Influence of Route of Administration on Drug Availability

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Abstract □ In therapeutics, dose requirements are sometimes larger for a drug given orally than are needed following parenteral administration. This might be the case despite complete and rapid absorption of the drug and arises when a large fraction of the oral dose is eliminated on first passage through the liver. The basis of determining clearance from the area under the blood or plasma concentration–time curve following an intravenous dose is examined. By using area analysis, an equation is derived which allows an estimate of the availability of a completely absorbed, orally administered drug. The availability of oral aspirin is examined with this equation. The importance of clearance concepts in bioavailability studies, drug design, and enzyme induction studies is discussed.

Keyphrases □ Bioavailability—application of intravenous clearance concepts in the calculation of oral availability □ Absorption, oral—application of intravenous clearance concepts to calculate bioavailability

Absorption may be defined as the loss of material from one bulk phase arising from the movement into another. In GI absorption, this would involve the loss of a substance from the luminal contents by passage into the gastric and intestinal mucosa. Availability may be defined as the extent to which an administered material reaches the point of measurement. Some drugs are poorly available because of incomplete absorption (perhaps due to poor dissolution properties), with a commensurate appearance of drug in the feces. Others, including aspirin (1, 2), salicylamide (3), and lidocaine (4), are well absorbed but are still poorly available when assessed at some reference point, such as a peripheral vein, away from the site of absorption. This arises when a fraction of the drug is metabolized as it passes across the gut wall and through the liver before reaching the systemic circulation. Schedl *et al.* (5, 6) emphasized the distinction between oral absorption and physiological activity in some steroids originating from extensive metabolism before appearing in a peripheral vein. Recently, Dollery *et al.* (7) attributed the 1000 to 1 ratio of intravenous to oral chronotrophic potency of isoproterenol in man to the formation of an inactive ethereal sulfate during transfer across the gut wall and passage through the liver.

The quantitative assessment of availability[1] can be determined by comparing the total area under the plasma or blood concentration–time curve (or total amount of the unchanged drug appearing in the urine) after giving the drug orally to the area (or total amount of unchanged drug appearing in the urine) following intravenous administration of an equivalent dose (1–3). When the areas are equal, the drug is fully available. If the area ratio is less than unity, the drug is incompletely available. This could arise because it is poorly absorbed, or because it is metabolized while entering the systemic circulation, or because of a combination of both. The picture can be clarified by fecal analysis or by quantitation of metabolite(s) entering the systemic circulation or appearing in the urine (1). However, it would be desirable to have some idea whether or not a drug is likely to be poorly available in man even though it exhibits excellent absorption characteristics in animals or in an *in vitro* preparation. Such information would help in deciding the suitability of the oral route as a mode of administration for a potential therapeutic agent. The present paper makes an attempt to gain this information from area analysis following intravenous drug administration.

[1] The method of assessing availability in this paper employs the intravenous dose as the standard. Some other methods measure the availability of an extravascularly administered drug dosage form relative to the most completely available form of the drug given by the same route.

DISCUSSION

Intravenous Clearance—The present analysis specifically relates to oral absorption and assumes that gut wall metabolism is zero. The analysis is based on clearance concepts. Consider the model depicted in Fig. 1, in which a drug is cleared *via* an eliminating organ. Let drug be introduced directly into the rest of the body, *i.e.*, an intravenous dose. Blood flow entering and leaving is assumed equal. Looking at the eliminating organ and ensuring mass balance:

$$dE = \dot{V}_B(C_{in} - C_{out})dt - dM \qquad \text{(Eq. 1)}$$

Integrating between times zero and infinity:

$$\int_{t=0}^{t=\infty} dE = \int_0^{\infty} \dot{V}_B(C_{in} - C_{out})dt - \int_{t=0}^{t=\infty} dM \qquad \text{(Eq. 2)}$$

If the drug is given intravenously and there is no irreversible binding, then the amount in the eliminating organ is zero at zero time and infinity while the total amount of drug lost (M_∞) is the dose administered. It then follows that:

$$(\text{dose})_{i.v.} = \int_0^{\infty} \dot{V}_B\,(C_{in} - C_{out})_{i.v.}\,dt \qquad \text{(Eq. 3)}$$

The blood flow, while it can vary, usually remains reasonably constant so:

$$(\text{dose})_{i.v.} = \dot{V}_B \int_0^{\infty} (C_{in} - C_{out})_{i.v.}\,dt \qquad \text{(Eq. 4)}$$

It should be noted that the last equation is applicable whether or not distribution and elimination obey first-order kinetics, although it does assume that only this organ clears the drug.

The instantaneous clearance ($\dot{V}_{CL}$), units volume per unit time, of a drug by an eliminating organ is given by:

$$\dot{V}_{CL} = \dot{V}_B \left(\frac{C_{in} - C_{out}}{C_{in}}\right) \qquad \text{(Eq. 5)}$$

and may be defined as the volume of blood entering the organ which is cleared of drug per unit time. Often the fraction in parentheses is referred to as the extraction ratio of the substance by the organ. When it is unity, *i.e.*, no substance leaves the organ, the clearance equals the blood flow to that organ.

Immediately following the bolus, V_{CL} varies as drug simultaneously distributes into and is removed by the eliminating organ. If the system is linear, eventually, when the distribution equilibrium of drug is established between blood and the tissue of the organ, a constant proportionality will exist between C_{in} and C_{out}. However, as will be shown in a later publication, although the clearance calculated from this proportionality constant and blood flow is constant, its value can differ from that derived from steady-state experiments. Even so, substituting Eq. 5 into Eq. 2 and integrating between $t = 0$, $t = \infty$ yields:

$$(\text{dose})_{\text{i.v.}} = \left(\int_0^\infty \dot{V}_{CL} C_{\text{in}}\, dt\right)_{\text{i.v.}} \qquad \text{(Eq. 6)}$$

which is a general equation that neither specifies constancy of clearance nor blood flow. The mean clearance ($\bar{\dot{V}}_{CL}$) is defined by:

$$\bar{\dot{V}}_{CL} = \frac{(\text{dose})_{\text{i.v.}}}{\left(\int_0^\infty C_{\text{in}}\, dt\right)_{\text{i.v.}}} = \frac{\left(\int_0^\infty \dot{V}_{CL} C_{\text{in}}\, dt\right)_{\text{i.v.}}}{\left(\int_0^\infty C_{\text{in}}\, dt\right)_{\text{i.v.}}} \qquad \text{(Eq. 7)}$$

To calculate the mean clearance, one could measure the concentration of drug entering the eliminating organ (C_{in}) or in any artery (as the arterial concentration is the same in all parts of the body), but for reasons of ease and safety, venous samples are usually taken. The vein is normally associated with a noneliminating organ, *e.g.*, the arm. Then the rate of change of drug in this organ (dA_T/dt) is:

$$\frac{dA_T}{dt} = \dot{V}_{BT} C_{\text{art}} - \dot{V}_{BT} C_{\text{venous}} \qquad \text{(Eq. 8)}$$

where $\dot{V}_{BT}$ is the blood flow into and out of the arm, and C_{art} (equal to C_{in}) and C_{venous} are, respectively, the concentration of drug in the arterial and venous blood entering and leaving the arm. By integrating between infinity and zero and realizing that, following an intravenous dose, the amount of drug in the noneliminating organ (A_T) at both these limits is zero:

$$\int_0^\infty (C_{\text{art}}\, dt)_{\text{i.v.}} = \int_0^\infty (C_{\text{venous}}\, dt)_{\text{i.v.}} \qquad \text{(Eq. 9)}$$

Substitution of Eq. 9 into Eq. 7 yields:

$$\bar{\dot{V}}_{CL} = \frac{(\text{dose})_{\text{i.v.}}}{\left(\int_0^\infty C_{\text{venous}}\, dt\right)_{\text{i.v.}}} \qquad \text{(Eq. 10)}$$

This last definition of the clearance is frequently employed in pharmacokinetics. For those drugs exhibiting dose-independent kinetics, *i.e.*, the system is linear and the area under the curve is proportional to dose, the clearance is assumed to be constant throughout drug elimination. If drug distributes rapidly so that the concentration in the eliminating organ is in equilibrium with that in the emergent venous blood and the system is linear, then the mean clearance ($\bar{\dot{V}}_{CL}$) equals the clearance determined under steady-state conditions. Likely causes of dose-dependent (nonlinear) kinetics are changes in the extent of protein binding and fractional rate of metabolism and excretion over the concentration range of interest. In a nonlinear system, mean clearance is then no longer constant and independent of dose.

Oral Availability—The oral route is the most popular mode of administration. Any drug passing across the intestinal tract is quantitatively collected by the mesenteric veins and passes *via* the hepatic portal vein directly into the liver before reaching the systemic circulation. Although the contribution from the hepatic artery distinguishes the physiologic situation from the model, the conclusions reached here are the same (see *Appendix*). In either case, a certain fraction of the oral dose is cleared in the first passage through the eliminating organ. Therefore, the availability of an oral dose is less than an intravenous dose when assessed at some reference point (peripheral vein) away from the site of administration.

For a drug exhibiting dose-independent kinetics, the fractional loss of the oral dose as it passes through the eliminating organ for the first time can be ascertained from intravenous data. Consider Fig. 1, except that drug is introduced directly before the eliminating organ at a concentration $C_{\text{in},OR}$. After passing through the organ, the drug mixes and distributes into the rest of the body, yielding a concentration $C_{\text{in},R}$. The total concentration entering the eliminating organ (C_{in}) equals the sum $C_{\text{in},OR} + C_{\text{in},R}$. Ensuring mass balance across the organ:

$$dE = \dot{V}_B (C_{\text{in}} - C_{\text{out}})dt - dM \qquad \text{(Eq. 11)}$$

Defining clearance by:

$$\dot{V}_{CL} = \dot{V}_B \frac{(C_{\text{in}} - C_{\text{out}})}{C_{\text{in}}} \qquad \text{(Eq. 12)}$$

substituting Eq. 12 into Eq. 11 appropriately, and integrating between $t = 0$ and $t = \infty$ give:

$$(\text{dose})_{\text{oral}} = \int_0^\infty \dot{V}_{CL} C_{\text{in}}\, dt \qquad \text{(Eq. 13)}$$

$$= \int_0^\infty \dot{V}_{CL} C_{\text{in},OR}\, dt + \int_0^\infty \dot{V}_{CL} C_{\text{in},R}\, dt \qquad \text{(Eq. 13}a\text{)}$$

The amount of drug cleared in the first pass through the eliminating organ is given by:

$$M_{\infty,OR} = \int_0^\infty \dot{V}_{CL} C_{\text{in},OR}\, dt \qquad \text{(Eq. 14)}$$

Remembering that the oral dose entering the system equals:

$$\dot{V}_B \int_0^\infty C_{\text{in},OR}\, dt$$

then the fraction of the dose cleared in the first passage is defined by:

$$\frac{M_{\infty,OR}}{(\text{dose})_{\text{oral}}} = \frac{\int_0^\infty \dot{V}_{CL} C_{\text{in},OR}\, dt}{\dot{V}_B \int_0^\infty C_{\text{in},OR}\, dt} \qquad \text{(Eq. 15)}$$

$$= \frac{\bar{\dot{V}}_{CL}}{\dot{V}_B} \qquad \text{(Eq. 15}a\text{)}$$

The availability of the oral dose (θ), *i.e.*, fraction of the administered dose appearing in the rest of the body, is:

$$\theta = 1 - \frac{\bar{\dot{V}}_{CL}}{\dot{V}_B} \qquad \text{(Eq. 16)}$$

or:

$$\theta = 1 - \frac{(\text{dose})_{\text{i.v.}}}{\dot{V}_B \left(\int_0^\infty C_{\text{venous}}\right)_{\text{i.v.}}} \qquad \text{(Eq. 16}a\text{)}$$

and, therefore, is equal to one minus the mean extraction ratio.

So far, reference has been made primarily to the model in Fig. 1. In practice, there are several sites of elimination, with the liver and kidney generally being the most important. Therefore, the clearance determined from area analysis is the total body clearance of the drug due to all processes of elimination. Renal elimination usually involves excretion of the unchanged drug. Knowing the fraction of the dose excreted unchanged in the urine (f_e) together with the total body clearance (T.B.C.), one can then calculate the renal clearance ($f_e \times$ T.B.C.). If the remaining fraction (f_m) of the dose is metabolized in the liver, then, for a drug that is completely absorbed, the equations corresponding to Eqs. 16 and 16*a* become:

fraction of oral dose appearing in systemic circulation (θ) =

$$1 - \frac{\text{hepatic clearance}}{\text{liver blood flow}} \qquad \text{(Eq. 17)}$$

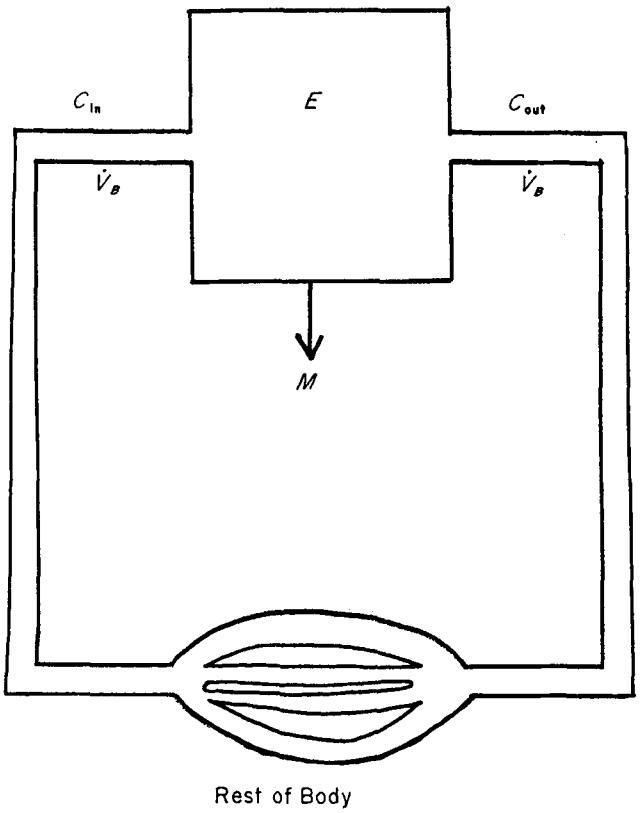

Figure 1—*Model depicting the body with elimination of a drug occurring from one organ only. Key: C_{in} = concentration of drug entering the eliminating organ, C_{out} = concentration of drug leaving the eliminating organ, $\dot{V}_B$ = blood flow into and out of the eliminating organ, E = amount of drug in the eliminating organ, and M = amount of metabolite formed.*

which can also be written as:

$$\theta = 1 - \frac{f_m(\text{dose})_{\text{i.v.}}}{\dot{V}_{BL}\left(\int_0^\infty C_{\text{venous}}\,dt\right)_{\text{i.v.}}} \qquad \text{(Eq. 17}a\text{)}$$

where $\dot{V}_{BL}$ is the liver blood flow. Equation 17 predicts the availability ($\theta \times 100$) of a completely absorbed oral dose.

From area considerations, availability is experimentally given by:

$$\text{availability} = \frac{\left(\int_0^\infty C_{\text{venous}}\,dt\right)_{\text{oral}}}{\left(\int_0^\infty C_{\text{venous}}\,dt\right)_{\text{i.v.}}} \times 100 \qquad \text{(Eq. 18)}$$

equal doses being administered by both routes. If the approximations made in Eq. 16 and subsequent equations are reasonable, the availability predicted from intravenous data (Eq. 17) should agree with that found experimentally (Eq. 18). Moreover, for drugs solely metabolized in the liver and assuming that both clearance and hepatic blood flow are a function of body surface area, a plot of availability (Eq. 18) against intravenous clearance (expressed per unit body surface area) for a group of subjects or animals whose clearance differs should yield a straight line, with an intercept on the availability axis of unity and a slope equal to the reciprocal of hepatic blood flow (per unit body surface area). When the hepatic clearance is high in all subjects and approaching liver blood flow, then the intravenous data will be very similar, although differences might be discernable following oral administration which depends on the difference between hepatic clearance and hepatic blood flow.

Should the area ratio in Eq. 18 be less than that predicted from hepatic clearance and blood flow data, then either absorption is incomplete or metabolism occurs in the gut contents or across the gut wall. Alternatively, the area ratio in Eq. 18 may be greater than that predicted from Eq. 17, because the concentration of drug in the hepatic portal vein following administration may be sufficiently high to saturate the metabolic enzymes. Obviously, in the last case, the availability becomes a function of dose and rate of absorption.

Blood *versus* Plasma Analysis—The question arises whether to analyze blood or plasma. In compartment models, concern is with mass balance and it is the blood that brings the drug to the liver (or any other organ). Also, in general, drugs equilibrate very rapidly between the erythrocytes and plasma, probably at least as rapidly as between plasma and tissues. Consequently, as drug passes from plasma water into the liver, it reequilibrates between plasma and red blood cells. In other words, transfer across the erythrocyte does not rate limit drug distribution, and blood may be conceived of as a single compartment. Therefore, when relating clearance to flow, $\dot{V}_{BL}$ must be blood flow and not the plasma flow to the liver, and clearance must be the total body *blood* clearance and not the total body *plasma* clearance of the drug. Many times, plasma concentrations rather than blood concentrations are measured. Then, defining the concentration ratio (λ) as: concentration of drug in blood/concentration of drug in plasma, Eq. 17*a* can also be written as:

$$\theta = 1 - \frac{f_m(\text{dose})_{\text{i.v.}}}{\dot{V}_{BL}\,\lambda\left(\int_0^\infty C_{\text{plasma}}\,dt\right)_{\text{i.v.}}} \qquad \text{(Eq. 19)}$$

Occasionally, one can relate plasma clearance measurements directly to plasma flow. The condition for this circumstance is best seen by examining the relationship between the concentration ratio λ and the hematocrit *H*:

$$\lambda = \frac{H}{K_p} + (1 - H) \qquad \text{(Eq. 20)}$$

where K_p is the apparent partition coefficient of the drug between plasma and erythrocytes. When K_p is very high (*e.g.*, Evans blue, bishydroxycoumarin, bilirubin, and other highly protein bound drugs), $\lambda = 1 - H$; since $(1 - H)\dot{V}_{BL}$ is the plasma flow to the liver, one can then use plasma concentrations and a plasma flow model. Also, when drug partitions equally between plasma and red blood cells ($K_p = 1$) (*e.g.*, alcohol and antipyrine), $\lambda = 1$. In this second case, one does not need to determine blood concentrations, but the flow must still be the blood flow to the organ. These considerations apply equally to clearance determinations across any organ. In pharmacokinetics, when relating clearance to flow, one should determine blood drug clearances and relate them to blood flows, but it is generally incorrect to relate plasma clearance to plasma flow. (The determination of the glomerular filtration rate using drug plasma analysis, correcting for protein binding, is appropriate since filtration occurs without disturbing the equilibrium of drug between water in plasma and erythrocytes.)

Availability and Compartment Models—In pharmacokinetics, measurements are made from a reference region, usually a peripheral vein. If, as occurs in oral absorption, an eliminating organ exists between the site of administration and the reference point, then a fraction of the dose may be metabolized before entering the compartment containing this reference region. To describe the influence of the route on the area under the plasma concentration–time curve, Gibaldi and Feldman (8) used a three-compartment model, defining the eliminating organ (in this case, the liver) as a separate compartment. Compartment models describe spatial and structural changes in the amount of a drug with time, and the rate constants associated with the model are mass rate constants. Also, as previously mentioned, one should relate drug blood clearances[2] to blood flow. However, even using a blood flow model, a major problem with the compartment model exists in estimating the appropriate rate constants. Usually, these constants are calculated from the plasma or blood level–time curve or from urinary excretion data. They also can be estimated from clearance values and compartment volumes (since clearance by a compartment equals the product of the rate constant and its respective volume constant).

[2] The definition of clearance can be applied to a noneliminating organ or compartment, but the clearance continually changes until at steady state when it is zero. Normally, clearance is associated with an eliminating organ and it is not zero under steady-state conditions.

In turn, volume constants are defined with respect to the volume of the central compartment which is measured from a reference region (in this case, blood). If the volume of the central compartment is the blood volume, then by knowing the perfusion to an organ (*e.g.*, liver) and partition of drug between that organ and blood, one might be able to obtain an estimate of the corresponding clearance and rate constants. However, for many drugs, significant distribution into the liver (the compartment of interest) and other well-perfused organs, *e.g.*, kidney, spleen, and brain (which have to be lumped as another compartment) occurs simultaneously with mixing of the compound in the vascular system. This makes it almost impossible to determine, from blood level and perfusion data, these required volume constants and, hence, rate constants. Rather than attempting to establish the liver as a separate compartment, an alternate approach is to integrate the availability, calculated using Eq. 18, with the compartment model that previously described the concentration–time curve following an intravenous dose. The latter approach was adopted to define the kinetics of aspirin given orally (9). Intravenous aspirin is described by a two-compartment open model (10). Because of hydrolysis within the gut wall and the liver, only a fraction of oral aspirin, determined by using Eq. 18, enters the central compartment for aspirin. The remaining hydrolyzed fraction was then represented as appearing directly in the central compartment of the metabolite, in this case, salicylic acid (9).

It should be possible to apply the present considerations, especially using Eq. 17*a*, to determine the lowest possible availability of an orally administered drug arising from its hepatic clearance. For example, the total body clearance of aspirin, determined by dividing an intravenous dose by the corresponding area under the blood concentration–time curve, is 810 ml./min. (10). Approximately 115 ml./min., determined as the product of the *in vitro* hydrolysis rate constant of aspirin in whole blood at 37° and the volume of the blood, may be accounted for by esterases in the blood. Assuming that the remaining 695 ml./min. is due to hepatic metabolism, a negligible fraction of aspirin appears unchanged in the urine, and using 1.53 l./min. for liver blood flow (11), then 55% [(1 − 0.695/1.53) × 100] is the lowest possible availability of completely absorbed oral aspirin. Experimentally, the availability of a solution of aspirin given orally was 68%. Incomplete absorption was excluded as the same amount of metabolite, salicylic acid, was present in the body following an equal dose of oral or intravenous aspirin. Therefore, hepatic clearance could completely account for the low availability of aspirin. Other evidence, however, indicates that some loss of availability arises from esterases in the gut wall which, in turn, implies that esterases (outside the vascular system) do not reside solely in the liver.

The low oral availability (0.22–0.48) of the local anesthetic and antiarrhythmic agent, lidocaine, is compatible with the high total blood clearance of this drug in man (12). From area measurements in the literature (13–15), the analgesic pentazocine also would appear to have a high total body clearance. Assuming this clearance to be substantially associated with hepatic metabolism, it could account for the observation by Beckett *et al.* (14, 15) that, whether given in solution or tablets, the availability of this drug is low. Supporting this hypothesis, the availability was highest in the subject with the largest area following intravenous administration (and, therefore, lowest clearance).

Drug Design—It should be stressed that when a drug has a high hepatic clearance, its availability from the oral route will be low, and manipulation of the formulation will do little to improve the situation. As a consequence, to achieve the same clinical response, oral doses have to be larger than those required in intravenous and, probably, intramuscular therapy. Metabolite levels may also be higher and if these materials are toxic, a greater incidence of side effects may be associated with the oral route. Also, when considering loss during oral absorption, it is important not to confuse the elimination half-life ($t_{1/2}$) of a drug with its clearance. Assuming a one-compartment model:

$$\text{clearance} = V_d \cdot \frac{0.693}{t_{1/2}} \qquad \text{(Eq. 21)}$$

where V_d is the apparent volume of distribution of the drug. Then, for a given clearance, the larger the V_d the longer is the half-life. Two drugs whose V_d and $t_{1/2}$ differ 10-fold can be equally cleared. Ideally, to avoid a decrease in availability, a drug intended for oral administration should have a low hepatic clearance. If liver metabolism is the only route of elimination and 450 ml./min. (30% of the liver blood flow) is the upper acceptable limit, the half-life is approximately 8 hr. for a drug with a V_d of 150 l. Should the clearance be lower or the V_d greater, the half-life of the drug may become too long if it is intended as a soporific or a stimulant. Evidently, to maintain a low hepatic clearance and relatively short half-life, the drug must be cleared by additional organs such as the kidneys. Usually, this requires the synthesis of a more polar molecule. Accordingly, in addition to all other factors, the pharmaceutical scientist must consider the volume of distribution, hepatic, renal, and perhaps biliary clearance, in the design of therapeutic agents.

Enzyme Stimulation—Many agents stimulate the enzymes responsible for the metabolism of drugs (16). Evidence for this phenomenon *in vivo* is often obtained by demonstrating an increase in the rate of drug elimination or formation of a metabolite, following intravenous administration of the drug to animals or man after treatment with the suspected enzyme stimulator. The intravenous mode is chosen to avoid absorption problems. An absence of effect is interpreted as a lack of enzyme stimulation. This conclusion may be erroneous. If the hepatic clearance of a drug approaches the liver blood flow, then even though enzymes in the liver are stimulated (and drug may be metabolized many times faster in an *in vitro* liver homogenate preparation), an increase in the clearance and, hence, the rate of decline of drug levels may not be evident when giving the drug intravenously. In contrast, provided malabsorption can be excluded, a decrease in availability of an oral dose will be evident. Suppose, for example, that enzyme stimulation increases the hepatic clearance of a drug, which is exclusively metabolized in liver, from 1.1 to 1.3 l./min. Correspondingly, the elimination half-life only decreases 20%. In contrast, the availability of the oral dose decreases from 28 [1 − (1.1/1.53) × 100] to 15 [1 − (1.3/1.53) × 100]%. Clearly, under these circumstances, the oral route is a much more sensitive index of enzyme stimulation. Conversely, if the hepatic clearance of the same drug is very low, enzyme stimulation would significantly shorten the elimination half-life with little change in the availability from the oral route.

The application of clearance concepts in the calculation of oral availability has been explained and illustrated. Numerous factors limit, to a greater or lesser extent, the use of this approach in predictions. Some of these factors were previously mentioned but others include the presence of metabolizing enzymes in the gut lumen and walls, dose-dependent (nonlinear) disposition kinetics, saturation of metabolizing enzymes in the liver by a high drug concentration in the hepatic portal vein with oral administration, the influence of dose on the extent of drug absorption, and the blood not acting as a single compartment as it passes through the eliminating organ. Nonetheless, this approach probably will be fruitful in other circumstances.

APPENDIX

Unlike the situation depicted in Fig. 1, the liver receives two blood supplies, the hepatic portal vein and the hepatic artery. The former collects blood from the mesenteric arteries after it passes through the viscera. The hepatic vein drains blood from the liver into the superior vena cava. Consider the recirculating model (Fig. 1) with these additional complexities. Let drug be infused directly into the hepatic portal vein, *i.e.*, analogous to oral administration, and $C_{HP,OR}$ be the concentration in this vein. Upon leaving the liver, drug distributes throughout the rest of the body, yielding an arterial concentration C_{art}. Imagine that this recirculated drug, which results in a concentration $C_{HP,R}$ in the hepatic portal vein, could be distinguished from $C_{HP,OR}$ (while their sum equals C_{HP}). The mean concentration ($\bar{C}_{in,L}$) entering the liver is given by:

$$\bar{C}_{in,L} = \frac{\dot{V}_{HP}C_{HP} + \dot{V}_{HA}C_{art}}{\dot{V}_{HV}} \qquad \text{(Eq. A1)}$$

where $\dot{V}_{HP}$, $\dot{V}_{HA}$, and $\dot{V}_{HV}$ are the blood flow in the hepatic portal vein, hepatic artery, and vein, respectively ($\dot{V}_{HV} = \dot{V}_{HP} + \dot{V}_{HA}$). Maintaining mass balance across the liver:

$$\frac{dE}{dt} = \dot{V}_{HV}(\bar{C}_{in,L} - C_{HV}) - \frac{dM}{dt} \qquad \text{(Eq. A2)}$$

where C_{HV} is the concentration of drug in the hepatic vein. With

appropriate substitution of instantaneous clearance ($\dot{V}_{CL}$), defined by:

$$\dot{V}_{CL} = \dot{V}_{HV}\frac{(\bar{C}_{in,L} - C_{HV})}{\bar{C}_{in,L}} \qquad \text{(Eq. A3)}$$

into Eq. A2 leads to:

$$\frac{dE}{dt} = \dot{V}_{CL}\bar{C}_{in,L} - \frac{dM}{dt} \qquad \text{(Eq. A4)}$$

Integrating Eq. A4 between $t = 0$ and $t = \infty$ and realizing that at both times $E = 0$ yield:

$$\text{dose} = \int_0^\infty \dot{V}_{CL}\bar{C}_{in,L}\,dt \qquad \text{(Eq. A5)}$$

Intravenous Clearance—When a drug is administered directly into the rest of the body, *i.e.*, analogous to an intravenous injection, $C_{HP,OR} = 0$ and the mean intravenous clearance ($\bar{\dot{V}}_{CL}$) is then defined by:

$$\bar{\dot{V}}_{CL} = \frac{(\text{dose})_{i.v.}}{\left(\int_0^\infty \bar{C}_{in,L}\,dt\right)_{i.v.}} = \frac{\left(\int_0^\infty \dot{V}_{CL}\bar{C}_{in,L}\,dt\right)_{i.v.}}{\left(\int_0^\infty \bar{C}_{in,L}\,dt\right)_{i.v.}} \qquad \text{(Eq. A6)}$$

Also, from Eq. A1:

$$\int_0^\infty \bar{C}_{in,L}\,dt = \frac{\dot{V}_{HP}\int_0^\infty C_{HP,R}\,dt + \dot{V}_{HA}\int_0^\infty C_{art}\,dt}{\dot{V}_{HV}} \qquad \text{(Eq. A7)}$$

If the viscera is a noneliminating organ, then:

$$\int_0^\infty C_{HP,R}\,dt = \int_0^\infty C_{art}\,dt \qquad \text{(Eq. A8)}$$

and by appropriate substitution of Eq. A8 into Eq. A7, it follows that:

$$\int_0^\infty \bar{C}_{in,L}\,dt = \int_0^\infty C_{art}\,dt \qquad \text{(Eq. A9)}$$

If venous blood is collected from a noneliminating organ, then it also follows from Eqs. 9 and A9 that Eq. A6 becomes:

$$\bar{\dot{V}}_{CL} = \frac{(\text{dose})_{i.v.}}{\left(\int_0^\infty C_{venous}\,dt\right)_{i.v.}} \qquad \text{(Eq. A10)}$$

which is the same definition for the mean clearance as given in Eq. 10.

Oral Availability—When given orally, it is apparent by substitution of Eq. A1 into Eq. A5 that:

$$(\text{dose})_{oral} = \frac{\dot{V}_{HP}}{\dot{V}_{HV}}\int_0^\infty \dot{V}_{CL}C_{HP,OR}\,dt + \frac{\dot{V}_{HP}}{\dot{V}_{HV}}\int \dot{V}_{CL}C_{HP,R}\,dt + \frac{\dot{V}_{HA}}{\dot{V}_{HV}}\int_0^\infty \dot{V}_{CL}C_{art}\,dt \qquad \text{(Eq. A11)}$$

Since all the drug enters the system *via* the hepatic portal vein:

$$(\text{dose})_{oral} = \dot{V}_{HP}\int_0^\infty C_{HP,OR}\,dt \qquad \text{(Eq. A12)}$$

and the amount of drug metabolized on the first passage through the liver ($M_{\infty,OR}$) is:

$$M_{\infty,OR} = \frac{\dot{V}_{HP}}{\dot{V}_{HV}}\int_0^\infty \dot{V}_{CL}C_{HP,OR}\,dt \qquad \text{(Eq. A13)}$$

Therefore, the fraction of oral dose metabolized in the first passage through the elimination organ is given by:

$$\frac{M_{\infty,OR}}{(\text{dose})_{oral}} = \frac{\int_0^\infty \dot{V}_{CL}C_{HP,OR}\,dt}{\dot{V}_{HV}\int_0^\infty C_{HP,OR}\,dt} = \frac{\bar{\dot{V}}_{CL}}{\dot{V}_{HV}} \qquad \text{(Eq. A14)}$$

and the availability (θ) of an oral dose given by one minus the fraction of the dose cleared in the first passage becomes:

$$\theta = 1 - \frac{\bar{\dot{V}}_{CL}}{\dot{V}_{HV}} \qquad \text{(Eq. A15)}$$

which is the same definition for θ as given in Eq. 15*a*.

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