutical studies (Gibaldi & others, 1971; Perrier, Gibaldi & Boyes, 1973; Johnsson, Norrby & Solvell, 1967; Boyes, Scott & others, 1971; Cohen, Bakke & Davies, 1974).

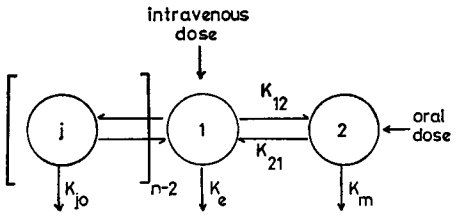

FIG. 1. A general linear mammillary model consisting of n compartments, of which n–1 are reversibly connected to the central compartment. Drug elimination is allowed from any compartment.

By definition $E_1 = K_e + \sum_{j=2}^{n} K_{1j}$; $E_2 = K_{21} + K_m$ and $E_j = K_{j1} + K_{j0}$ for $j = 3$ to n. K_e and K_m are the first-order rate constants for urinary excretion and drug metabolism respectively; K_{1j} and K_{j1} are the first-order constants for drug transference from compartments 1 to j and from compartment j to 1 respectively; K_{j0} is the first-order rate constant for drug elimination from compartment j for $j = 3$ to n.

The purpose of this communication is to demonstrate that eqn 1 is only strictly applicable to drugs that are *exclusively* eliminated from the body by hepatic metabolism and to derive an equation applicable to drugs that are eliminated by urinary excretion and hepatic metabolism.

The ratio of the total areas below the blood level-time curves after oral ($area^{oral}$) and intravenous ($area^{iv}$) drug administration, or the ratio of the cumulative urinary excretion of unchanged drug, normalized in respect to the doses, is given by:

$$\frac{Area^{oral}}{Area^{iv}} = \frac{K_{21}F}{K_{21} + K_m} = \frac{K_{21}F}{E_2} \qquad (2)$$

In eqn 2 K_{21} is the first-order rate constant for drug transfer from the peripheral compartment (designated compartment 2) to the central compartment (designated compartment 1) and K_m is the first-order rate constant for drug metabolism or elimination in compartment 2 (see Fig. 1); F is the fraction of the oral dose absorbed.

The expression (eqn 2) is true for all linear mammillary models of the type shown in Fig. 1 and is independent of both the absorption rate constant and the urinary excretion rate constant (Vaughan & Trainor, 1975).

Equation 1 can be derived from eqn 2; this requires the multiplication of the numerator and denominator on the right hand side of eqn 2 by V_2 (the volume of compartment 2) and substitution of $K_{21}V_2$ for flow rate (Bischoff & Dedrick, 1968). Assuming the identity of $K_mV_2 \equiv F$ dose/$area^{oral}$ (Gibaldi & others, 1971) then substitution into eqn 2 results in eqn 1.

However, the total area below the blood level-time curve following oral drug administration is given by eqn 3 (Vaughan & Trainor, 1975) as:

$$Area^{oral} = \frac{F\,DK_{21}}{V_1E_2\left[E_1 - \sum_{j=2}^{n} \frac{K_{1j}K_{j1}}{E_j}\right]} \qquad (3)$$

In eqn 3; D is the dose of orally administered drug; E_1, E_2 and E_j are the sums of first-order exit rate constants out of compartments 1, 2 and j respectively ($j = 3$ to n); K_{1j} and K_{j1} are the respective first-order rate constants for drug transfer from compartment 1 to j and from compartment j to 1; n is the number of compartments in the phamacokinetic model (see Fig. 1).

Assuming that drug elimination occurs only from compartments 1 and 2 (i.e. via metabolism and urinary excretion) then in eqn 3 $E_j = K_{j1}$ for $j = 3$ to n. From eqn 3 by using the identity $V_1/V_2 = K_{21}/K_{12}$ it can be shown that $K_m V_2$ = F dose/ $\text{area}^{\text{oral}}$ only when

$$E_1 = \sum_{j=2}^{n} K_{1j}$$

This latter condition does not allow drug to be excreted from the central compartment via the urine (i.e. the total dose of administered drug is eliminated by metabolism). Clearly this condition does not apply for most drugs.

When urinary excretion as well as drug metabolism occurs in the body, the ratio $FD/\text{area}^{\text{oral}}$ is given by eqn 3 as

$$\frac{F.D.}{\text{Area}^{\text{oral}}} = \frac{V_1 E_2}{K_{21}} \left[K_e + K_{12} - \frac{K_{12}K_{21}}{E_2} \right] = V_2 \left[K_m + \frac{K_e E_2}{K_{12}} \right] \quad (4)$$

The last term in eqn 4 is obtained by substitution of V_2K_{21}/K_{12} for V_1. Using eqn 4 and the identity flow rate $= V_2K_{21}$ then:

$$\frac{\text{Flow rate}}{\text{Flow rate} + \frac{\text{Dose. F}}{\text{area}^{\text{oral}}}} \equiv \frac{K_{21}}{E_2 \left(1 + \frac{K_e}{K_{12}}\right)} \quad (5)$$

Solving eqn 5 for K_{21}/E_2 and substitution into eqn 2 gives:

$$\frac{\text{Area}^{\text{oral}}}{\text{Area}^{\text{iv}}} = \frac{K_{21}.F}{E_2} = F \left(\frac{\text{flow rate}}{\text{flow rate} + \frac{\text{Dose.F}}{\text{area}^{\text{oral}}}} \right) \left(1 + \frac{K_e}{K_{12}} \right) \quad (6)$$

The last term in eqn 6, $\frac{K_e}{K_{12}}$ is identical to $\frac{K_e V_1}{K_{12} V_1}$. Since $V_1/V_2 = K_{21}/K_{12}$ and $V_2K_{21} \equiv$ flow rate then V_1K_{12} = flow rate. The term K_eV_1 is identical to the renal clearance of a drug. Renal clearance is the gradient of a plot of urinary excretion rate of unchanged drug versus the blood concentrations of drug. Substitution of these latter two identities into eqn 6 gives

$$\frac{\text{Area}^{\text{oral}}}{\text{Area}^{\text{iv}}} = F \left(\frac{\text{flow rate}}{\text{flow rate} + \frac{\text{F.dose}}{\text{area}^{\text{oral}}}} \right) \left(1 + \frac{\text{renal clearance}}{\text{flow rate}} \right) \quad (7)$$

The equation presented is general and independent of the number of compartments in the disposition model (see Fig. 1). If the fraction of the oral dose absorbed is equated to one then eqn 8 can be used to estimate the extent of hepatic "first pass" metabolism in situations where for various reasons it is not possible to administer an intravenous drug dose.

To estimate F, the fraction of an oral dose that is absorbed into the hepatic portal system, a rearranged form of eqn 7 can be useful, viz:

$$F = \frac{\text{Area}^{\text{oral}}.\ \text{flow rate}}{\left[\text{Area}^{\text{iv}} \left(1 + \frac{\text{renal clearance}}{\text{flow rate}} \right).\ \text{flow rate} \right] - (\text{dose})} \quad (8)$$

As is indicated by eqn 8, neglect of renal drug clearance results in underestimation of the percentage of an oral drug dose not absorbed (i.e. (1–F).100). The following abstract example illustrates the importance of renal clearance values in these calculations. Consider two drugs with respective renal clearances of 120 and 500 ml min^{-1} whose total areas below the blood concentration time curves after oral and intravenous administration of a unit dose are 0·373 and 1·12 respectively. Then by neglect of renal clearances the amount of drug unabsorbed after oral administration is calculated (eqn 1) as 20%, whereas by application of eqn 8, 32 (renal clearance = 120 ml min^{-1}) and 53% (renal clearance = 500 ml min^{-1}) of the drug dose remains unabsorbed.

Since in eqn 8 the $area^{iv}$, $area^{oral}$ and renal clearance are subject to individual variations the estimated value of F is also subject to statistical variation. Since these variables are not directly controllable their influence can be best diminished by increasing the number of determinations to obtain a better estimate of F. An estimation of the expected standard deviation of F can be obtained by considering the three variables as stochastically independent and using the addition theorem: this gives $\delta_F = \sqrt{2\delta^2_{iv} + \delta^2_{or} + \delta^2_{rc}}$ where δ^2_{iv}, δ^2_{or} and δ^2_{rc} are the respective variances of $area^{iv}$, $area^{oral}$ and renal clearance. Assuming a standard deviation of 5–10% about the mean values of $area^{iv}$, $area^{oral}$ and renal clearance then δ_F would have a standard deviation between 10 to 20% about its mean value. Standard deviations of 3% about the mean cumulative urinary excretion of pentazocine, codeine and dihydrocodeine, under conditions of an acidic urinary pH, have been observed (Vaughan, 1972) and recent observations on the renal clearance of pethidine (Vaughan & Chan, unpublished data) indicate a similar deviation. Consequently, it would seem that standard deviations of between 5–10% for the three variables are realistic.

The application of eqns 8 and 9 assume that the total area under the blood concentration-time curves for both oral and intravenous drug administration are linearly related to the dose (i.e., the principle of superposition applies). Some drugs show dose dependent kinetics and their availability increase with dose. However, the applications of eqns 7 and 8 are valid provided the doses used lie within a range in which the total areas under the blood-concentration time curves for both oral and intravenous administration are apparantly linear with respect to the dose and parallel to each other.

In conclusion, despite urinary excretion of unchanged drug the blood flow equations (eqns 7 and 8) provide a minimum estimation of the "first-pass" effect and can be useful for estimating the biological availability of orally administered drugs.

School of Pharmacy and Biology,
Sunderland Polytechnic, Chester Road,
Sunderland SR1 3SD, U.K.

D. P. VAUGHAN

October 11, 1974

REFERENCES

BISCHOFF, K. D. & DEDRICK, R. L. (1968). *J. pharm. Sci.*, **57**, 1346–1351.

BOYES, R. N., SCOTT, D. B., JEPSON, P. J., GOODMAN, M. J. & JULIAN, D. G. (1971). *Clin. Pharmac. Ther.*, **12**, 105–116.

BRADLEY, S. E., INGELFINGER, F. J. & BRADLEY, G. P. (1952). *Circulation*, **5**, 419–429.

COHEN, G. M., BAKKE, O. M. & DAVIES, D. S. (1974). *J. Pharm. Pharmac.*, **26**, 348–357.

GIBALDI, M., BOYES, R. N. & FELDMANN, S. (1971). *J. pharm. Sci.*, **60**, 1338–1340.

JOHNSSON, G., NORRBY, A. & SOLVELL, L. (1967). *Acta. pharmac. tox.*, **25**, *Suppl.*, **2**, 95–105.

PERRIER, D., GIBALDI, M. & BOYES, R. N. (1973). *J. Pharm. Pharmac.*, **25**, 256–257.

VAUGHAN, D. P. (1972). Ph.D. Thesis, University of London.

VAUGHAN, D. P. & BECKETT, A. H. (1974). *J. Pharm. Pharmac.*, **26**, 789–798.

VAUGHAN, D. P. & TRAINOR, A. (1975). *Br. J. clin. Pharmac.*, in the press.