Prediction of systemic availability from plasma-level data after oral drug administration

The extent to which an orally administered dose of a drug reaches the systemic circulation intact can be defined as its systemic or physiologic availability. Determination of systemic availability usually requires that the area under the plasma concentration-time curve following oral administration be compared to the corresponding area after the intravenous administration of an equal dose of the drug being studied. However, many drugs cannot be administered intravenously and availability must be determined relative to some standard oral dosage form such as an aqueous solution. Although the test dosage form may have a relative availability of 100%, its systemic availability may be substantially less if the drug under study is subject to appreciable metabolism on its initial pass through the liver. Therefore, it would be desirable to be able to predict the extent to which an orally administered drug reaches the systemic circulation from plasma concentration-time data.

Equations have been developed to estimate the extent to which an orally administered drug is metabolized on its first-pass through the liver (Gibaldi, Boyes & Feldman, 1971). These investigators have pointed out that the following relation may be used to predict the maximum fraction of an orally administered drug reaching the systemic circulation.

$$f = \frac{\text{Flow Rate}}{\text{Flow Rate} + \text{Dose}/\int_0^\infty C_o dt} \quad .. \quad .. \quad .. \quad (1)$$

where f represents the fraction of an orally administered drug that actually reaches the systemic circulation, Flow Rate is the hepatic blood flow rate, "Dose" is the oral dose, and $\int_0^\infty C_o\, dt$ is the area under the plasma concentration versus time curve from time $t = 0$ to $t = \infty$ after oral drug administration.* This equation should yield a reasonable estimate of the systemic availability of a drug administered by the oral route provided the drug is eliminated only by apparent first-order biotransformation in the liver and the dose of the drug is completely absorbed. If the latter assumption is not valid, the above equation may be modified to account for that fraction of the oral dose which is not absorbed (Gibaldi & others, 1971).

A recent report by Wagner, Welling & others (1972) on the availability of propoxyphene indicated that the availability of various capsule forms was 100% relative to a solution of propoxyphene. However, application of the above equation to the average data presented by Wagner & others (1972) suggests that the systemic availability of propoxyphene is substantially less than 100%. Using a hepatic blood flow rate of 1.53 litre min^{-1} (Bradley, Ingelfinger & Bradley, 1952), and the reported data (Study number 1, treatments A and D) this equation predicts that 27 and 36% of the 65 and 130 mg oral doses of propoxyphene respectively would be available to the systemic circulation. These findings are in reasonable agreement with a previous report (Perrier & Gibaldi, 1972) where, based on the intravenous data of Wolen, Gruber & others (1971), an average of 18% of the 65 mg dose and 28% of the 130 mg dose of propoxyphene was calculated to be systemically available after oral administration.

In a study by Johansson, Regardh & Sjogren (1971), 100 mg of alprenolol was administered orally in a solid dosage form. The literature data enabled the calcu-

* The assumptions made are: the drug obeys dose independent kinetics, should be subject to virtually complete hepatic metabolism, is not metabolized before reaching the liver, is completely absorbed from the gastrointestinal tract into the hepatoportal system; there is blood flow rate limited transfer of drug from the blood into the liver; the clearance into the liver equals the clearance out of the liver.

lation of the areas under the plasma level-time curves for each subject. Areas were evaluated by means of the trapezoidal rule after extrapolation of each curve to time infinity. The fraction of alprenolol reaching the systemic circulation, as predicted by the above equation, was calculated to be 9% of the orally administered dose:

Subject	1	2	3	4	mean ± s.d.
Predicted availability*	0·07	0·11	0·02	0·14	0·09 ± 0·05

* Eqn 1, with hepatic blood flow rate of 1·53 litre min^{-1}. Data from Johansson & others (1971) for the ordinary 100 mg tablet.

This finding is supported by a report which indicates that the pharmacologic response to an oral dose of alprenolol is about one-tenth that observed when an equivalent dose was administered intravenously (Johnsson, Norrbey & Solvell, 1967). Johansson & others (1971) indicated that in another study the fraction of unchanged alprenolol in the serum was about ten times higher after intravenous than after oral administration. This also supports the present results.

Therefore, based on these observations, it would appear that the above equation may be a useful predictive tool for estimating the maximal systemic availability that could be expected for an orally administered drug.

This study was supported in part by General Research Support Grant No. FR5-501RR-05454-10 from the National Institutes of Health and by a studentship for Donald Perrier from the Medical Research Council of Canada.

Department of Pharmaceutics,
School of Pharmacy,
State University of New York at Buffalo,
Buffalo, New York 14214, U.S.A.

DONALD PERRIER
MILO GIBALDI
R. N. BOYES*

October 9, 1972

* Present address: Drug Disposition Section, Astra Pharmaceutical Products, Inc., Worcester, Massachusetts 01606.

REFERENCES

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

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

JOHANSSON, R., REGARDH, C. G. & SJOGREN, J. (1971). *Acta pharm. suec.*, **8**, 59–70.

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

PERRIER, D. & GIBALDI, M. (1972). *J. clin. Pharmac.*, **12**, 449–452.

WAGNER, J. G., WELLING, P. G., ROTH, S. B., SAKMAR, E., LEI, K. P. & WALKER, J. E. (1972). *Int. J. clin. Pharmac.*, **5**, 371–380.

WOLEN, R. L., GRUBER, C. M., JR., KIPLINGER, G. F. & SCHOLZ, N. E. (1971). *Toxic. Appl. Pharmac.*, **19**, 480–492.