Failure of General Anesthesia to Potentiate Propranolol Activity

Stephen Slogoff, M.D.,* Arthur S. Keats, M.D.,* C. Wayne Hibbs, M.S.;† Charles H. Edmonds, M.S.† Deborah A. Bragg, B.S.†

To determine whether halothane and morphine, commonly used during anesthesia for cardiac operations, potentiate the beta blocking activity of propranolol, hemodynamic changes induced by five incremental doses of propranolol (10, 20, 50, 120, 200 μg/kg) were measured during halothane, 1 per cent, in oxygen, and morphine, 4 mg/kg. Against a background of constant beta stimulation by infusion of isoproterenol, 0.1 μg/kg/min, and vagal blockade by atropine, 3 mg, propranolol produced significant dose-related decreases in heart rate, cardiac index, stroke volume index, and left ventricular dP/dt max, and significant increases in mean aortic pressure, systemic vascular resistance, and pulmonary capillary wedge pressure. Compared with basal anesthesia with pentobarbital, 15 mg/kg, neither morphine nor halothane increased sensitivity to any measured effect of propranolol expressed as the slope of the log dose-response relationship. It is concluded that the beta blocking activity of propranolol is not potentiated by morphine and halothane anesthesia but, rather, their effects are additive. (Key words: Heart, propranolol; Heart, myocardial function; Heart, isoproterenol; Sympathetic nervous system, sympatholytic agents; Sympathetic nervous system, propranolol; Sympathetic nervous system, beta-adrenergic receptors; Anesthetics, volatile; halothane; Anesthetics, intravenous; morphine; Anesthetics, intravenous, pentobarbital.)

Preoperative withdrawal of propranolol or, more currently, reduction of dosage has been recommended to prevent excessive myocardial depression during general-artery occlusive disease. This practice, however, is not innocuous, and in many patients, abrupt withdrawal or tapering precipitates tachyarrhythmias, crescendo angina, myocardial infarction, and death. The critical question is whether the risks of propranolol withdrawal are greater than those associated with its continuation in preoperative patients who have angina from coronary-artery disease. Reluctance to continue propranolol is based on the belief that general anesthetics potentiate the beta blocking effects of propranolol. In animals, the effects of propranolol on hemodynamics during general anesthesia are qualitatively identical to changes in unanesthetized animals. The question of whether potentiation occurs is the subject of this investigation, and was answered by quantifying propranolol dose-response relationships during anesthesia with two different anesthetics, morphine and halothane, both commonly used for anesthesia during cardiac operations.

Methods

The design of the experiment was a complete crossover in which the same dog received pentobarbital, morphine, and halothane anesthesia in random order on different occasions at least five days apart. Eight dogs weighing 20–32 kg were studied. Pentobarbital served as the basal anesthetic for placement of catheters and as the control. For each anesthetic, the effects of propranolol were measured against a background of constant beta stimulation.

In every experiment, the dog was anesthetized initially with pentobarbital, 30 mg/kg, intravenously, and mechanically ventilated with oxygen. Arterial partial pressure for oxygen was maintained above 100 torr, for carbon dioxide between 35 and 45 torr, pH between 7.32 and 7.45, and rectal temperature between 36 and 38 C throughout the experimental period. Through a small incision in the neck, a balloon-tipped four-channel Swan-Ganz catheter was placed via an external jugular vein into the pulmonary artery and 5 per cent dextrose in lactated Ringer’s solution was infused via the proximal lumen at a rate of 100–125 ml/hour. Through a common carotid artery, a Millar pressure transducer-tipped catheter was placed in the left ventricle and a polyvinyl catheter in the ascending aorta. Lead II electrocardiogram was monitored continuously. With these catheters mean aortic pressure (AΔP), left ventricular pressure (LVP), left ventricular end-diastolic pressure (LVEDP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), and left ventricular dP/dt max were continuously measured and recorded. Cardiac output was determined intermittently in triplicate by thermodilution. Cardiac index (CI) and stroke volume index (SVI) were derived using body weight. Systemic vascular resistance (SVR) was calculated. Ninety minutes after induction of pentobarbital anesthesia, vagal blockade was produced with atropine, 3 mg, intravenously, followed by a randomly selected anesthetic consisting of pentobarbital, 15 mg/kg, morphine, 4 mg/kg, or

*Division of cardiovascular anesthesia.
†Cardiovascular Research Laboratories.
Received from the Division of Cardiovascular Anesthesia and Cardiovascular Research Laboratories, Texas Heart Institute, Houston, Texas 77030. Accepted for publication June 16, 1977.
Address reprint requests to Dr. Slogoff.
halothane, 1 per cent in oxygen. After 30 minutes, baseline measurements for anesthetic effects were obtained and infusion of isoproterenol, 0.1 μg/kg/min, was begun and continued throughout the experiment. In preliminary investigations in five dogs, the hemodynamic effects of this dose of isoproterenol were constant for at least five hours with no evidence of tachyphylaxis during administration of any of the anesthetics used in this study. When isoproterenol effects were maximal and steady, the initial dose of propranolol, 10 μg/kg, was administered. Additional increments of propranolol were given at 15-minute intervals to produce cumulative doses of 10, 30, 80, 200, and 400 μg/kg. Hemodynamic effects were measured 12 minutes after each dose. The average duration of the experiment was four hours. At the end of each experiment, completeness of beta blockade was estimated by increasing isoproterenol infusion to 0.3 μg/kg/min. This dose produced less than 10 per cent increases in heart rate, LV dP/dt max and cardiac output. Catheters were then removed and the vessels repaired primarily. All dogs recovered completely their behavioral and eating patterns before being studied again. Statistical significance of differences was determined by analysis of variance, t test for paired replicates, and analysis of covariance as appropriate.5

Results

In the data presentation that follows, we have assumed that values measured during pentobarbital anesthesia represent the effects of the basal anesthesia and considered them control values, with which halothane and morphine values are compared. Both morphine and halothane tended to depress indices of myocardial function more than pentobarbital, but the differences were not large and were significant only for cardiac index and mean aortic pressure after morphine (table 1). The decrease in pulmonary capillary wedge pressure after morphine probably reflected its venodilator action. Changes in left ventricular end-diastolic pressure and pulmonary arterial pressure were not included in the tables because they were small and not quantitatively related to propranolol dose.

Isoproterenol produced its anticipated effects of increasing heart rate, left ventricular dP/dt max, cardiac index, and stroke volume index, and decreasing systemic vascular resistance. Although isoproterenol effectively antagonized the myocardial depressant effects of halothane and morphine, the magnitude of the cardiac response to isoproterenol was significantly less than during pentobarbital anesthesia (table 1). Despite this, the initial dose of propranolol, 10
Fig. 1. Cumulative doses of propranolol produced significant dose-related decreases in cardiac index and left ventricular $dp/\,dt_{\text{max}}$. The slopes of the three curves for both measures were not significantly different from each other.

Fig. 2. Cumulative doses of propranolol produced a significant dose-related decrease in heart rate and increase in systemic vascular resistance for each anesthetic. The slopes of the three curves for systemic vascular resistance were not significantly different from each other. The slope of the heart rate curve for morphine was significantly greater ($P < 0.5$) than those for halothane and pentobarbital. See text for explanation of increased slope of heart rate during morphine anesthesia.
μg/kg, produced approximately the same proportionate changes in all hemodynamic variables during anesthesia with all three anesthetics, with the exception of the significantly different changes in heart rate during morphine anesthesia and blood pressure during halothane anesthesia. The significant increase in blood pressure during halothane anesthesia was related to the large decrease in systemic vascular resistance produced by isoproterenol during anesthesia with halothane.

The effects of cumulative doses of propranolol are presented as log dose–effect curves. Best-fit curves were obtained when percentage changes rather than absolute values were plotted against log dose. Against the background of a constant isoproterenol infusion, propranolol produced dose-related decreases in heart rate, left ventricular dP/dt max, cardiac index, and stroke volume index, and dose-related increases in mean aortic pressure, systemic vascular resistance, and pulmonary capillary wedge pressure (fig. 1 and 2; table 2). These were the anticipated directions of change by antagonism of isoproterenol. The slope of each dose–effect curve was significant, and slopes were not significantly different among the three anesthetic states with the exception of those for heart rate, left ventricular dP/dt max, and stroke volume index. The significantly greater slope for heart rate during morphine anesthesia was entirely attributable to atypical responses in two dogs. In each dog, decrease in heart rate was related to the dose of propranolol, but the final heart rates in these two dogs were 74 and 75 beats/min, in contrast to the next two lowest values, which were 96 and 115 beats/min. Final heart rate was found to correlate with time since atropine administration. This time varied with the duration of the control isoproterenol infusion required to obtain stable values. The time since atropine administration was more than 60 minutes longer in the two atypical dogs compared with the six typical dogs. The slope of the propranolol–heart rate curve for morphine for the six typical dogs were not different from the slopes of the halothane and pentobarbital curves. We, therefore, attribute the significantly greater slope for morphine to waning atropine effects and not increased sensitivity to propranolol. We have no explanation for the significantly smaller slope for left ventricular dP/dt max and reversed slope for stroke volume index during morphine anesthesia, although changes in stroke volume index could be secondary to the increased bradycardia. In any case, since we interpret the slopes of these curves to indicate sensitivity to propranolol, the direction of these two significant differences indicates lesser rather than greater sensitivity during morphine anesthesia. Neither halothane nor morphine increases responsiveness to the beta blocking effects of propranolol (table 2). After the final dose of propranolol, the highest pulmonary capillary wedge pressure and left ventricular end-diastolic pressure observed in any dog were 15 and 10 torr, respectively.

**Discussion**

The primary purpose of this experiment was to determine whether general anesthetics potentiate the hemodynamic effects of propranolol. The answer required that dose–effect curves for the major actions of propranolol be determined and their slopes be compared. The animal model and experimental design finally selected were well suited to accomplish this objective. In our preliminary experiments almost no change was detectable following the first two incremental doses of propranolol and particularly heart rate, which during morphine anesthesia was low, did not change. Since the major action of propranolol is to block beta activity, hemodynamic changes should be most apparent in the presence of high beta stimulation, a condition not characteristic of either halothane or morphine anesthesia. For this reason vagal blockade and constant isoproterenol infusion were then included in the study design.

In contrast to its effects in man, the dose of morphine used depressed hemodynamic measures as much as halothane. Although this was anticipated from known hemodynamic effects of morphine in dogs, the lesser response to isoproterenol in the morphinized dogs was not anticipated, since a beta stimulating action of morphine has been suggested.
to occur in both animals and man. Fortunately, responsiveness to isoproterenol was well maintained at the pentobarbital dose selected for control animals and provided the desired contrast to the effects of halothane and morphine. Cyclopropane anesthesia would have provided an even more dramatic contrast for study of propranolol activity, but would have had less relevance to current practice in anesthesia for cardiac operations.

Many previous investigators have studied the effects of one or two doses of beta blockers during anesthesia, particularly halothane, with results consistent with those presented here. During halothane anesthesia in dogs unstimulated by isoproterenol, Craythorne observed that 200 μg/kg of propranolol produced only a 10 per cent decrease in heart rate, with no change in cardiac output or myocardial contractility. In a similar study of light cyclopropane anesthesia, he found that this dose of propranolol induced more significant hemodynamic effects. After propranolol, the circulatory statuses of halothane- and cyclopropane-treated animals were almost identical. Others have also reported that magnitudes of beta blocking effects were related to degrees of beta stimulation, including those induced by altered carbon dioxide tension. Finally, Moran showed that the sensitivity to isoproterenol challenge in dogs anesthetized with halothane was identical to that in awake animals despite large differences in baseline values. He concluded that halothane did not exert its effects on circulation by beta blockade. Our observations are similar.

Only Roberts has attempted to answer the question we posed. He treated dogs with propranolol, 20 mg/kg/day, by mouth, for three weeks before studying their responses to several concentrations of halothane. He found that circulatory depression was greater in the treated animals and equivalent to the addition of halothane, 0.5 per cent, at all anesthetic levels. He concluded that propranolol effects were simply added to those of halothane. From our study in which doses of propranolol rather than halothane were varied, we arrived at the same conclusion. Although morphine and halothane produced greater circulatory depression and lesser absolute responsiveness to isoproterenol than the control, response to propranolol was proportionate to the initial values. Sensitivity to propranolol effects expressed as the slope of the log dose effect curve was not significantly greater for halothane and morphine. Propranolol therefore did not potentiate the circulatory effects of the two general anesthetics studied; their effects were additive. Of additional interest was the observation that myocardial failure, expressed in terms of cardiac index, left ventricular end-diastolic pressure, or pulmonary capillary wedge pressure, did not occur in this preparation even at a propranolol dose of 400 μg/kg added to the anesthetic.

Although the dog model with a normal heart, beta stimulation, and vagal blockade is not totally analogous to the clinical situation, these data do confirm our clinical impressions that propranolol induces predictable changes in patients undergoing cardiac operations during general anesthesia and that morphine and halothane anesthesia do not potentiate propranolol activity. Since we have found small doses of propranolol highly effective in treating intraoperative arrhythmias and ischemic electrocardiographic patterns during general anesthesia for cardiac operations, we continue to have no reluctance in administering increments of 0.5–1.0 mg propranolol during general anesthesia, recognizing its additive effects to the circulatory changes induced by halothane and morphine that we have described.

References