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Pharmacokinetics of Esmolol in Anesthetized Patients Receiving Chronic Beta Blocker Therapy

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The pharmacokinetics of esmolol, a new, ultra-short-acting beta adrenergic blocking drug, were studied in 19 patients undergoing coronary artery surgery. Esmolol was administered as a continuous infusion, and blood concentrations were measured at intervals up to 40 min after discontinuation of the infusion. In all patients, a bi-exponential equation best described the esmolol concentration—time curve. Half-lives for the distribution and elimination phases were 1.34 ± 0.77 min and 9.9 ± 4.55 min (mean ± SD), respectively. The mean values for V_β and V_c were 1.9 ± 1.24 $l \cdot kg^{-1}$ and 0.41 ± 0.31 $l \cdot kg^{-1}$, respectively, and the total clearance was 128 ± 41 $ml \cdot kg^{-1} \cdot min^{-1}$. (Key words: Pharmacokinetics: esmolol. Surgery: cardiac. Sympathetic nervous system, beta adrenergic blockade: esmolol.)

ESMOLOL (methyl 3-(4-(2-hydroxy-3-(isopropylamino propoxy) phenyl) proprionate hydrochloride)) (fig. 1) is a cardioselective, watersoluble, β-adrenoceptor antagonist recently described by Zaroslinski *et al.*[1] The drug is extensively and rapidly metabolized in blood and liver by hydrolysis of the methyl ester, resulting in an ultrashort duration of action.[2]

Esmolol prevents or abolishes the increases in heart rate (HR) and systemic blood pressure (SBP) occurring during general anesthesia and surgery in response to increased sympathetic activity.[3] Well-recognized stimuli leading to such increases in HR and SBP are laryngoscopy, endotracheal intubation, skin incision, and, in patients undergoing cardiac surgery, median sternotomy and sternal retraction.[4,5]

The pharmacokinetics of esmolol were described by Sum *et al.*[2] in normal volunteers, but the kinetic behavior of the drug in a clinical, therapeutic situation has not been reported. We studied the pharmacokinetics of esmolol in patients with coronary artery disease, chronically treated with β-adrenergic blocking drugs undergoing elective coronary artery bypass grafting.

Methods

With Institutional Review Board approval and written informed consent, 19 patients scheduled for elective CABG were studied. All patients received their regular morning dose of β-blocking drug at least 4, and not more than 6, h before initiation of the study. Premedication consisted of 0.15 $mg \cdot kg^{-1}$ of diazepam po, scopolamine 0.2–0.3 mg im, and morphine 0.1 $mg \cdot kg^{-1}$ im 2 h prior to surgery.

After placement of a pulmonary artery catheter, an indwelling arterial catheter, and central and peripheral venous catheters, a 10-min stabilization period was observed. Esmolol was started after the stabilization period, and was administered into a peripheral vein, according to the regimen outlined in Table 1, in order to avoid a high peak esmolol concentration. Anesthesia was induced after 7 min of esmolol infusion with diazepam 0.5 $mg \cdot kg^{-1}$ iv, pancuronium 100 $mcg \cdot kg^{-1}$, and enflurane 0.4%.

Venous blood was sampled immediately before the start of the esmolol infusion from a short cannula in the right internal jugular vein, and then at induction of anesthesia, at endotracheal intubation (4 min after induction of anesthesia), at skin incision, at sternotomy, at maximal sternal spread, at the end of the esmolol infusion (5 min after maximal sternal spread), and at 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 18, 21, 25, 30, and 40 min after discontinuation of esmolol. Blood sampling was completed before the initiation of cardiopulmonary bypass. Blood samples were collected in fluoride-treated syringes, and immediately extracted using methylene chloride (10 ml), the internal standard ASL-9038 (2 mcg) and 0.1 ml of water. After shaking for at least 10 min on a mechanical shaker, the blood samples were centrifuged at 3000 rpm for 10 min. The sample was subsequently deproteinized with 0.5 ml of 14% perchloric acid. After centrifugation, the methylene chloride layer was stored at −60° C. Later, analysis was performed with a GC-MS method described by Sum

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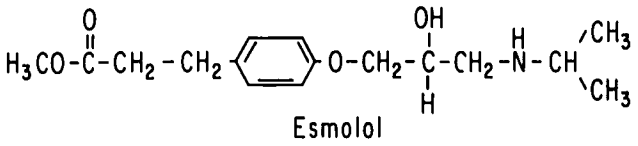

FIG. 1. Structural formula of esmolol.

and Yacobi.* The sensitivity of the assay is 0.025 ng · ml^{-1}, the coefficient of variation (COV) at this level was 6.41% COV, and at 0.1, 1, and 5 ng · ml^{-1} it was 1.63, 1.55, and 0.436%, respectively. The esmolol blood level-time data were fitted to a two-compartment open model using NONLIN 84. The weight used was 1/c (c = esmolol concentration). Convergence was assumed when the relative change in the weighted sum of squares was $<10^{-4}$. For modeling purposes, a constant iv input and first-order output were assumed.

Results

Patient characteristics are presented in Table 2. Figure 2 shows the blood concentration—time profile of esmolol in two typical patients after discontinuation of the infusion. Kinetic analysis was performed on the blood concentration—time data, and the results are listed in Table 3. Blood concentration—time data of six patients were not used for kinetic analysis because of incomplete sampling or sampling errors. The distribution half-life and the elimination half-life were 1.3 and 9.9 min, respectively. The apparent volume of distribution was 1.9 l · kg^{-1}, the apparent volume of the central compartment was 0.413 l · kg^{-1}. The total clearance was 128 ± 41 ml · kg^{-1} · min^{-1}. The total duration of the infusion at the final infusion rate was 54.8 ± 5.6 min.

Discussion

Esmolol has undergone clinical trials in an intraoperative setting for several years, and is a unique new beta adrenergic blocking drug.[1] Beta blocking drugs play an increasingly important role in the perioperative period. Preoperatively, they are used for the treatment of hypertension, angina pectoris, and cardiac arrhythmias. Most anesthesiologists maintain their patients on beta blocking drugs to protect the heart from sympathetically mediated increases in heart rate and contractility. Intraoperatively, beta-adrenergic blocking drugs are used to treat arrhythmias, to depress LV-function in hyperdynamic states, to decrease the requirements for sodium nitroprusside, and to treat the reflex tachycardia that may result from the use of vasodilators. The potential dangers of perioperative beta blockade are not negligible, however. The addition of anesthetic agents which may have negative chronotropic, negative dromotropic, or negative inotropic properties interact with the beta-adrenergic blocking drugs, and can cause inappropriate cardiac depression,[6] which may not be rapidly reversible, due to the relatively long duration of action of the beta blockers in current clinical use. Furthermore, the adverse effects of beta blockers on bronchial smooth muscle are well known. Although esmolol is a selective beta blocker with less effects on bronchial muscle tone, any bronchospasm that might result from esmolol would be more short-lived than after any other cardioselective beta blockers.

Given the metabolism of esmolol in blood, the site where blood is sampled is important. In an animal study, investigators at American Critical Care found that blood esmolol concentrations were 3–7-fold higher in arterial blood than in peripheral venous blood.† It is hypothesized that the exposure time of the drug between infusion in a peripheral vein and sampling arterial blood is too short to allow for sufficient equilibration and exposure to the blood esterases, so that arterial concentrations may be expected to be higher. Sum *et al.*[2] do not report where they acquired their blood samples, however, so comparison is not possible.

The pharmacokinetic profile of esmolol is remarkable for its high total body clearance, which has been previously reported to be four times the cardiac output.[2] Consequently, it has a short terminal elimination half-life. The high esmolol clearance is mainly due to its rapid metabolism by esterases in the blood. However, some esmolol

TABLE 1. Esmolol Infusion Regimen

Infusion rate (mcg · kg^{-1} · min^{-1})	Duration (min)
500	1
100	4
500	1
200	4
500	1.5
300	Until 5 min after sternal spread

* Sum CY, Yacobi A: A gas chromatographic-mass spectrometric assay for ASL-8052: An ultra short acting beta blocker. Proceedings 33rd National Meeting of the Academy of Pharmaceutical Sciences, San Diego, 1982.

† ACC study #8052-82-14-02.

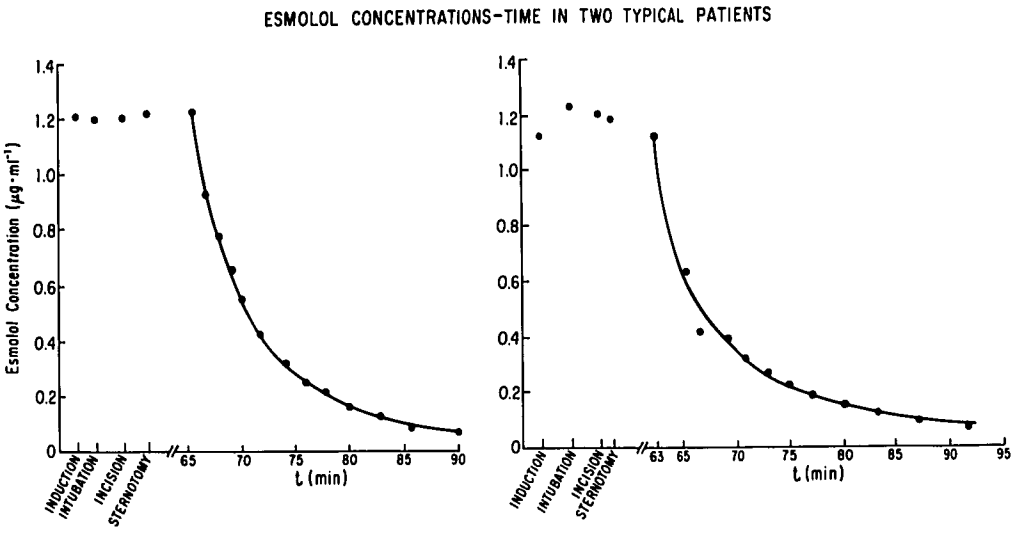

FIG. 2. Blood concentrations during and after a continuous infusion of esmolol in two typical patients. A two-compartment model best fits the decay curve. The times indicated on the horizontal axis refer to the time after the start of the infusion. Only the decay phase was fitted.

is probably also cleared by esterases in well-perfused organs, such as kidneys and liver. Thus, esmolol should be more suitable for perioperative use than the currently available beta blocking drugs, because of the extremely short duration of action and the relative ease with which the drug can be titrated to effect.

The clearance of esmolol was 128 $ml \cdot kg^{-1} \cdot min^{-1}$ in this study, which is significantly lower than the 285 $ml \cdot kg^{-1} \cdot min^{-1}$ that Sum *et al.* reported[2] (Table 4). We found a similar elimination half-life, however, because the volume of distribution in our study is also significantly smaller than that in the study by Sum *et al.*

The lower clearance found in our group of anesthetized patients, compared with the awake volunteers, may well have been caused by the decreased blood flow to the kidneys and the liver, which, although not measured in this study, has been well documented[7] to be an effect of general anesthesia. In addition, all of our patients were chronically treated with beta adrenergic blockers. These agents are known to decrease their own metabolism, probably due to a decrease in hepatic blood flow.[8] This may also, in part, explain why the drug was cleared more slowly in our patients, compared with the healthy volunteers. Cardiac index (CI), however, was not significantly decreased by esmolol in these patients (Baseline CI = 2.3 ± 0.3 $l \cdot min^{-1} \cdot m^{-2}$ *versus* at skin incision 2.2 ± 0.5 $l \cdot min^{-1} \cdot m^{-2}$, P = NS). Another possible explanation for the difference in pharmacokinetic parameters that we found compared to the study by Sum *et al.* would be differences in methodology concerning data acquisition and measurement of blood concentrations, and in the performance of the nonlinear regression data fitting. Critical review of their report does not reveal any significant differences between the study by Sum *et al.* and the present study concerning the factors mentioned above.

An interesting observation in Sum *et al.*'s study was the large intersubject variation, with terminal elimination half-life varying between 4.98 and 15.8 min, a 300% range. The coefficient of variation (COV) for the half-life was 38%, and those for the volume of distribution and total clearance was 41.4% and 36.5%, respectively. We found similar variation with a COV of 46.4% for $t_{1/2}\beta$, 31.3% for clearance, and 75.1% for the volume of the central compartment. The plasma concentration of esmolol at steady state had a COV of 27.1%. However, even a 300% range in elimination half-life in an extremely short-acting drug like esmolol will not have a major clinical impact, but it emphasizes the need for dosage regimens based on effect and individual needs.

In conclusion, we have described the overall pharmacokinetic characteristics of esmolol in anesthetized, beta-

TABLE 2. Demographic Data

Male	17
Female	2
Total	19
Chronic β-blockers:	
Atenolol	8
Metoprolol	1
Nadolol	1
Propranolol	9
Oral nitrates	11
Calcium entry blockers	11
Weight (kg)*	: 77.6 ± 12.8 (53–100)
Body surface area (m^2)*	: 1.89 ± 0.17 (1.53–2.21)
Age (yr)*	: 57 ± 8.4 (40–69)
Ejection fraction*	: 58 ± 10 (29–73)

* mean ± SD; range in parentheses.

TABLE 3. Pharmacokinetic Parameters of Esmolol

Patient	α (min^{-1})	$t_{\frac{1}{2}}\alpha$ (min)	β (min^{-1})	$t_{\frac{1}{2}}\beta$ (min)	Css ($\mu g \cdot ml^{-1}$)	Cl ($ml \cdot kg^{-1} \cdot min^{-1}$)	$V\beta$ ($l \cdot kg^{-1}$)	V_c ($l \cdot kg^{-1}$)	AUC ($\mu g \cdot min \cdot ml^{-1}$)
1	0.249	2.78	0.03	23.1	1.89	158	5.05	0.736	126
2	2.58	0.27	0.135	5.13	1.39	216	0.542	0.035	284
3	0.668	1.05	0.0845	8.21	1.52	197	2.12	0.715	109
4	0.523	1.33	0.0774	8.95	2.52	119	1.65	0.327	142
5	0.475	1.46	0.105	6.60	2.67	112	1.79	0.648	104
6	0.398	1.74	0.0664	10.4	2.07	145	3.02	0.709	92.5
7	1.44	0.48	0.106	6.53	3.40	88.2	0.445	0.039	450
8	0.813	0.85	0.0922	7.52	2.87	105	1.33	0.296	185
9	0.735	0.94	0.0761	9.11	2.99	100	1.65	0.245	155
10	0.238	2.92	0.0511	13.6	2.42	24	3.31	1.030	102
11	0.553	1.25	0.0621	11.2	3.31	90.6	1.78	0.279	174
12	0.614	1.13	0.0638	10.9	6.04	49.7	0.712	0.891	434
13	0.619	1.12	0.0873	7.94	2.39	126	2.21	0.480	105
Mean	0.749	1.34	0.0783	9.90	2.53	128	1.90	0.413	194
SD	0.601	0.77	0.0259	4.55	0.68	41	1.24	0.310	120
Coefficient of variation	82.2	57.8	40.1	46.4	27.1	31.9	65.2	75.1	58.0

TABLE 4. Comparison of Esmolol Pharmacokinetic Parameters

	Present Study		Sum *et al*	
	Mean ± SD	COV (%)	Mean ± SD	COV (%)
α (min^{-1})	0.749 ± 0.601	82.2	0.364 ± 0.095	NA
$t_{\frac{1}{2}}\alpha$ (min)	1.34 ± 0.77	57.8	2.030 ± 0.544	NA
β (min^{-1})	0.078 ± 0.026	40.1	0.085 ± 0.031	NA
$t_{\frac{1}{2}}\beta$ (min)	9.9 ± 4.55	46.4	9.190 ± 3.510	38
C_{ss} ($\mu g \cdot ml^{-1}$)	2.53 ± 0.68	27.1	1.59 ± 0.605	NA
Cl ($ml \cdot kg^{-1} \cdot min^{-1}$)	128 ± 41	31.9	285 ± 104	36.5
$V\beta$ ($l \cdot kg^{-1}$)	1.90 ± 1.24	65.2	3.430 ± 1.420	41.4
V_c ($l \cdot kg^{-1}$)	0.41 ± 0.31	75.1	0.867 ± 0.259	NA
AUC ($\mu g \cdot min \cdot ml^{-1}$)	194 ± 120	58.0	NA	NA

NA = not available; COV = Coefficient of variation.

blocked patients. Because most adrenergic responses during anesthesia and surgery are short-lived, the very short elimination half-life of esmolol makes it a desirable drug for perioperative use from a pharmacokinetic point of view.

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