Presystemic Elimination of Drugs: Theoretical Considerations for Quantifying the Relative Contribution of Gut and Liver

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Abstract □ From a consideration of the basic processes involved in drug elimination, the fraction of drug cleared by the gut and by the liver were described as functions of availability and hepatic clearance. For a drug given orally, a plot of the fraction of drug cleared by the gut or liver against α, a proportionality constant relating gut elimination following intravenous administration to that following oral administration, allowed an estimate of the possible contribution of gut and liver to presystemic elimination. This method was dependent only on the measurement of peripheral blood drug concentrations and urine levels. Application of the theory to published data for several drugs known to have a reduced availability after oral administration was used to illustrate the procedure.

Keyphrases □ Liver—relative contribution to presystemic elimination □ Gut—relative contribution to presystemic elimination □ Presystemic elimination—quantification of contribution of gut and liver, theoretical considerations

When given orally, many drugs undergo significant presystemic metabolism in the gut and liver, reducing their pharmacological activity by decreasing systemic availability (1). In experimental animals, the relative contribution of the liver and gut to presystemic elimination can be quantified by measuring portal and peripheral blood drug concentrations following oral and intravenous administration (2–4). However, as pointed out by Routledge and Shand (1), such procedures cannot be readily carried out in humans because of technical and ethical limitations and, therefore it has not been possible to demonstrate which site of metabolism is more important during presystemic elimination in humans. In the present study, a theoretical approach to quantifying the contribution of gut and liver to presystemic elimination was considered and equations derived which, for drugs obeying certain criteria, allowed calculation of the fraction of drug cleared in the gut or liver using clearance and availability estimates obtained by measurement of drug concentrations in systemic blood.

THEORY

The presystemic elimination of a drug in a linear system was considered. Availability (F) can be estimated by:

$$F = \frac{AUC_{oral}\, D_{iv}}{AUC_{iv}\, D_{oral}} = (1 - f_G)(1 - f_L) \qquad \text{(Eq. 1)}$$

where AUC_{oral} and AUC_{iv} are the areas under the blood drug concentration–time curves following an oral (D_{oral}) and an intravenous (D_{iv}) dose respectively, f_G is the fraction of dose cleared in gut, and f_L is the fraction of dose reaching the portal blood system which is cleared by the liver.

When such a drug is given intravenously, elimination may occur in the liver or in the gut if significant diffusion of the drug from the portal blood into the gut wall occurs. The rate of drug elimination in the liver (dE_L/dt) can be described by:

$$\frac{dE_L}{dt} = (Q_L - Q_G)f_L C_1 + Q_G f_L C_G \qquad \text{(Eq. 2)}$$

where Q_L is the total hepatic blood flow, Q_G is the intestinal blood flow, C_1 is the peripheral blood concentration, and C_G is the concentration of drug entering the liver *via* the portal system. The rate of drug elimination in the gut wall following intravenous administration (dE_G/dt) is given by:

$$\frac{dE_G}{dt} = \alpha Q_G f_G C_1 \qquad \text{(Eq. 3)}$$

where $1 \geq \alpha \geq 0$. The proportionality constant, α, allows for the fact that the fraction of drug cleared after entering the gut from the general circulation may not be equal to that cleared after entering the gut from the lumen. Total elimination rate from the splanchnic circulation (dE/dt) can be described by the addition of Eq. 2 and 3.

$$\frac{dE}{dt} = (Q_L - Q_G)f_L C_1 + Q_G f_L C_G + \alpha Q_G f_G C_1 \qquad \text{(Eq. 4)}$$

Since $C_G = (1 - \alpha f_G)C_1$, then:

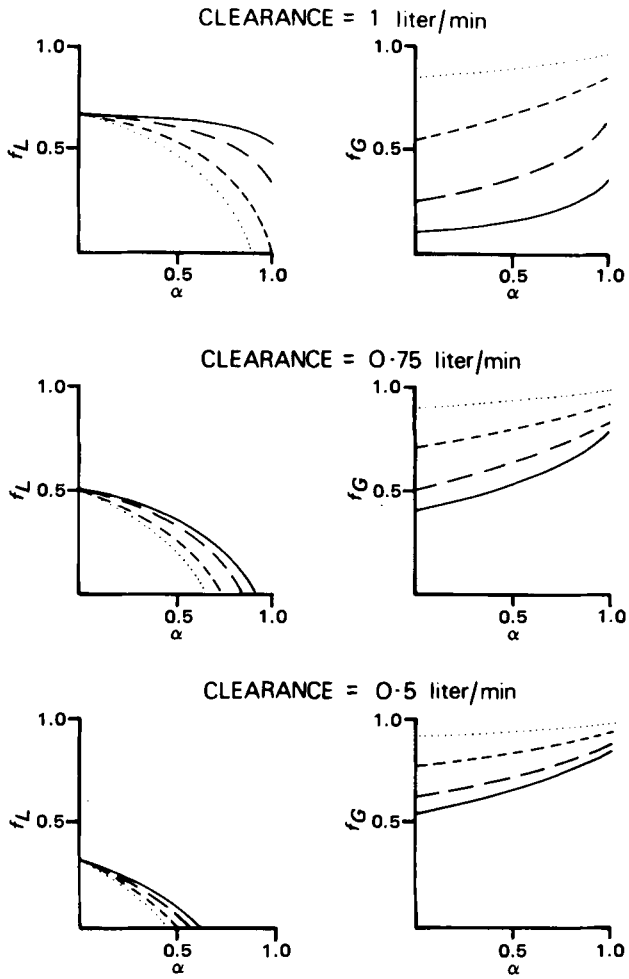

Figure 1—*Dependence of* f_L *and* f_G *on availability, clearance, and* α. *Assuming* Q_L *and* Q_G *to be 1.5 and 1.2 liters/min, respectively,* f_L *and* f_G *were calculated according to Eqs. 8 and 9. Key: Availability = 0.3 (——), 0.25 (— —), 0.15 (– – –), and 0.05 (. . .).*

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Table I—Kinetic Data for Drugs Known to Undergo Significant Presystemic Elimination

Drug	Availability	Plasma Clearance, liter/min	Blood-Plasma Distribution Ratio	Fraction Excreted in Urine	Hepatic Blood Clearance[a], liters/min	Reference
Imipramine	0.47	1.05	1.34	0.0	0.784	8
Propranolol	0.36	0.702	0.78	0.0	0.90	9
Quinidine	0.795	0.256	0.66	0.276	0.281	10
Pentazocine	0.184	1.38	1.07	0.154	1.09	11
Oxprenolol	0.462	0.372	0.80	0.03	0.457	12
Nortriptyline	0.505	0.527	1.49	0.02	0.347	13
Lidocaine						
Healthy subjects	0.37	0.77	0.83	0.01	0.918	14
Epileptics	0.15	0.85	0.83	0.01	1.014	14
Phenacetin[b]						
Controls	0.452	0.00276	1.06	0.0	0.0026	15
Induced	0.058	0.01763	1.06	0.0	0.0166	15

[a] Calculated as $[1-f_R]Cl_T/\lambda$ where f_R = fraction of drug excreted in urine, Cl_T = total plasma clearance, and λ = blood to plasma distribution ratio. [b] Study undertaken in rats, controls were pretreated with saline, while induced were pretreated with 3-methylcholanthrene; Q_L = 21 ml/min, Q_G = 16.8 ml/min.

$$\frac{dE}{dt} = (Q_L - Q_G)f_L C_1 + Q_G f_L(1 - \alpha f_G)C_1 + \alpha Q_G f_G C_1 \quad \text{(Eq. 5)}$$

Equation 5 simplifies to:

$$\frac{dE}{dt} = C_1[Q_L f_L + \alpha Q_G f_G(1 - f_L)] \quad \text{(Eq. 6)}$$

The term enclosed by the square brackets is equivalent to the classical hepatic clearance constant (Cl_H) where gut and liver are considered as a single functional unit. Thus:

$$Cl_H = Q_L f_L + \alpha Q_G f_G(1 - f_L) \quad \text{(Eq. 7)}$$

From Eq. 1:

$$f_G = 1 - [F/(1 - f_L)] \quad \text{(Eq. 8)}$$

Substituting Eq. 8 into Eq. 7 and rearranging:

$$f_L = \frac{Cl_H - \alpha Q_G(1 - F)}{(Q_L - \alpha Q_G)} \quad \text{(Eq 9)}$$

Exact solutions of f_L, f_G, and α are not possible from the above equations, since the three parameters are described by only two independent equations (Eqs. 8 and 9). However, a plot of f_L and f_G *versus* α for $1 \geq \alpha \geq 0$ may allow some conclusions concerning the overall contribution of gut and liver to the presystemic elimination of a drug to be made.

RESULTS AND DISCUSSION

The proportionality constant α in Eq. 9 relates gut elimination following oral to that following intravenous drug administration. The role of the GI tract in drug metabolism, particularly after intravenous administration, has not been comprehensively investigated. Theoretically, α is equal to unity when the gut contributes equally to the elimination of a drug after its oral and intravenous administration. During absorption, a drug must cross the mucosal epithelium, basement membrane, and the capillary endothelium. Movement of drug in the opposite direction may be equal to or less than the corresponding rate of absorption depending on its physicochemical properties, the pH gradient across the gut wall, the blood flow rate, and the degree of drug binding to blood constituents. All these factors may cause α to be less than unity. For some drugs such as isoproterenol (5, 6) and pentazocine (7) which have been shown to undergo significant biotransformation in the gut following oral administration but not after infusion into the mesenteric arterial blood supply, α is equal to zero.

Using Eqs. 8 and 9, f_L and f_G have been computed at various clearance and availability values for $1 \geq \alpha \geq 0$, Q_L = 1.5 liters/min, and Q_G = 1.2 liters/min (Fig. 1). For a given oral availability, the importance of the liver to overall presystemic elimination decreases, while that for gut increases as clearance is reduced. Furthermore, regardless of the value of α, the gut becomes increasingly more important as availability is reduced at a constant clearance. In general, the liver is the site of greater elimination in systems of relatively high clearance and high availability, whereas the gut is dominant in systems of relatively low clearance and low availability.

Using kinetic data (Table I) obtained from the literature (8–15), curves of *f versus* α were constructed to determine the contribution of gut and

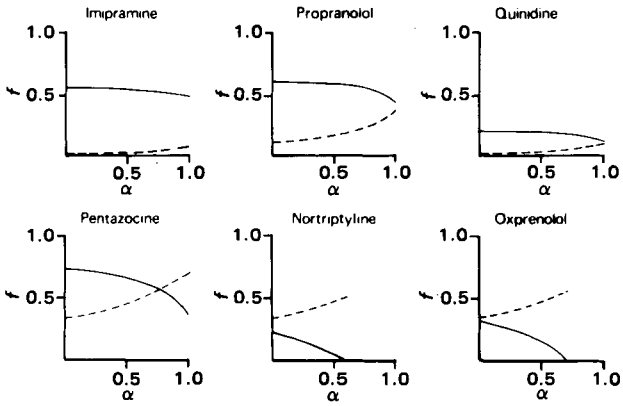

Figure 2—*The* f *versus* α *curves for several drugs known to undergo significant presystemic elimination (see Table I). Key:* —— f_L; *and* — — — f_G.

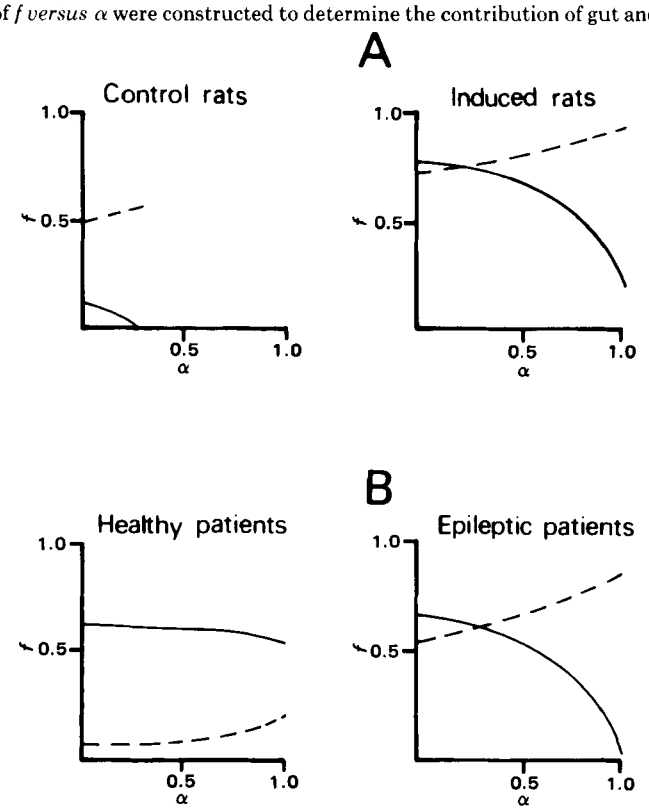

Figure 3—*Effect of induction on the* f versus α *curves for phenacetin (A) and lidocaine (B). For phenacetin, rats were pretreated with saline (controls) or 3-methylcholanthrene (induced) before receiving an oral or intravenous dose of phenacetin. For lidocaine, data were collected from healthy subjects and also from epileptic patients who were receiving enzyme-inducing drugs such as phenobarbital. Key:* —— f_L, *and* — — — f_G.

liver to the presystemic elimination of a number of drugs. Total hepatic clearance was calculated as $(1 - f_R)Cl_T/\lambda$ where f_R is the fraction of drug eliminated unchanged in the urine, Cl_T is the total plasma clearance, and λ is the blood to plasma distribution ratio. For all drugs considered, it was assumed that significant elimination occurred only in gut, liver, and kidney. Total hepatic and intestinal blood flows were assumed to be 1.5 and 1.2 liters/min, respectively (16). For the phenacetin data that were obtained from experiments in rats, Q_L and Q_G were taken to be 21.0 and 16.8 ml/min, respectively, assuming a body weight of 240 g (17).

The contribution of the liver to presystemic elimination was greater than that of the gut for imipramine, propranolol, and quinidine regardless of the value of α (Fig. 2). However, with oxprenolol and nortriptyline, the gut was generally more important. For both these drugs, the boundaries of α were reduced to $0.708 \geq \alpha \geq 0$ and $0.584 \geq \alpha \geq 0$, respectively, since, by definition, $1 \geq f_L \geq 0$ and $1 \geq f_G \geq 0$. Because of the nature of Eqs. 8 and 9, it is possible that plotting f_L and f_G *versus* α will produce curves which suggest that the gut is more important than the liver at one extremity of α ($\alpha \rightarrow 1$), while the reverse is true at the other extremity ($\alpha \rightarrow 0$). This is exemplified by the f *versus* α curves for pentazocine Fig. 2) where the gut eliminated 33% of an oral dose if $\alpha = 0$, but 71% if $\alpha = 1$. In such a case, plotting f_L and f_G against α would not assist in assessing the relative contribution of gut and liver to the reduced availability, and information concerning the magnitude of α would have to be obtained from isolated human gut loops, experiments in patients undergoing portocaval anastomosis, or by extrapolation from animal data.

The use of f *versus* α curves also may reveal how induction or inhibition of enzymatic systems can affect availability. In Fig. 3, the change in f_L and f_G for phenacetin in rats and lidocaine in humans was illustrated before and after induction. For control rats, it could be calculated that at least 88% of the total dose eliminated before reaching the systemic circulation was due to clearance in the gut. After pretreatment with 3-methylcholanthrene, there was a small increase in f_G, but a far more marked increase in f_L for all values of α suggesting that the decrease in availability in induced animals was due to a greater contribution from the liver. However, the change in lidocaine availability from 37% in healthy subjects to only 15% in epileptic patients was primarily due to an increase in gut elimination. It should be noted that f_G may be a function of a number of factors such as gut lumen metabolism, gut wall metabolism, or incomplete absorption. The greater contribution of gut to the presystemic elimination of lidocaine in epileptic patients was also reflected in the lack of any change in plasma half-life (14) which should have been reduced by a significant increase in liver metabolism since f_L was much less than 1 in healthy subjects, (greatest value of f_L was 0.612 for $\alpha = 0$).

Finally, it should be noted that the use of this method in humans is dependent on reliable estimates of Q_L and Q_G. While numerous studies have shown relatively constant estimates for these values in healthy subjects, both may be markedly altered in patients with cardiovascular, hepatic, or renal disease, or by the drug under investigation. For example, the f *versus* α curves for propranolol, oxprenolol, quinidine, and lidocaine should be interpreted cautiously considering the known hemodynamic effects of these drugs. This limitation could be avoided by individual measurement of Q_L and Q_G. Hepatic blood flows may be estimated using well-established invasive techniques (18, 19) which usually involve direct infusion of a radiolabeled inert gas such as xenon or krypton into the liver.

REFERENCES

(1) P. A. Routledge and D. G. Shand, *Ann. Rev. Pharmacol. Toxicol.*, **19,** 447 (1979).

(2) W. A. Colburn, *J. Pharmacokinet. Biopharm.*, **7,** 407 (1979).

(3) K. Iwamoto and C. D. Klaassen, *J. Pharmacol. Exp. Ther.*, **200,** 236 (1977).

(4) M. K. Cassidy and J. B. Houston, *J. Pharm. Pharmacol.*, **32,** 57 (1980).

(5) C. F. George, E. W. Blackwell, and D. S. Davies, *ibid.*, **26,** 265 (1974).

(6) K. F. Ilett, C. T. Dollery, and D. S. Davies, *ibid.*, **32,** 362 (1980).

(7) R. D. Anderson and K. F. Ilett, *Clin. Exp. Pharmacol. Physiol.*, in press.

(8) L. F. Gram and J. Christiansen, *Clin. Pharmacol. Ther.*, **17,** 555 (1975).

(9) D. M. Kornhauser, A. J. J. Wood, R. E. Vestal, G. R. Wilkinson, R. A. Branch, and D. G. Shand, *ibid.*, **23,** 165 (1978).

(10) D. J. Greenblatt, H. J. Pfeifer, H. R. Ochs, K. Franke, D. S. MacLaughlin, T. W. Smith, and J. Koch-Weser, *J. Pharmacol. Exp. Ther.*, **202,** 365 (1977).

(11) M. Ehrnebo, L. O. Boreus, and U. Lonroth, *Clin. Pharmacol. Ther.*, **22,** 888 (1977).

(12) W. D. Mason and N. Winer, *ibid.*, **20,** 401 (1976).

(13) L. F. Gram and K. F. Overo, *ibid.*, **18,** 305 (1976).

(14) E. Perucca and A. Richens, *Br. J. Clin. Pharmacol.*, **8,** 21 (1979).

(15) R. M. Welch, C. R. Hughes, and R. L. Deangelis, *Drug Metab. Dispos.*, **4,** 402 (1976).

(16) N. Benowitz, R. P. Forsyth, K. L. Melmon, and M. Rowland, *Clin. Pharmacol. Ther.*, **16,** 87 (1974).

(17) L. I. Harrison and M. Gibaldi, *J. Pharm. Sci.*, **66,** 1138 (1977).

(18) D. P. Leiberman, R. T. Mathie, A. M. Harper, and L. H. Blumgart, *Br. J. Surg.*, **65,** 578 (1978).

(19) A. M. Holroyd and A. M. Peters, *ibid.*, **67,** 178 (1980).

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