Influence of Temperature on In Vitro Metabolism of Esmolol

J.A. Melendez, MD, J.G. Stone, MD, E. Delphin, MD, and C.Y. Quon, PhD

Esmolol has been used to improve hemodynamic stability during sternotomy and aortic manipulation for coronary artery bypass graft surgery. In order to investigate the alterations of esmolol metabolism by hypothermic cardiopulmonary bypass (CPB), the effect of temperature on the metabolism of esmolol in vitro was determined. Samples of human whole blood were combined with esmolol solution (50 μg/mL in 0.9 mol/L NaCl) and incubated at 4°C, 15°C, 25°C, and 37°C. Aliquots were sampled at 1, 5, 10, 15, 30, 60, and 120 minutes; esmolol concentration was determined using high-pressure liquid chromatography. There was a temperature-dependent decrease in the degradation of esmolol. The half-life for esmolol in human blood was 19.6 ± 3.8 minutes at 37°C, 47 ± 10.1 minutes at 25°C, 152 ± 46.6 minutes at 15°C, and 226.7 ± 60.1 minutes at 4°C. This study clearly shows marked reduction of esmolol metabolism with hypothermia possibly leading to persistent β-adrenergic blockade following the discontinuation of CPB. Persistent β-blockade may provide additional protection to the ischemic myocardium during hypothermic arrest and/or result in difficulty in weaning from CPB.

SEVERAL RECENT studies have confirmed the safety and efficacy of esmolol for preventing increases in heart rate associated with coronary artery bypass graft (CABG) surgery, and it has been suggested that a continuous esmolol infusion may confer some degree of myocardial protection during the perioperative period.[1-4] Newsome et al[1] demonstrated that esmolol-treated patients had a significant decrease in the incidence of heart rate response to surgical stimuli when compared with a matched placebo-treated control group, and Wynands et al[2] showed that the incidences of ventricular dysrhythmias upon aortic dissection and pre-cardiopulmonary bypass (CPB) ischemia were reduced. These investigators must have assumed standard kinetics because the esmolol infusion was maintained constant until after aortic cross-clamping.

However, the authors hypothesize that once hypothermic cardiac arrest has been instituted, metabolism of esmolol is markedly slowed due to a decrease in red cell and hepatic esterase activity. If this is the case, significant levels of esmolol might persist throughout the bypass period, possibly improving ischemic myocardial protection or, conversely, impairing myocardial performance upon discontinuation of CPB. To quantitate the effect of hypothermia on esmolol metabolism, the in vitro half-life ($T_{1/2}$) of esmolol in human whole blood was determined at temperatures that are commonly used during hypothermic CPB.

MATERIALS AND METHODS

Whole blood from human volunteers was collected in heparinized test tubes and placed on ice. Esmolol solution (50 μg/mL in 0.9 mol/L NaCl) and flasks containing aliquots of human whole blood (5 mL) were incubated separately at a constant temperature for 5 minutes prior to the start of each experiment. The incubating temperatures were 37°C, 25°C, 15°C, and 4°C. Five-milliliter aliquots of the esmolol solution were transferred into each flask containing whole blood without allowing the temperature of the mixture to vary. One-milliliter aliquots were removed after incubation for 1, 5, 15, 30, 60, 90, and 120 minutes. Enzymatic activity was promptly arrested by adding 2 mL of acetonitrile to the blood-esmolol mixture. The suspension was vortexed for 15 seconds, followed by centrifugation at 3,000 rotations/min for 15 minutes. The supernatant was decanted and the esmolol concentration was determined by high-pressure liquid chromatography.

The in vitro $T_{1/2}$ was determined by plotting the logarithm of esmolol concentration against time. The $T_{1/2}$ values were expressed as mean ± SD. Statistical analysis was performed using an analysis of variance. A $P < 0.05$ was regarded as significant.

RESULTS

There was a highly significant temperature-dependent increase in esmolol $T_{1/2}$ as the incubation temperature was decreased from 37°C to 4°C (Fig 1). The $T_{1/2}$ for esmolol in human blood was 19.6 ± 3.8 minutes, 47 ± 10 minutes, 152 ± 47 minutes, and 227 ± 60 minutes at 37°C, 25°C, 15°C, and 4°C, respectively. For the temperature

From the Department of Anesthesiology, College of Physicians and Surgeons, Columbia University, New York, NY.

Presented in abstract form at the 1989 Annual Meeting of the American Society of Anesthesiologists, New Orleans, LA.

Address reprint requests to Jose A. Melendez, MD, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, Room C308, New York, NY 10021.

0888-6296/90/0406-0006$03.00/0

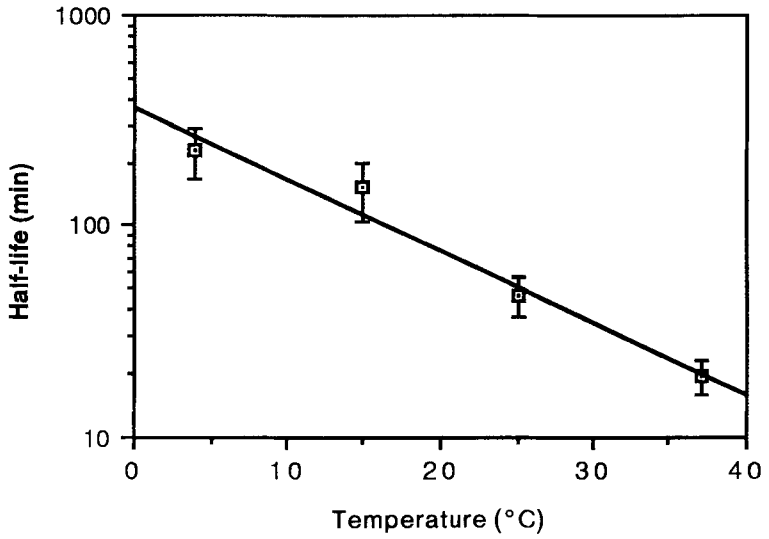

Fig 1. Plot of mean half-life versus temperature.

variation studied, the relation to $T_{1/2}$ was described by the equation

$$T_{1/2} = 364 \times 10^{-0.034\text{Temperature}}$$

with an $r = 0.98$.

DISCUSSION

Esmolol, an ultrashort-acting cardioselective β-blocker, has an elimination half-life of 9 minutes in normothermic subjects.[5] Total clearance of esmolol has been measured at 285 mL/min/kg, indicating significant nonhepatic clearance. Kinetic studies performed at normothermia in humans show a plateau blood level of 1 μg/mL after a 2-hour infusion of 400 μg/kg/min. The metabolism of esmolol by blood esterases has been characterized in several different species, including humans. Results in rats and guinea pigs suggest that esmolol is hydrolyzed by an aliphatic esterase, whereas in humans and dogs an aryl esterase is responsible for its metabolism.[6]

Although the administration of esmolol prior to CPB has been shown to benefit patients with coronary artery disease, it is assumed that β-blockade rapidly ceases soon after the discontinuation of the infusion. The data in this study suggest that hypothermia significantly decreases esmolol hydrolysis in whole blood. The observed changes approximate the 50% decrease in enzymatic activity associated with a 10°C drop in temperature described by Q_{10} kinetics. At 4°C, the optimal temperature for myocardial preservation, esmolol metabolism virtually ceases. At 28°C, the temperature of extracorporeal perfusate, esmolol hydrolysis is markedly reduced; thus, after 2 hours of CPB, circulating esmolol concentration may have decreased by approximately 25% of its initial level, which is potentially sufficient to result in persistent β-blockade.

Administration of a β-adrenergic blocker has been shown to contribute to myocardial protection during hypothermic arrest for cardiac surgery.[7-12] Three possible mechanisms have been proposed: decreased metabolic requirement, increased O_2 supply, and structural membrane stabilization. β-Adrenergic blockade limits increases in myocardial metabolism and reduces O_2 and adenosine triphosphate consumption caused by endogenous norepinephrine.[8,13,14] Furthermore, β-blockade competitively inhibits catecholamine-induced increases in sarcolemmal phospholipase and lipoprotein lipase activities, which are known to adversely affect ischemic myocardial cells.[9,15] Propranolol pretreatment of myocardium improves blood flow to the ischemic regions, resulting in an enhanced O_2 demand-supply relationship.[10,16-18] β-Blockers inhibit mitochondrial and microsomal Ca^{++} and myocardial fatty acid uptake, reducing Ca^{++} influx and fatty acid injury following reperfusion.[10,11,14,19]

These data suggest that hypothermia during CPB may alter the metabolism of esmolol, reducing its hydrolysis. Recently, Acampora et al[20] have shown that esmolol at a dose of 400 μg/kg/min can be a myocardial depressant. Thus, the possibility of persistent β-adrenergic

blockade and myocardial depression could jeopardize the ability to wean a patient from CPB. The assumption that pharmacologically significant levels of the drug are not detectable within 35 minutes of discontinuation may not apply in this clinical setting. This study suggests that further in vivo studies should be performed to evaluate esmolol kinetics during hypothermic CPB.

REFERENCES

1. Newsome LR, Roth JV, Hug CC, et al: Esmolol attenuates hemodynamic response during fentanyl-pancuronium anesthesia for aortocoronary bypass surgery. Anesth Analg 65:451-456, 1986

2. Harrison L, Ralley FE, Wynands JR, et al: The role of an ultrashort-acting β-blocker (esmolol) in patients undergoing coronary artery surgery. Anesthesiology 66:413-418, 1987

3. Girard D, Shulman BJ, Thys DM, et al: The safety and efficacy of esmolol during myocardial revascularizations. Anesthesiology 65:157-164, 1986

4. Henlig CE, Reves JG, Samuelson PN, et al: Hemodynamic effect of continuous infusion of esmolol during cardiac operation. Anesth Analg 65:S1-S170, 1986

5. Sum CY, Yacobi A, Karyzinel R, et al: Kinetics of esmolol, an ultrashort acting β-blocker, and of its metabolite. Clin Pharmacol Therap 34:427-434, 1983

6. Quon CY: Biochemical properties of blood esmolol esterase. Drug Metab Disp 13:420-424, 1985

7. Nayler WG: Protection of the myocardium against postischemic reperfusion damage. J Thorac Cardiovasc Surg 84:897-905, 1982

8. Nayler WG, Ferreri R, Williams A: Protective effect of pretreatment with verapamil, nifedipine, and propranolol on mitochondrial function in the ischemic and reperfused myocardium. Am J Cardiol 46:242-248, 1980

9. Pasque MK, Wechsler AS: Metabolic intervention to affect myocardial recovery following ischemia. Ann Surg 200:1-7, 1984

10. Ziegelhoff A, Das PK, Sharma GP, et al: Propranolol effects on myocardial ultrastructures and high-energy phosphates in anesthetized dogs subject to ischemia and reperfusion. Can J Phys Pharmacol 57:979-986, 1979

11. Opie LH: Myocardial infarct size, part 1: Basic consideration. Am Heart J 100:355-372, 1980

12. Miyazawa K, Fukuyama H, Komatsu E, et al: Effects of propranolol on myocardial damage resulting from coronary artery occlusion followed by reperfusion. Am Heart J 11:519-524, 1985

13. Peiper GM, Todd GL, Wu ST, et al: Alterations of myocardial acidosis by propranolol during ischemic arrest and perfusion: Evidence with ^{31}P NMR. Cardiovasc Res 14:646-653, 1980

14. Reynolds RD, Burmeister WE, Gorczynski RJ, et al: Effect of propranolol on myocardial infarct size with and without coronary artery reperfusion in the dog. Cardiovasc Res 15:411-420, 1981

15. Franson RC, Pang DC, Weglicki WB: Modulation of lipolytic activity in isolated canine cardiac sarcolemma by isoproterenol and propranolol. Biochem Biophys 90:956, 1979

16. Becker LC, Fortuin NJ, Pitt B: Effect of ischemia and antianginal drugs on the distribution of radioactive microspheres in the canine left ventricle. Circ Res 28:263-269, 1971

17. Becker LC, Pitt B: Regional myocardial blood flow in acute ischemia. Ann Clin Res 3:353-361, 1980

18. Pitt B, Craven P: Effect of propranolol on regional myocardial blood flow in acute ischemia. Cardiovasc Res 4:176-179, 1970

19. Nayler WG, Fassold E, Yepez C: Pharmacological protection of mitochrondial function in hypoxic heart muscle: Effects of verapamil, propranolol, and methylprednisone. Cardiovasc Res 12:152-161, 1978

20. Acampora G, Shah N, Del Valle O, et al: Myocardial depression by esmolol during nitroprusside hypotension. Anesthesiology 71:A19, 1989