μg/kg/min infusion. The half-life of the formation of ASL-8123 averaged 2.82 min, and the calculated fraction of the overall metabolite generated was 82.9%. The elimination half-lives of esmolol and ASL-8123 averaged 9.19 and 223 min, respectively, suggesting accumulation and relatively slow elimination of the metabolite in humans. The peak concentration of ASL-8123 averaged 77.9 μg/ml and occurred 26 min after the cessation of the esmolol infusion. This peak concentration was ~50 times larger than the steady-state concentration of esmolol at which maximum β-blockade was observed.

The total clearance of esmolol was 4 times greater than the total cardiac output (70 ml/min/kg) and 14 times greater than hepatic blood flow (5), suggesting that the high clearance was primarily due to metabolism by esterases in the blood. The rapid metabolism of ASL-8052 results in a very short duration of action. The fact that there was no noticeable β-blockade 30 min after cessation of the infusion (which is the time of peak concentration of the metabolite) also suggests that ASL-8123 does not possess β-blocking activity at the concentrations generated in these subjects.

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Received November 26, 1982.
Accepted for publication January 20, 1983.

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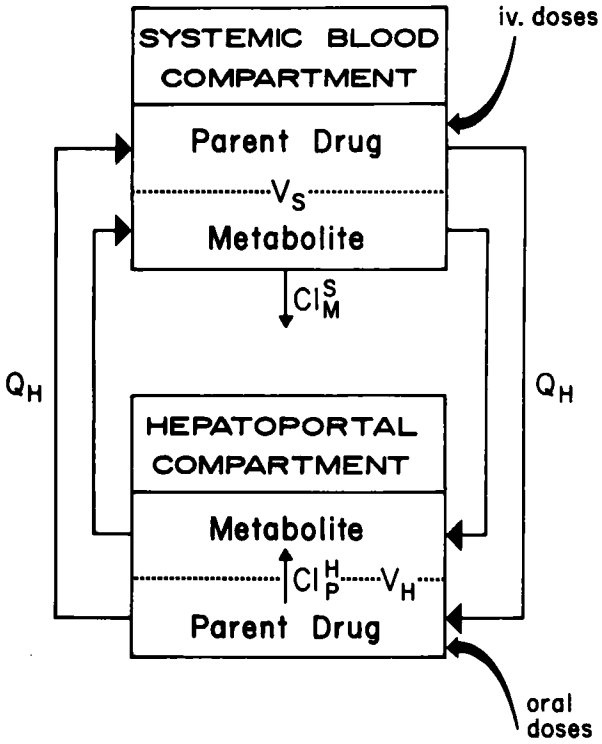
First-Pass, Formation-Rate-Limiting Metabolism

Keyphrases □ First-pass metabolism—impact on pharmacokinetic parameters, use of simulation techniques, formation-rate-limited metabolism □ Formation-rate-limited metabolism—pharmacokinetic parameters, use of simulation techniques □ Pharmacokinetic parameters—use of simulation techniques for first-pass and formation-rate-limited metabolism studies

To the Editor:

It has become increasingly apparent that there is a general misunderstanding of the driving forces that control first-pass and formation-rate-limited metabolism. In fact, a single metabolite can be the result of both first-pass and formation-rate-limited metabolism. To clarify this issue, simulation techniques were used to delineate the causative factors that determine both first-pass and formation-rate-limited metabolism.



Scheme I—First pass metabolism model used to simulate both parent drug and metabolite plasma concentrations under various conditions. Q_H is the hepatic blood flow, CL_M^S is the systemic clearance of the metabolite, CL_P^H is the hepatoportal clearance of parent drug to metabolite, V_P^S, V_P^H, V_M^S, and V_M^H are the systemic and hepatoportal volumes of parent and metabolite, respectively. The volume of distribution for the metabolite ($V_M^S + V_M^H$) is assumed to be equivalent to the systemic volume of distribution (V_P^S) of the parent drug and V_M^H is set equal to 1; e.g., the metabolite is not retained in the liver after formation (60 mg administered). Oral doses (60 mg) are absorbed into the hepatoportal compartment with the rate constant k_a, and intravenous doses (60 mg) are administered instantly into the systemic blood compartment.

The differential equations (see *Appendix*) needed to describe the first-pass metabolism model shown in Scheme I were used for the simulation of plasma concentration–time data for both parent drug and a single metabolite following oral and intravenous doses. The differential equations required to describe the model were used in conjunction with the nonlinear regression program NONLIN (1), to simulate parent drug and metabolite concentration–time data for drugs with varied pharmacokinetic characteristics. A 60-mg dose was used for each simulation. Several biopharmaceutic and pharmacokinetic parameters such as the time (t_{max}) of the maximum observed concentration (C_{max}) following oral doses, the areas under the plasma concentration–time curve (AUC) for parent drug and metabolite following oral (AUC_P^O and AUC_M^O) and intravenous (AUC_P^{IV} and AUC_M^{IV}) doses, the terminal elimination half-lives for parent drugs ($t_{1/2P}$) and metabolite ($t_{1/2M}$), the ratio of oral to intravenous area of parent (F_P) and metabolite (F_M), and the ratio of metabolite–parent drug following oral (R_O) and intravenous (R_{IV}) doses were calculated from the simulated plasma concentration–time data. The constants used for

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Table I—Effect of First-Pass, Formation-Rate-Limited Metabolism on Various Pharmacokinetic Parameters [a]

Simulation Constants	Case I A	I B	I C	II A	II B	II C	III A	III B	III C	IV A	IV B	IV C
k_a, hr^{-1}	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Q_H, liter/hr	90	90	90	90	90	90	90	90	90	90	90	90
CL_P^H, liter/hr	450	450	450	4,500	4,500	4,500	450	450	450	4,500	4,500	4,500
CL_M^S, liter/hr	600	6,000	60,000	600	6,000	60,000	18	180	1,800	18	180	1,800
V_P^S, liter	60	600	6,000	60	6,000	60,000	60	600	6,000	60	600	6,000
V_P^H, liter	60	60	60	600	600	600	60	60	60	600	600	600
V_M^S, liter	59	599	5,999	59	599	5,999	59	599	5,999	59	599	5,999
V_M^H, liter	1	1	1	1	1	1	1	1	1	1	1	1
Biopharmaceutic Parameters												
t_{maxP}, hr	1.0	2.5	4.5	1.0	2.5	4.5	1.0	2.5	4.5	1.0	2.5	4.5
C_{maxP}, μg/ml	53.3	12.2	2.57	5.80	1.39	0.184	53.3	12.2	1.57	5.80	1.39	0.184
t_{maxM}, hr	0.5	0.5	0.5	0.5	0.5	0.5	2.0	2.0	2.0	2.0	2.0	2.0
C_{maxM}, μg/ml	61.4	5.87	0.584	68.3	6.80	0.679	571	50.9	4.98	591	58.4	5.82
$t_{1/2P}$, hr	0.57	5.6	55.4	0.47	4.7	47.1	0.57	5.6	55.4	0.47	4.7	47.1
$t_{1/2M}$, hr	0.57	5.6	55.4	0.47	4.7	47.1	2.3	5.6	55.4	2.3	4.7	47.1
Pharmacokinetic Parameters												
AUC_P^0, μg hr/ml	133	133	133	12.5	13.3	13.3	133	133	133	12.5	13.3	13.3
AUC_M^0, μg hr/ml	797	800	800	680	680	680	797	800	800	680	680	680
AUC_M^O, μg hr/ml	99	9.91	1.00	100	10	1.0	3290	329	32.9	3,290	329	32.9
AUC_M^{IV}, μg hr/ml	100	10.0	1.00	100	10	1.0	3290	329	32.9	3,290	329	32.9
F_P	0.17	0.17	0.17	0.02	0.02	0.02	0.17	0.17	0.17	0.02	0.02	0.02
F_M	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
R_O	0.74	0.074	0.0075	8.0	0.75	0.075	24.7	2.47	0.25	263	24.7	2.47
R_{IV}	0.13	0.013	0.0013	0.15	0.015	0.0015	4.13	0.411	0.041	4.83	0.483	0.048
$CL_{B,P}$ liter/hr	75	75	75	88	88	88	75	75	75	88	88	88
$C_{B,M}$ liter/hr	600	6,000	60,000	600	6,000	60,000	600	6,000	60,000	600	6,000	60,000

[a] Parameters defined in text.

the simulations as well as the calculated pharmacokinetic and biopharmaceutic parameters are presented in Table I.

Substantial first-pass metabolism occurs in all cases, because the metabolic organ clearance (CL_P^H) exceeds hepatic blood flow (Q_H). t_{maxP} is earlier than t_{maxM} when the metabolite is not formation-rate limited, (Table I, Cases IIIA and IVA); *i.e.*, the half-life of the metabolite exceeds the half-life of the parent drug. Therefore, it is apparent that t_{maxM} occurs earlier than t_{maxP} only when the metabolite is the result of first-pass metabolism and the elimination of the metabolite is limited by the parent half-life. In addition, it is apparent that the volume of distribution of the parent drug is the controlling factor in determining whether a first-pass metabolite will ultimately be formation-rate limited. Although the clearance of parent drug does not change as the volume of distribution for the parent drug increases, the half-life of the parent drug ($t_{1/2P}$) will ultimately limit the *apparent* rate of elimination of the metabolite ($t_{1/2M}$) as the metabolite formation rather than its elimination becomes rate determining (Table I, Case IIIA–C and Case IVA–C).

The effective hepatic volume of distribution for the parent drug is important to the extent of first-pass metabolism (2). Although the half-life does not change (Table I, Case IA–C *versus* Case IIA–C and Case IIIA–C *versus* Case IVA–C), the extent of first-pass metabolism increases as the hepatic organ clearance (CL_P^H) increases as a function of increasing effective hepatic volume (2), such that the data reflect a decrease in the bioavailability parameter (F_P). The relative bioavailability of the metabolite (F_M) does not change, since all of the administered drug is ultimately converted to metabolite in the simplistic model used for these simulations. If an alternative route of elimination exists for the parent drug, then relative metabolite bioavailability would change as well. The ratios of the metabolite AUC to the parent AUC following oral (R_O) and intravenous (R_{IV}) doses increase as the effective hepatic volume increases (Table I, Case I *versus* Case II). However, due to first-pass metabolism, the increase in R_O is much higher than the increase in R_{IV}.

Additional observations became apparent as a result of the simulation procedures. The concentration–time data simulated from Case IVB are presented in Fig. 1 to illustrate various phenomena that were observed. First, under the conditions of this simulation, metabolite concentrations following oral doses decrease with an apparent half-life shorter than that of the parent drug for an interval of 48 hr before becoming formation-rate limited. If the analytical sensitivity is limiting or its sampling is restricted to 24 hr or less, it would appear that the metabolite was being eliminated more quickly than the parent drug.

In conclusion, it has been demonstrated that first-pass and formation-rate metabolism are not mutually exclusive. In fact, even first-pass metabolites with reasonably long elimination half-lives can be formation-rate limited if the volume of distribution of the parent drug is sufficiently large. This results because the driving force for first-pass metabolism is a high extraction ratio for the parent compound, *i.e.*, high organ clearance, whereas the driving force for formation-rate limited metabolism is a shorter half-life for the metabolite than that of the parent compound. This can occur easily if the volume of distribution of the parent compound is extremely large. Finally, the impact of first-

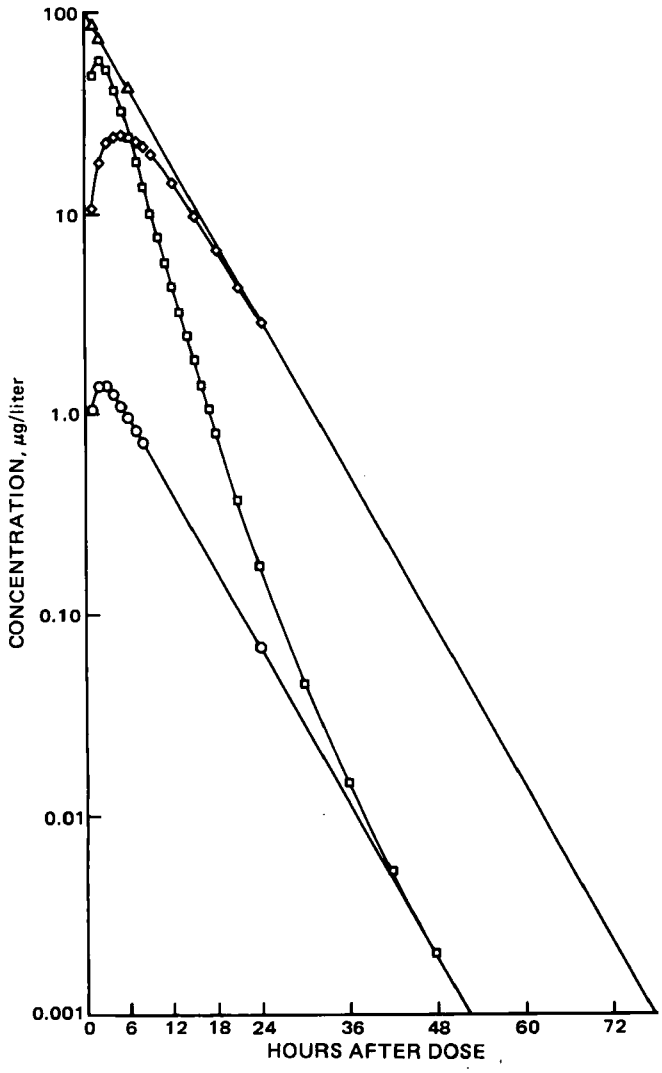

Figure 1—*Blood concentrations of drug and metabolite following oral (○ and □) and intravenous (△ and ◇) doses, respectively, simulated according to Case IVB.*

pass metabolism on various pharmacokinetic parameters has been delineated using simulation techniques.

APPENDIX

The following differential equations were used to simulate the plasma concentration–time data presented in this report.

$$\frac{dC_P^S}{dt} = Q_H \cdot (C_P^H - C_P^S)/V_P^S \qquad \text{(Eq. A-1)}$$

$$\frac{dC_M^S}{dt} = [Q_H \cdot C_M^H - (Q_H + CL_M^S) \cdot C_M^S]/V_M^S \qquad \text{(Eq. A-2)}$$

$$\frac{dC_P^H}{dt} = [k_a De^{-k_{at}} + Q_H \cdot C_P^S - (Q_H + CL_P^H) \cdot C_P^H]/V_P^H \qquad \text{(Eq. A-3)}$$

$$\frac{dC_M^H}{dt} = [Q_H \cdot C_M^S + CL_P^H C_P^H - Q_H C_M^H]/V_M^H \qquad \text{(Eq. A-4)}$$

Where D is the oral dose and the remaining terms have been identified in the text and legend to Scheme I. The $k_a De^{-k_{at}}$ term is the source of drug input for the oral dose. This source is not used for the IV dose, whereas the initial condition for C_P^S is set equal to D/V_P^S for the IV dose.

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Received March 10, 1982.
Accepted for Publication January 5, 1983.

Factors Affecting the Accuracy of Estimated Mean Absorption Times and Mean Dissolution Times

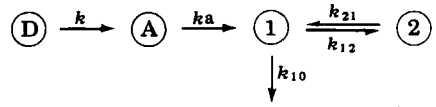
Keyphrases □ Statistical moment analysis—estimation of absorption and dissolution rates, effects of the sampling schedule, importance of the estimate of the terminal elimination rate constant (β)

To the Editor:

Recent discussions in the literature concerning the application of the concept of statistical moments to pharmacokinetic analysis has stimulated interest in the method and its potential utility in the evaluation of pharmacokinetic and bioavailability data. The most appealing aspect of statistical moment analysis is the potential for model-independent estimates of *in vivo* dissolution and absorption rates. A thorough discussion of this method and its potential applications was presented by Riegelman and Collier (1) and Yamaoka *et al* (2).

Using simulation techniques, the present study evaluates the ability of statistical moment analysis to provide accurate estimates of absorption and dissolution rates and the effects of sampling schedule, random error, and the estimate of the terminal elimination rate constant (β) on the accuracy of these estimates.

Simulations of drug concentration–time data corresponding to administration of an intravenous bolus, oral solution, and tablet dosage forms were generated by the CSSL-IV simulation program (3) based on the pharmacokinetic models presented in Scheme I. Unless otherwise specified, the parameter values presented in Table



Scheme I—Two-compartment pharmacokinetic model with sequential first-order dissolution and absorption, where k = *first-order dissolution rate constant and* k_a = *first-order absorption rate constant. To simulate intravenous data, the dose was entered into compartment 1; for oral solution data, the dose was entered into the absorption compartment (A); and for solid oral dosage form data, the dose was entered into the dissolution compartment (D).*

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