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Influence of First-Pass Effect on Availability of Drugs on Oral Administration

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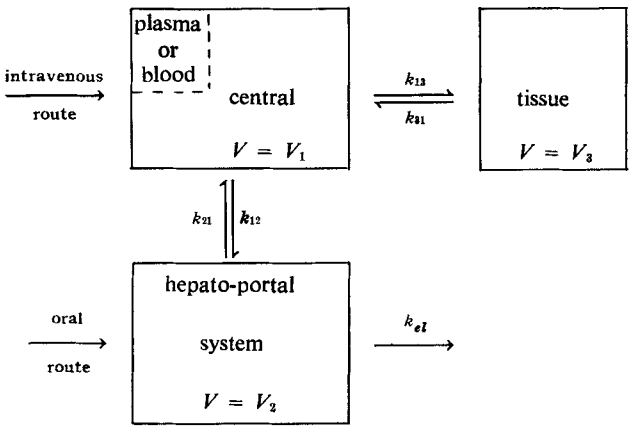
Abstract □ Currently used pharmacokinetic models assume that drug administered both intravenously and orally initially enters the same vascular pool. However, literature data suggest that although a drug is completely absorbed, the area under the plasma level–time curve after oral administration may be considerably less than the corresponding area following intravenous therapy. This has been explained on the basis of a "first-pass" effect in the liver. Simple equations have been derived, allowing prediction of the extent of this first-pass effect for a particular drug. Plasma level data for propranolol in man have been used to indicate the utility of these equations. The significance of these calculations to the design of clinical studies with new drugs intended for oral use is discussed.

Keyphrases □ Bioavailability, estimate calculations—from plasma levels, first-pass effect □ Absorption kinetics, oral—plasma level data, first-pass effect

Pharmacokinetic analysis of plasma level data for drugs generally assumes that the site of elimination is an integral part of the same compartment as the sampled plasma. For drugs eliminated by hepatic metabolism, this assumption may not be valid under all circumstances. Two recent papers (1, 2) indicated that the areas under the blood level–time curves for aspirin and lidocaine were considerably greater when a dose of the drug was infused into a peripheral vein as compared to results observed upon infusion of an equal dose into the portal vein of the dog. Administration of a drug directly into the portal vein is, in most instances, equivalent to the pathway followed after oral administration. The reduction in area under the blood level–time curves following portal vein infusion has been attributed to the fact that the drugs were exposed to the liver before reaching the vascular site being sampled. This phenomenon has been commonly termed the "first-pass" effect. Clearly, then, differences in areas under blood level–time curves as a function of route of administration may reflect not only differences in the amount of drug absorbed but the first-pass phenomenon as well. Based on these considerations, a somewhat different model or a correction factor may be required to compare plasma levels of certain drugs following oral and intravenous administration. The purpose of this communication is to present a simple method of calculation which can be used to predict, from plasma levels following intravenous or oral administration, the approximate reduction in area under the curve due to the first-pass phenomenon.

THEORETICAL

In a previous report (3), a linear three-compartment open model was proposed to explain the influence of route of administration (*i.e.*, intravenous *versus* oral) on the area under the plasma concentration–time curve. A modification of the model is shown in Scheme I. The essential feature of this model is that the hepatoportal system is treated as being, or being within, a compartment distinct from the compartment containing the vascular site sampled. Moreover, it was suggested that it often is exceedingly difficult to justify the existence of three distinct compartments solely on the basis of curve-fitting plasma concentration–time data after intravenous administration. Hence, although the plasma concentration data suggest simply a two-compartment model, an additional, rapidly accessible compartment might well exist and, in fact, must exist, from a mathematical point of view to explain certain pharmacokinetic anomalies (1, 2).



Scheme I—Three-compartment open model

If the vascular system being sampled is a component of the central compartment (inset of Compartment 1 of Scheme I), a difference will indeed occur with respect to the area under the drug concentration *versus* time curve as a function of route of administration (3). When the drug is given directly into Compartment 1, a situation comparable to intravenous administration, the total area under the plasma concentration–time curve is given by:

$$(\text{area})_1 = \text{dose}\ (k_{21} + k_{el})/(V_1 k_{12} k_{el}) \qquad \text{(Eq. 1)}$$

Table I—Ratio of Areas (f)[a] after Oral and Intravenous Administration of Propranolol Obtained Experimentally and Calculated by Means of Eq. 8

Subject[b]	Experimental[b]	Calculated: Blood Flow Model[c]	Calculated: Plasma Flow Model[d]
O. F.	0.60	0.64	0.50
D. S.	0.30	0.38	0.25
G. Y.	0.32	0.39	0.26
J. C.	0.20	0.27	0.17
J. F.	0.17	0.22	0.13

[a] Ratio of area under the plasma curve after oral administration to that after intravenous administration, assuming equivalent doses. [b] Data obtained from *Reference 7*, intravenous dose = 10 mg., oral dose = 80 mg. [c] Based on hepatic blood flow of 1.7 l./min. [d] Based on hepatic plasma flow of 0.94 l./min.

On the other hand, when the drug is given directly into Compartment 2, a situation comparable to administration *via* the hepatic portal vein and often comparable to oral administration, then the total area under the plasma level–time curve is given by:

$$(\text{area})_2 = \text{dose}\ (k_{21})/(V_1 k_{12} k_{el}) \qquad \text{(Eq. 2)}$$

By combining Eqs. 1 and 2, it can been seen (Eq. 3) that the relative area under the plasma level curve, when a dose of drug is administered into Compartment 2 as compared to an equivalent dose into Compartment 1, is given by the following relationship:

$$f = \frac{(\text{area})_2}{(\text{area})_1} = \frac{k_{21}}{k_{21} + k_{el}} \qquad \text{(Eq. 3)}$$

In Eq. 3, f represents the proportion of the drug administered into Compartment 2 that actually reaches the plasma or central compartment.

Although Eq. 3 provides an exact solution to the ratio of areas, it is of little practical value since the rate constants cannot be determined. If certain assumptions are made, however, a general relationship, analogous to Eq. 3, may be written which may be quite useful in a predictive sense for a given drug.

Multiplying the numerator and denominator of Eq. 3 by V_2 yields:

$$f = (k_{21}V_2)/(k_{21}V_2 + k_{el}V_2) \qquad \text{(Eq. 4)}$$

By assuming that clearance from one compartment to another is equal in both directions (4), $k_{21}V_2 = k_{12}V_1$. Substitution of $k_{12}V_1$ for $k_{21}V_2$ in Eq. 4 yields:

$$f = k_{12}V_1/(k_{12}V_1 + k_{el}V_2) \qquad \text{(Eq. 5)}$$

If one assumes further that transfer between Compartments 1 and 2 is blood or plasma flow rate limited (5, 6), then $k_{12}V_1 \cong$ flow rate and:

$$f = (\text{flow rate})/(\text{flow rate} + k_{el}V_2) \qquad \text{(Eq. 6)}$$

The product of k_{el} and V_2 may be evaluated from Eq. 2.

Since $V_1k_{12} = V_2k_{21}$, then:

$$k_{el}V_2 = \text{dose}/(\text{area})_2 \qquad \text{(Eq. 7)}$$

In the previous report (3), it was suggested that $k_{el}V_2$ could be approximated by the term dose/(area)$_1$. As demonstrated here, this is clearly not the case.

Substituting Eq. 7 into Eq. 6 yields:

$$f = \frac{\text{flow rate}}{\text{flow rate} + [\text{dose}/(\text{area})_2]} \qquad \text{(Eq. 8)}$$

If plasma level data are available following oral administration of a drug, substitution of the oral dose and respective plasma level–time curve area, as well as the appropriate flow rate, into Eq. 8 should yield a reasonable estimate of f, provided the dose of the drug is completely absorbed. If the latter assumption is not correct, then Eq. 8 must be modified to take into account the differences in areas under the plasma concentration–time curve after oral and intravenous administration that are due to a difference in the amount absorbed as well as the first-pass effect. In this case, one may write:

$$f = \frac{F\ (\text{flow rate})}{\text{flow rate} + [(F \cdot \text{dose})/(\text{area})_2]} \qquad \text{(Eq. 9)}$$

where F is the fraction of the administered oral dose absorbed. Under certain conditions, F may be determined independently from urinary excretion data based on total metabolites or an isotopic tag.

Perhaps a more realistic approach is the evaluation of f from plasma concentration–time data obtained after intravenous administration of the drug. This is readily accomplished by rearranging Eq. 8. Since $f = (\text{area})_2/(\text{area})_1$, then:

$$\frac{(\text{area})_2 \cdot \text{flow rate}}{(\text{area})_1} + \frac{\text{dose}}{(\text{area})_1} = \text{flow rate} \qquad \text{(Eq. 10)}$$

or

$$f = 1 - \frac{\text{dose}}{(\text{area})_1 \cdot \text{flow rate}} \qquad \text{(Eq. 11)}$$

Substitution of the intravenous dose and respective plasma level–time curve area, as well as the appropriate flow rate, into Eq. 8 should yield an estimate of the extent to which the first-pass effect is contributing to a reduction in the area under the curve after oral administration relative to that observed after peripheral intravenous administration. If one finds experimentally a value of f that is lower than that calculated by Eq. 11, it would suggest that oral administration does not lead to complete absorption. In this case, the difference in areas under the plasma level–time curve as a function of route of administration would reflect differences in the amount absorbed as well as the first-pass effect.

APPLICATIONS

The value of flow rate to be used in solving Eq. 8 depends upon the physiologic significance of the various compartments. For example, if one views Compartment 2 as simply the hepatoportal system, it is appropriate to use an hepatic flow rate. If the drug in the blood is restricted to the plasma, or if the portion of drug in the blood that is partitioned in the erythrocytes is not "instantaneously" exchanged with drug in the plasma, then the transfer process is best described in terms of plasma flow rates. This approach was used successfully by Bellman *et al.* (6). If, on the other hand, rapid transport could be envisioned between red cells and plasma, then whole blood flow rates may be useful, as suggested by Bischoff and Dedrick (5).

Application of the calculation presented here to recently reported plasma level data for propranolol leads to some interesting results. Shand *et al.* (7) estimated the total area under the plasma level *versus* time curve in fasting adult volunteers after oral administration of 80 mg. propranolol in tablet form and after intravenous administration of 10 mg. of the drug. These data permit a direct and independent test of Eqs. 8 and 11 for the estimation of f.

Substitution of the area under the plasma level–time curve after oral administration for each subject reported by Shand *et al.* (7), the

Table II—Ratio of Areas (f)[a] after Oral and Intravenous Administration of Propranolol Obtained Experimentally and Calculated by Means of Eq. 11

Subject[b]	Experimental[b]	Calculated: Blood Flow Model[c]	Calculated: Plasma Flow Model[d]
O. F.	0.60	0.66	0.29
D. S.	0.30	0.55	0.19
G. Y.	0.32	0.51	0.11
J. C.	0.20	0.46	0.03
J. F.	0.17	0.44	—[e]

[a] Ratio of area under the plasma curve after oral administration to that after intravenous administration, assuming equivalent doses. [b] Data obtained from *Reference 7*, intravenous dose = 10 mg., oral dose = 80 mg. [c] Based on hepatic blood flow of 1.7 l./min. [d] Based on hepatic plasma flow of 0.94 l./min. [e] f calculated to be a negative member.

oral dose (80 mg.), and either hepatic blood flow (1.7 l./min.) (8) or hepatic plasma flow (0.94 l./min.) into Eq. 8 yields the values of f shown in Table I. Equation 8, based either on hepatic plasma or hepatic blood flow rate, predicts a substantial first-pass effect with propranolol. The blood flow model predicts that if the oral dose is completely absorbed, the area under the plasma level–time curve will only be, on the average, 38% of that observed after intravenous administration of an equivalent dose. The plasma flow model suggests an even greater effect, yielding a mean f-value of 0.26. The experimentally determined mean f-value of 0.32 falls midway between these estimates (7). While either a plasma or blood flow model provides an excellent estimate of the experimental results, it is suggested that the hepatic blood flow model is the more realistic. It must be stressed that Eq. 8 provides a minimum estimate of $(1 - f)$, since it is assumed that the oral dose is completely absorbed. If this is not the case, then the experimentally determined value of f will be smaller than that generated by Eq. 8. In fact, if one assumes that only 70% of the oral propranolol dose is actually available to the hepatoportal system, *i.e.*, only 70% is absorbed as such, then according to Eq. 9, using hepatic blood flow, the mean value of f is 0.32, which is identical to the experimental observation.

A similar approach was employed to test Eq. 11. Estimates of the area under the plasma level *versus* time curve after intravenous administration for each subject, as reported by Shand *et al.* (7), the intravenous dose (10 mg.), and the value for either hepatic blood or plasma flow rate were substituted into Eq. 11, and f was determined for each individual. These data are reported in Table II. The blood flow model predicts that the oral administration of an equivalent dose of propranolol will at best provide a plasma level–time curve area that is 45–65% of that determined after intravenous administration. The difference in area predicted by Eq. 11 based on blood flow is smaller than that actually observed. On the other hand, the plasma flow model predicts substantially larger differences than are actually observed and, in this particular case, is unrealistic. Again, it must be noted that Eq. 11 provides a minimum estimate of $(1 - f)$, since it does not take into account possible differences in the amount absorbed as a function of route of administration. Accordingly, if one assumes, as before, that only 70% of the oral propranolol dose is actually available to the hepatoportal system, then using the hepatic blood flow model with the intravenous data, one estimates a mean f-value of 37%, which is in excellent agreement with the experimental value of 32%.

Application of Eq. 11 to preclinical and early phase I clinical studies with new drugs intended for oral administration is of considerable practical importance. Reasonable predictions can be made from plasma level data following intravenous administration as to the minimum relative dose required when the drug is to be given orally. Stated another way, one can estimate the maximum physiologic availability that can be anticipated from oral administration of a drug regardless of how well it is absorbed. Viewed in this light, the inability of intact drug to reach the central compartment and tissues of distribution results in decreased physiologic availability and the net effect is completely equivalent to that observed when a compound is poorly absorbed from the GI tract because of its intrinsic physical–chemical properties or because of faulty formulation.

Several significant clinical problems may arise with compounds that are subject to substantial first-pass effects. Since the intersubject dose variation is expected to be large, it would be important to titrate each patient to his effective dose. In clinical studies carried out double-blind against a placebo, this could be very awkward. Another problem arises because even though a small amount of the dose is available for pharmacologic effect, in general, it is expected that the total dose will be largely absorbed and produce metabolites. If these metabolites have little desired effectiveness but do, in fact, produce untoward responses, patients receiving high doses of the drug necessary for pharmacological results may also have a higher incidence of side effects due to the large amounts of metabolites formed.

Hence, for a variety of reasons, it would seem desirable to screen new compounds with respect to the first-pass phenomenon. By carrying out a few well-controlled intravenous experiments with a new drug and then applying a calculation similar to Eq. 11, it may be possible to save considerable time and expense in terms of extensive clinical trials in the evaluation of new compounds intended for oral use.

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