Theoretical Relationships between Area under the Curve and Route of Administration of Drugs and Their Precursors for Evaluating Sites and Pathways of Metabolism

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Abstract □ The bioavailability of a drug administered extrasystemically is a measure of the initial extraction of a compound by a series of eliminating events involving the intestinal mucosal enzymes, the gut bacterial microflora, the liver, and the lung. A theoretical analysis is presented to differentiate the processes of gut wall elimination and hepatic removal of a drug during this first-pass effect. The area under the blood concentration–time curve (*AUC*) for a drug and its metabolite is shown to be useful in determining the presence of these processes when a drug and its metabolite are administered concomitantly by different routes of administration. Furthermore, the fraction of a precursor transformed to its metabolite also can be determined by pharmacokinetic analysis of the *AUC* of a drug and its metabolite after administration of both substances.

Keyphrases □ Pharmacokinetics—theoretical analysis to differentiate gut wall elimination and hepatic removal, relationship between area under the curve and administration route □ Metabolism, drug—sites and pathways evaluated, theoretical analysis to differentiate gut wall elimination and hepatic removal, relationship between area under the curve and administration route

The effect of the route of administration on the bioavailability (defined as the fraction of drug reaching the site of sampling from the site of administration) of drugs has been the subject of several publications (1–6). An orally administered drug must be absorbed, survive the initial degradation by intestinal mucosal enzymes (7, 8) and bacterial flora (9–11), and escape hepatic elimination before it arrives at the site of sampling, usually a remote venous site. The lung, a potential organ of drug elimination (12), also interposes between the site of sampling and administration and can interact in this chain of eliminating events which constitutes the first-pass effect (3). The plasma also was reported to be an eliminating tissue (13).

DISCUSSION

The bioavailability on intravenous drug administration is usually taken as unity in the absence of removal of drug by either the plasma or the lung. Thus, the classical method of ascertaining the oral bioavailability is by the ratio of the area under the curve, *AUC* (14):

$$F = \frac{AUC_{po}}{AUC_{iv}} \frac{dose_{iv}}{dose_{po}} \quad \text{(Eq. 1)}$$

The overall availability, F, is furnished by a series of eliminating processes as described earlier and is the product of the fraction absorbed, f_{abs}, and the availabilities, f, of each eliminating organ in series:

$$F = f_{abs} f_{GW} f_L f_{lung} \quad \text{(Eq. 2)}$$

where the subscripts GW and L denote the gut wall and the liver, respectively. The lung does not often serve the role of a drug eliminating organ, although it reportedly eliminates many endogenous substances (12) and some drugs (15, 16). The general impact on the first-pass effect is thus usually attributable to gut wall and hepatic elimination. However, these two processes are often not differentiated.

The purpose of this paper is to present some theoretical considerations to enable identification of each process. This purpose can be achieved by coadministration of a drug, D, and its precursor, P, by various routes of administration. The situation is simplest when the kinetics of P and D are linear, and thus clearance is dose independent. The following discussion is restricted to those occasions in which the kinetics of P and D are linear, the conversion of the precursor to the drug takes place only in the liver, and the clearance of P by the liver is greater than that by other eliminating organs. Both P and D are also assumed to be completely absorbed unchanged through the portal venous blood during intraperitoneal administration.

Hepatic Extraction—When the precursor is converted to the drug solely in the liver, the fractional conversion of P to D will be f_m regardless of the administration route of P. The drug, generated *in situ* in hepatocytes after the administration of P, may undergo further metabolism in the liver before it enters the blood. The fraction of D extracted by the liver, $ER_{(D)}$, can be expressed in terms of the available fraction $f_{L(D)}$; *i.e.*, $ER_{(D)} = 1 - f_{L(D)}$. Moreover, the drug may be eliminated by extrahepatic tissues. Therefore, after the administration of the precursor and with the assumption that the precursor is completely absorbed from the various sites of administration, the area under the blood concentration–time curve of D is given by:

$$AUC_{(D)} \text{ from } P = \frac{f_m(1 - ER_{(D)})dose_{(P)}}{TBC_{(D)}} \quad \text{(Eq. 3)}$$

where the dose of P, $dose_{(P)}$, is expressed in moles, the blood concentration of P is expressed as molar concentration, and $TBC_{(D)}$ is the intravenous systemic or total body clearance of D. The intravenous total body clearance of D can be estimated on intravenous administration of D:

$$TBC_{(D)} = \frac{dose_{(D)iv}}{AUC_{(D)iv}} \quad \text{(Eq. 4)}$$

Substitution of Eq. 4 into Eq. 3 gives the extraction ratio of D:

$$ER_{(D)} = 1 - \frac{AUC_{(D) \text{ from } P}}{AUC_{(D)iv}} \frac{dose_{(D)iv}}{f_m dose_{(P)}} \quad \text{(Eq. 5)}$$

When the value of f_m is known, the extraction ratio of D is easily evaluated from Eq. 5. The value of f_m is normally estimated from the cumulative amount of the drug in the urine divided by the dose, but this value is underestimated when the drug is further metabolized by the liver once it is formed from its precursor and is almost impossible to estimate when the secondary and tertiary metabolites are formed by several pathways. It may be estimated from the $AUC_{(D)}$ value obtained after the intraperitoneal administration of D and that from P. When complete absorption of the drug occurs, the $AUC_{(D)}$ following an intraperitoneal administration of D is given by:

$$AUC_{(D)ip} = \frac{(1 - ER_{(D)})dose_{(D)ip}}{TBC_{(D)}} \quad \text{(Eq. 6)}$$

Dividing Eq. 3 by Eq. 6 and solving the resultant equation for f_m give:

$$f_m = \frac{AUC_{(D) \text{ from } P}}{AUC_{(D)ip}} \frac{dose_{(D)ip}}{dose_{(P)}} \quad \text{(Eq. 7)}$$

An alternative method of estimating the extraction ratio of D is by comparing the areas under the curve following intraperitoneal and intravenous administration of D:

$$ER_{(D)} = 1 - \frac{AUC_{(D)ip}}{AUC_{(D)iv}} \frac{dose_{(D)iv}}{dose_{(D)ip}} \quad \text{(Eq. 8)}$$

Other combinations of *AUC* measurements may be used to check the validity of the assumptions made in deriving the equations. The following treatment can be applied to ascertain if absorption is complete and if gut wall elimination occurs for the precursor. The area under the blood concentration–time curve of the precursor after a single oral dose is:

$$AUC_{(P)po} = \frac{f_{abs(P)} f_{GW(P)} f_{L(P)} dose_{(P)po}}{TBC_{(P)}} \quad \text{(Eq. 9)}$$

The equation of the area under the curve of the precursor following intraperitoneal administration upon complete absorption of the precursor is:

$$AUC_{(P)\text{ip}} = \frac{f_{L(P)}\text{dose}_{(P)\text{ip}}}{TBC_{(P)}} \quad \text{(Eq. 10)}$$

Substitution of Eq. 10 into Eq. 9 gives:

$$f_{\text{abs}(P)}f_{GW(P)} = \frac{AUC_{(P)\text{po}}}{AUC_{(P)\text{ip}}}\frac{\text{dose}_{(P)\text{ip}}}{\text{dose}_{(P)\text{po}}} \quad \text{(Eq. 11)}$$

Complete absorption and the absence of gut wall metabolism are indicated when the areas for oral and intraperitoneal administration are equal after correcting for the doses given.

Gut Wall Elimination—By a similar procedure, the overall available fraction after gut wall elimination may be obtained by administering the drug orally and intraperitoneally. Assuming the drug given intraperitoneally is completely absorbed, then:

$$f_{\text{abs}(D)}f_{GW(D)} = \frac{AUC_{(D)\text{po}}}{AUC_{(D)\text{ip}}}\frac{\text{dose}_{(D)\text{ip}}}{\text{dose}_{(D)\text{po}}} \quad \text{(Eq. 12)}$$

However, this estimate of availability also may be obtained by administering P intravenously and D orally. The drug D formed from P is subjected only to hepatic elimination before it is ultimately detected, and Eq. 3 is applied. A comparison of the area under the curve for D after its oral administration with that obtained after administration of its precursor (correcting for differences in doses) yields the fraction available subsequent to gut wall elimination and prior to hepatic elimination:

$$f_{\text{abs}(D)}f_{GW(D)} = \frac{AUC_{(D)\text{po}}}{AUC_{(D)\text{ from }P,\text{iv}}}\frac{f_m\text{dose}_{(P)\text{iv}}}{\text{dose}_{(D)\text{po}}} \quad \text{(Eq. 13)}$$

Multiple Doses—The single-dose method to evaluate the hepatic extraction ratio of the drug can be extrapolated to steady-state situations. After chronic drug administration of D by intravenous infusion (inf) and intraperitoneal injections (ip), the steady-state drug concentration in blood, $C_{ss(D)}$, is related to the drug administration rate, R, and the intravenous total body clearance as well as the extraction ratio in the following manner:

$$C_{ss(D)\text{inf}} = \frac{R_{(D)\text{inf}}}{TBC_{(D)}} \quad \text{(Eq. 14)}$$

$$\overline{C}_{ss(D)\text{ip}} = \frac{(1 - ER_{(D)})R_{(D)\text{ip}}}{TBC_{(D)}} \quad \text{(Eq. 15)}$$

Also, with chronic administration of the precursor, the steady-state concentration of D in blood can be expressed as:

$$\overline{C}_{ss(D)\text{ from }P} = \frac{f_m(1 - ER_{(D)})R_{(P)}}{TBC_{(D)}} \quad \text{(Eq. 16)}$$

where $R_{(P)}$ is the administration rate for P in moles per unit time. The hepatic extraction ratio under steady-state conditions is evaluated as:

$$ER_{(D)} = 1 - \frac{\overline{C}_{ss(D)\text{ from }P}}{C_{ss(D)\text{inf}}}\frac{R_{(D)\text{inf}}}{f_m R_{(P)}} \quad \text{(Eq. 17)}$$

$$ER_{(D)} = 1 - \frac{\overline{C}_{ss(D)\text{ip}}}{C_{ss(D)\text{inf}}}\frac{R_{(D)\text{inf}}}{R_{(D)\text{ip}}} \quad \text{(Eq. 18)}$$

Similar relationships are seen for chronic drug administrations as for single doses. The fractions available after gut wall elimination in these instances are:

$$f_{\text{abs}(D)}f_{GW(D)} = \frac{\overline{C}_{ss(D)\text{po}}}{\overline{C}_{ss(D)\text{ from }P}}\frac{f_m R_{(P)}}{R_{(D)\text{po}}} \quad \text{(Eq. 19)}$$

and:

$$f_{\text{abs}(D)}f_{GW(D)} = \frac{\overline{C}_{ss(D)\text{po}}}{\overline{C}_{ss(D)\text{ip}}}\frac{R_{(D)\text{ip}}}{R_{(D)\text{po}}} \quad \text{(Eq. 20)}$$

The coadministration of the precursor and the drug provides a distinct advantage over the administration of the drug on two different occasions, because the day-to-day variation even within the same subject can be avoided. However, an assay that can distinguish the drug as obtained from the administration of P from that obtained from the administration of D must be available. The problem can be overcome when the precursor and the drug are labeled with different isotopes, in which case it is possible to quantitate the area under the curve for D as generated from the precursor, or from the administration of D, within the same study.

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