(8) S. G. Johnsen, *ibid.*, 1473 (1974).
(9) "The United States Pharmacopeia," 18th rev., U.S. Pharmacopeial Convention, Rockville, Md., p. 934.
(10) D. Wurster and P. Taylor, *J. Pharm. Sci.*, **54**, 670 (1965).
(11) H. Ibayashi, M. Nakamura, and K. Nakao, *Steroids*, **2**, 559 (1964).
(12) W. Futterweit, N. L. McNiven, and R. I. Dorfman, *ibid.*, **1**, 628 (1963).

COMMUNICATIONS

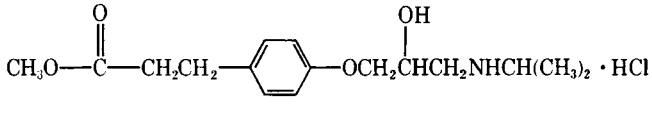
Esmolol: A Pharmacokinetic Profile of a New Cardioselective β-Blocking Agent

Keyphrases □ β-Adrenergic blocking agents—esmolol hydrochloride, pharmacokinetic profile, metabolism □ Pharmacokinetic profile—cardioselective β-adrenergic blocking agent, methyl 3-[4-(2-hydroxy-3-(isopropylamino)propoxy]phenylpropionate hydrochloride □ Esmolol—cardioselective β-adrenergic blocking agent, pharmacokinetic profile

To the Editor:

β-Adrenergic receptor blocking drugs exert their effects by competitively inhibiting the binding of catecholamines to β-adrenergic receptors. To attain therapeutic levels rapidly, intravenous bolus or infusions of β-blockers are usually instituted. However, since these agents have cardiac depressant properties, they are initially used at low doses, and slowly increased until the desired effects are obtained. Because currently available β-adrenergic blocking agents are long acting, the emergence of side effects, especially acute cardiac failure, poses a significant problem in their use because their action cannot be readily terminated. Therefore, there is a need for a β-adrenergic blocking drug with a short onset of action which can be rapidly terminated if side effects develop.

Esmolol (ASL-8052, Scheme I) is a new cardioselective intravenous β-receptor blocking agent with a very short duration of action in humans (unpublished data) and dogs (1). It is extensively metabolized in blood and liver by hydrolysis of the methyl ester functionality to form its major metabolites, ASL-8123 and methanol.



Esmolol (ASL-8052)

Methyl 3-[4-(2-Hydroxy-3-(isopropylamino)propoxy]phenylpropionate hydrochloride

Scheme I

To study the pharmacokinetics of esmolol, eight healthy male subjects (21–27 years old) weighing 62.4–76.2 kg received constant intravenous infusions of 50, 150, and 400 μg/kg/min for 2 hr on three different days. Each subject received an intravenous dose of isoproterenol, which had previously been determined to produce a 50% increase in heart rate. The suppression of the isoproterenol-induced increase in heart rate and blood pressure was determined on several occasions during and up to 60 min after the cessation of the esmolol infusion. At each dose level, blood samples were collected for determinations of esmolol and ASL-8123 by gas chromatography–mass spectrometry and high performance liquid chromatography, respectively (2). Esmolol and ASL-8123 concentrations, as a function of time during and after the infusion, were fitted to equations describing a two-compartment open model (3, 4) and modified one-compartment open model, respectively, by nonlinear least-squares regression analysis.

Esmolol infusion significantly blocked the isoproterenol effects with its action being most evident at the 400-μg/kg/min dose. The duration of action of esmolol was, however, very short with no significant effect evident 30 min after cessation of the infusion at all three doses. There was a significant correlation between the reduction of the isoproterenol-induced increase in heart rate and blood pressure and the logarithm of esmolol blood concentrations. Blood levels of 0.3 and 1 μg/ml esmolol were associated with 50 and 80%, respectively, reduction in heart rate and 30 and 50%, respectively, reduction in blood pressure.

The steady-state concentrations of esmolol increased proportionally with the dose ($r = 0.866$, $p < 0.001$, $n = 24$). The mean concentrations (±*SD*) were 0.164 ± 0.068, 0.569 ± 0.204, and 1.59 ± 0.605 μg/ml, respectively, after 2-hr infusions of 50, 150, and 400 μg/kg/min. The respective values for the total clearance were 363 ± 184, 298 ± 112, and 285 ± 104 ml/min/kg, which were not correlated with dose ($r = 0.210$, $p > 0.3$, $n = 24$). These findings suggest that the elimination of esmolol is linear within the 50–400 μg/kg/min dosing range given for 2 hr.

Table I summarizes several of the key pharmacokinetic parameters for esmolol and ASL-8123 after the 400

Table I—Summary of Some Pharmacokinetic Parameters of Esmolol and its Metabolite after Administration of 400 μg/kg/min infusion of the Drug for 2 hr in Normal Subjects

Pharmacokinetic Parameters	Esmolol	ASL-8123
Steady-state concentration, μg/ml	1.59 ± 0.605[a]	—
Peak concentration, μg/ml	—	77.9 ± 3.93
Peak time, min	—	146 ± 11.1
Terminal half-life, min	9.19 ± 3.51	223 ± 14.0
Half-life of formation of metabolite(s), min	—	2.82 ± 0.592
Total clearance, ml/min/kg	285 ± 104	1.28 ± 0.19
Volume of distribution, liters/kg	3.43 ± 1.42	0.411 ± 0.057
Calculated fraction of metabolite formed[b]	—	0.829

[a] Mean ± *SD*; $N = 8$. [b] Ratio of formation and elimination rate constants (k_f/k_{10}).

0022-3549/83/0600-0710$01.00/0

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.

(1) J. Zaroslinski, R. J. Borgman, J. P. O'Donnell, W. G. Anderson, P. W. Erhardt, S. T. Kam, R. D. Reynolds, R. J. Lee, and R. J. Gorczynski, *Life Sci.*, **31**, 899 (1982).

(2) C. Y. Sum and A. Yacobi, "Proceedings of the 33rd National Meeting of the Academy of Pharmaceutical Sciences," 1982.

(3) M. Gibaldi, and D. Perrier, "Drugs and The Pharmaceutical Sciences, vol. 1, Pharmacokinetics," Dekker, New York, N.Y., 1975, p. 69.

(4) J. G. Wagner, "Fundamentals of Clinical Pharmacokinetics," 1st ed., Drug Intelligence Publication, Hamilton, Ill., 1975, p. 90.

(5) A. C. Clayton, "Textbook of Medical Physiology," 4th ed., W. B. Saunders, 1971, p. 369.

*Avraham Yacobi**x
Ronald Kartzinel
Chii-Ming Lai
Check Y. Sum,
Research and Development
American Critical Care
McGaw Park, IL 60085

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

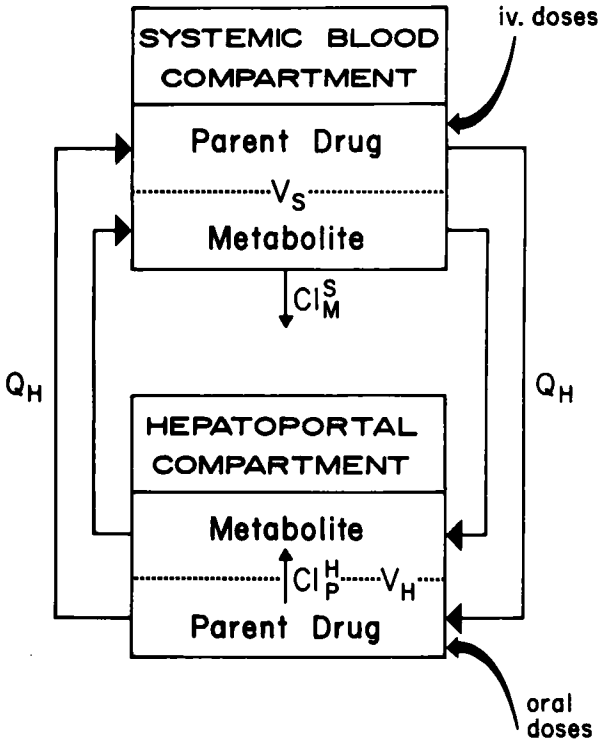
* Present address:
Medical Research Div.
American Cyanamid Co.
Pearl River, NY 10965

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

0022-3549/83/0600-0711$01.00/0