Esmolol, the first ultra-short-acting intravenous beta blocker for use in critically ill patients

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β-Adrenergic blockade is well recognized as a therapeutic tool in acute care settings for the treatment of supraventricular tachyarrhythmias (SVT), ischemic heart disease, and hypertension. β-Blockers compete with adrenergic mediators for β-adrenergic receptors: β_1 receptors of heart muscle and β_2-receptors of bronchial and vascular smooth muscle. With these receptor sites blocked,

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the chemical mediators of the sympathetic nervous system, norepinephrine and epinephrine, are unable to activate the receptor site and therefore cannot initiate the responses (such as chronotropic, inotropic, electrophysiologic, vasodilator, and bronchodilator responses) to β-adrenergic stimulation.[1,2]

β-Blockers may possess the properties of β_1- and β_2-selectivity, intrinsic sympathomimetic activity (ISA) and membrane-stabilizing activity (MSA).[1,2] Cardioselective β-blockers (e.g., metoprolol, atenolol) predominantly block the β_1-receptors and are preferred in patients with peripheral vascular disease, chronic lung disease, and insulin-dependent diabetes mellitus. Noncardioselective β-blockers (e.g., propranolol, nadolol) block the effects of epinephrine and norepinephrine on both β_1- and β_2-receptors.

β-Blockers with ISA possess both partial agonist activity and β-blocking activity. ISA thus provides some degree of adrenergic stimulation in addition to blockade of β-receptor sites. Consequently, agents with this property reduce resting heart rate and myocardial contractility to a lesser degree than do agents without this property.[1,2]

The local anesthetic membrane-stabilizing effect on cardiac action potential possessed by some β-blockers is similar to that exerted by quinidine. This property, known as MSA, is exhibited when very high doses of a β-blocker are administered. Generally, MSA is present clinically only during incidents of β-blocker intoxication and is not responsible for the antiarrhythmic action of these agents.[1,2]

Propranolol and metoprolol, the only other currently available intravenous β-blockers, have relatively long elimination half-lives. Esmolol (Brevibloc), a new short-acting intravenous cardioselective β-blocker with no significant ISA or MSA, has recently been approved by the U.S. Food and Drug Administration and is available for clinical use. Structurally, esmolol is similar to other β-blockers except for the ester linkage responsible for its short elimination half-life (9 minutes).[3] This short half-life allows for titration to desired effect and rapid reversal of β-blockade after discontinuation of esmolol, thus providing an element of safety and control in treating critically ill patients. The purpose of this review is to discuss the pharmacokinetics, pharmacodynamics, and clinical use of esmolol.

PHARMACOKINETICS

Unlike most β-blockers, which are metabolized by the liver, esmolol is metabolized by esterases located in red blood cells. Metabolism of esmolol results in the formation of an acid metabolite (ASL-8123) and methanol.[4] The acid metabolite exhibits only 1/1500 of the activity of esmolol, with no noticeable β-blocking effects observed at the time of peak concentration of the metabolite (30 minutes after infusion).[4] Methanol blood levels have been found to be within endogenous levels and are less than 2% of those levels associated with methanol toxicity.[5]

Esmolol has a rapid distribution half-life of approximately 2 minutes, and blood levels increase linearly with dose. Total body clearance is approximately 20 L/kg/hr, consistent with the nonhepatic route of metabolism. In accordance with the high rate of metabolism in the blood, less than 2% of the drug is excreted unchanged in the urine. Esmolol has been shown to be 56% bound to human plasma protein, whereas the acid metabolite is only 7% bound,[6] indicating that there would not be a significant change in the kinetics of esmolol and other drugs.

With the use of an appropriate 1-minute loading dose (500 μg/kg/min), steady state blood concentration (1.59 μg/ml) of esmolol is achieved within 5 minutes, is well maintained during infusion, and decreases rapidly after termination of the infusion. Esmolol blood levels of 0.3 and 1 μg/ml have been shown to produce reductions in heart rate (HR) of 50% and 80% and reductions in blood pressure (BP) of 30% and 50%, respectively. Blood levels of esmolol are quickly altered by a change in infusion rate or rapidly eliminated by discontinuing the infusion.[4]

Since the liver is not involved in the disposition of esmolol and clearance is almost entirely by nonrenal routes, the pharmacokinetic profile of esmolol in patients with hepatic disease (cirrhosis) and end-stage renal disease does not differ from that of normal subjects.[7,8] On the other hand, the acid metabolite of esmolol is cleared by the kidney, and hence severe renal impairment increases the maximum blood concentration of this metabolite and its elimination half-life is prolonged tenfold. Severe hepatic disease has also been shown to increase maximum blood concentration of the acid metabolite. Consequently, care should be taken when esmolol is administered to patients with decreased renal or hepatic function.

The pharmacokinetic profile of esmolol was evaluated at steady state levels in the presence of digoxin, morphine, and warfarin. Concurrent administration of intravenous digoxin and esmolol to normal volunteers resulted in a 10% to 20% increase in digoxin blood levels at some time points. Digoxin had no effect on esmolol pharmacokinetics.[9] When intravenous morphine and

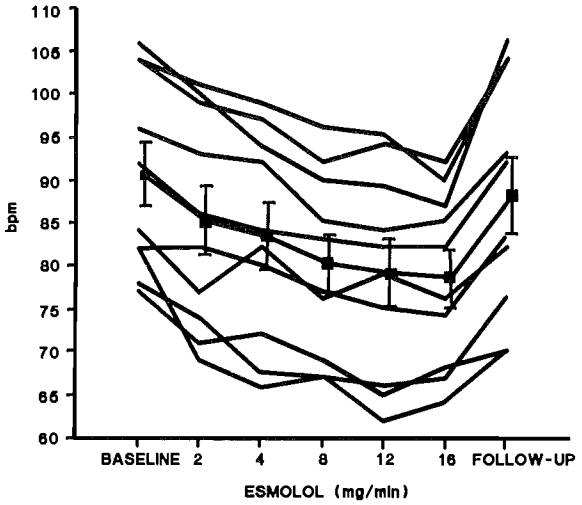

Fig. 1. Individual changes in HR with esmolol infusion in 10 patients. Follow-up took place 10 to 30 minutes after cessation of infusion. Vertical bars indicate mean ± SEM.

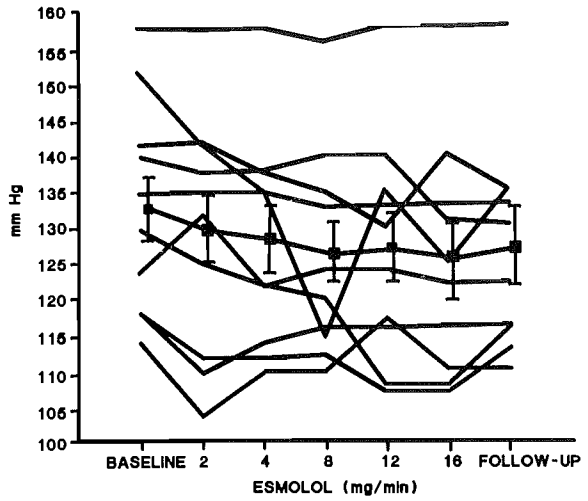

Fig. 2. Individual changes in arterial SBP with esmolol infusion in 10 patients. Follow-up took place 10 to 30 minutes after cessation of infusion. Vertical bars indicate mean ± SEM.

esmolol were administered concurrently, no effect on morphine blood levels was seen; however, esmolol blood levels increased by 46%. Similarly, concomitant administration of esmolol and warfarin did not influence warfarin plasma levels, and esmolol concentrations were modestly increased.

Succinylcholine, a short-acting muscle relaxant dependent on plasma cholinesterases for its rapid hydrolysis and inactivation, is commonly used during induction of anesthesia to facilitate rapid endotracheal intubation. Since the effects of succinylcholine may be altered by inhibition of plasma cholinesterases by esmolol, an interaction study was undertaken in surgical patients. Esmolol was shown to have no significant effect on the development of neuromuscular blockade, although the duration of blockade was prolonged by a period of 3 minutes (from 5 to 8 minutes), which is still considered to be within the clinically accepted normal range. The digoxin, morphine, warfarin, and succinylcholine interactions with esmolol were considered clinically insignificant; nevertheless, caution is advised when esmolol is administered to patients who are being treated with these agents. The short half-life of esmolol does, however, allow for rapid alteration in esmolol blood concentration by a simple decrease in the infusion rate or discontinuation of the infusion if an adverse effect appears.

PHARMACODYNAMICS

The relative cardioselectivity of esmolol in comparison with propranolol was demonstrated in patients with asthma and chronic obstructive pulmonary disease (COPD).[10] In mildly asthmatic patients, therapeutically effective esmolol infusions ranging from 100 to 300 μg/kg/min produced no significant increase in specific airway resistance in comparison with placebo. The bronchospastic potential of propranolol, however, was demonstrated when two of six patients receiving 1 mg of propranolol experienced significant, symptomatic bronchospasm requiring bronchodilator treatment. Furthermore, no adverse pulmonary effects were reported in patients with mild COPD (N = 51) who received esmolol for the treatment of SVT or during the perioperative period (N = 32).

Because of the cardioselectivity of esmolol, there are important clinical indications for the treatment of critically ill patients who frequently have a history of mild COPD or asthma. Rapid reversal of action, in conjunction with the relative cardioselectivity of esmolol, allows safe initiation of β-blockade, if indicated, in these high-risk patients. Since β-selectivity is not absolute, esmolol should be carefully titrated to obtain the lowest possible effective dose. If airway resistance increases significantly during esmolol infusion, the infusion should be reduced or discontinued and an appropriate β_2-stimulating agent administered.

The pharmacodynamics of esmolol in patients with acute myocardial ischemia (myocardial infarction, postmyocardial infarction angina, or acute unstable angina) has also been evaluated.[11]

A clinically significant reduction in mean HR (pretreatment, 92 ± 11 beats/min; treatment, 83 ± 11 beats/min) occurred within the first 5 minutes of esmolol titration (50 μg/kg/min), with maximum reduction in HR observed at a maintenance dose of 150 μg/kg/min. Similar reductions in systolic blood pressure (SBP) and diastolic blood pressure (15% and 13%, respectively) occurred at the end of titration. Maximum reduction in HR occurred at doses below those causing maximal reduction in BP. Consistent with the decrease in HR and BP, there was a significant decrease in rate-pressure product. No effect on left ventricular filling pressure or systemic vascular resistance was noted, but cardiac index decreased significantly by the end of titration (2.8 ± 0.6 to 2.2 ± 0.6 L/min/m^2). Because of the short elimination half-life of esmolol, all hemodynamic parameters returned to near baseline levels within 30 minutes after the infusion was terminated.

In the same study, six of eight patients receiving concurrent administration of intravenous nitroglycerin and esmolol required discontinuation of nitroglycerin therapy to maintain SBP at 90 mm Hg or greater. Although SBP rapidly increased in response to the termination of nitroglycerin infusion, close monitoring of a patient's hemodynamic state is recommended during concomitant administration of these two agents. If required, the dosage of either esmolol or nitroglycerin may be adjusted to maintain SBP.

Patients admitted to critical care areas with varying degrees of left ventricular dysfunction may be candidates for the use of β-blocking agents. Depression of the myocardium as a result of prolonged β-blockade can, however, lead to cardiac failure. Thus the short half-life of esmolol also makes it useful in the therapeutic armamentarium for these patients when the drug is properly administered.

Ten patients with a diagnosis of coronary artery disease and left ventricular dysfunction assessed by means of radionuclide angiography or contrast angiography were infused with incremental doses of 2 to 16 mg/min of esmolol (equivalent to 25 to 200 μg/kg/min in an 80 kg patient).[12] Nine of ten patients had a history of recent (range, 2 to 27 days) myocardial infarction with postinfarction angina. Baseline left ventricular ejection fraction (LVEF) was less than 25% in five patients and between 25% and 36% in the remaining five patients. Significant decreases in HR and BP occurred at the lowest doses (2 and 4 mg/min, respectively), as shown in Figs. 1 and 2. At the maximum dose titrated (16 mg/min),

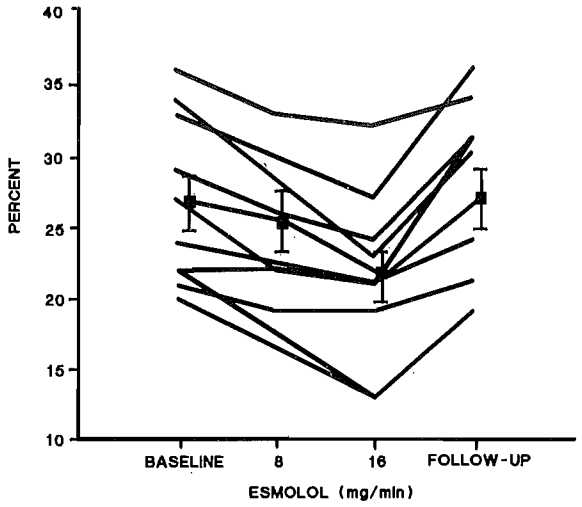

Fig. 3. Individual changes in LVEF with esmolol infusion in 10 patients. In some patients the ejection fraction was also measured at a dose of 8 mg/min. Follow-up took place 10 to 30 minutes after cessation of infusion. Vertical bars indicate mean ± SEM.

esmolol produced a significant increase from baseline in pulmonary artery wedge pressure (11 ± 1 to 15 ± 2 mm Hg), mean pulmonary artery pressure (17 ± 2 to 22 ± 2 mm Hg), and mean right atrial pressure (8 ± 1 to 10 ± 1 mm Hg), as well as a significant decrease from baseline in cardiac output (4.9 ± 0.3 to 4.3 ± 0.3 L/min), accompanied by an increase in systemic vascular resistance (15 ± 1.7 to 16.9 ± 1.2 dynes • sec • cm^{-5}).

Ejection fraction measurements obtained during infusion of the 8 and 16 mg/min doses revealed that esmolol produced a significant decrease in LVEF, with more marked changes at the 16 mg/min dose than at the 8 mg/min dose (Fig. 3). Despite this finding, all patients remained asymptomatic. As evidenced by significant HR reduction (91 ± 4 beats/min at baseline; 85 ± 4 beats/min at 2 mg/min), β-blockade was achieved in these ischemic patients at doses well below those which produced peak hemodynamic deterioration (i.e., 16 mg/min). Thus the titratability of esmolol allows for control of β-blockade without the danger of further reduction of LVEF in patients with low LVEF. The esmolol dose increment should be very gradual in such patients. Bedside hemodynamic monitoring is suggested if higher doses are used. Furthermore, caution is advised during the administration of esmolol in patients who have more severe left ventricular dysfunction than those evaluated in this study.

When SVT patients were divided into two age

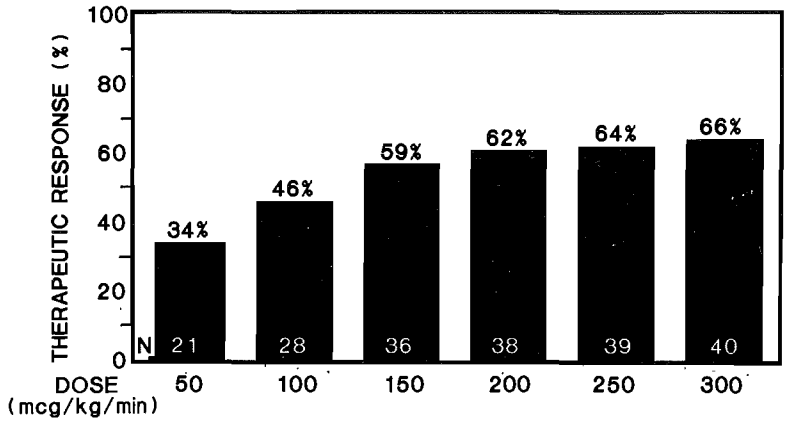

Fig. 4. Percentage of efficacy-study patients with therapeutic response during initial and crossover esmolol titration periods by esmolol dosage.

groups (<65 or ≥65 years of age), no difference in response to esmolol or incidence of hypotension with esmolol treatment was found. Moreover, recovery of HR after discontinuation of the esmolol infusion was similar for both groups.

CLINICAL INDICATIONS

Supraventricular tachycardia. The efficacy and safety of esmolol infusions has been investigated in patients with SVT (atrial flutter, atrial fibrillation, and sinus tachycardia) in several wall-controlled (placebo and propranolol) studies.[13-16] Maintenance doses administered in these studies ranged from 25 to 300 μg/kg/min, each preceded by a 1-minute 500 μg/kg/min loading dose. Criteria for desired therapeutic effect included 20% reduction in HR, decrease in HR to less than 100 beats/min, or conversion to normal sinus rhythm. Esmolol was found to be superior to placebo in the treatment of SVT.[13] Sixty-two percent of patients (38/61) achieved a therapeutic response at an esmolol dose ≤200 μg/kg/min. As shown in Fig. 4, the increase in percentage of responders beyond the 200 μg/kg/min dose was minimal.

Esmolol administered by continuous infusion has also been found to be as effective as propranolol (3 to 6 mg intravenous bolus) in controlling HR, and it compared favorably with propranolol in conversion to normal sinus rhythm in patients with SVT.[14] Consistent with its brief duration of action, recovery from β-blockade during the post infusion period occurred within 10 minutes in esmolol-treated patients. In contrast, β-blockade persisted for 4½ hours after the administration of propranolol. Therapeutic response was achieved in 70% of esmolol-treated patients (35/50) at doses of 200 μg/kg/min or less (Fig. 5). Furthermore, esmolol was well tolerated in patients with SVT during infusion for up to 24 hours.[15,16]

Incremental doses of esmolol from 2 to 16 mg/min for 10 minutes each, after 30-second loading doses of 10 or 20 mg boluses, have been shown to compare favorably with verapamil (5 or 10 mg intravenous boluses) in the short-term treatment of patients with atrial fibrillation and flutter.[17] Of 11 patients, nine (82%) achieved a ventricular rate of ≤100 beats/min in the esmolol-treated group, in comparison with 5 of 10 (50%) in the verapamil-treated group. Side effects (asymptomatic and symptomatic hypotension) were reported in 27% of the esmolol-treated and 60% of the verapamil-treated patients.

Potential risks have recently been reported with the use of intravenous verapamil for treatment of atrial flutter and fibrillation when the underlying arrhythmia is incorrectly identified or the presence of a bypass tract is not identified.[18-20] These reports include patients with atrial fibrillation and unrecognized Wolff-Parkinson-White syndrome in whom verapamil therapy resulted in ventricular fibrillation or a marked increase in ventricular rate with consequent profound hypotension. Furthermore, the onset of severe hypotension requiring emergency cardioversion after verapamil therapy in patients with ventricular tachycardia misdiagnosed as SVT with aberrant ventricular conduction has also been reported. Consequently, if the hemodynamic status of the patient does not allow time for a thorough assessment of the arrhythmia, cardioversion, rather than treatment with verapamil, is now indicated.

Since esmolol has a rapid onset and offset of action, is easily titratable, and has compared

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