Hemodynamic and Metabolic Response After Abrupt Withdrawal of Long-Term Propranolol

J. Hurley Myers, Ph.D. and Lawrence D. Horwitz, M.D.

SUMMARY  Because the mechanism of adverse reactions to abrupt withdrawal of propranolol in patients with coronary disease is an enigma, we studied the effect of cessation of propranolol on beta receptor reactivity to catecholamine stimulation. Heart rate and maximum rate of rise of left ventricular pressure (dP/dt max) during isoproterenol infusions and plasma free fatty acids (FFAs) after epinephrine infusions were measured in six conscious dogs before, during and after four weeks of oral propranolol (40 mg. p.o. q8h). Rises in heart rate, dP/dt max and FFAs were blocked during propranolol administration. Twenty-four hours after withdrawal from propranolol, heart rate and dP/dt max responses remained significantly attenuated, although FFA responses were at premedication levels. The 72-hour, 96-hour and one week postmedication responses did not differ from premedication values. Thus, partial beta blockade of the heart was still present at 24 hours and no evidence of heightened beta receptor sensitivity was detected on repeated study one week after withdrawal from a long-term, high dose propranolol regimen.

SEVERAL CLINICAL REPORTS have concluded that abrupt discontinuance of propranolol may result in untoward ischemic events in patients with coronary artery disease.1-7 Typically, these events occurred in patients who had anginal pain which was substantially relieved by the drug but recurred with increased frequency, intensity or duration within a few days after cessation of propranolol therapy.

The cause of this phenomenon has been an enigma. It has been proposed that incidental progression of the coronary atherosclerotic process or a tendency to become habituated to a relatively high level of physical activity while medicated with propranolol increases inquieties between myocardial oxygen supply and demand during the withdrawal period.3-5 However, an intriguing possibility is that beta adrenergic receptor blockade by propranolol results in increased sympathetic stimulation of the heart soon after the drug is discontinued.8 Such a drug-induced physiological rebound could increase myocardial oxygen consumption and precipitate ischemic events. Possible mechanisms include increased rates of catecholamine turnover, increased numbers of beta receptor binding sites, altered affinities of receptors for catecholamines or increased rates of activation of cyclic AMP without alteration in receptor binding.

There has been very little data either to support or cast doubt upon the possibility of enhanced sympathetic effects after withdrawal of propranolol or other beta adrenergic blocking agents. This study evaluated responsiveness to beta-adrenergic mediated stimulation of cardiac dynamics and lipolysis in a group of conscious, healthy dogs before, during and after withdrawal from chronic administration of propranolol.

Methods

Animal Preparation, Instrumentation and Analytical Methods

Under halothane anesthesia, sterile thoracotomies were performed in 10 adult mongrel dogs weighing 17-27 kg. A precalibrated Konigsberg P-18 solid state pressure transducer was implanted within the left ventricle near the apex and polyvinyl catheters were inserted into the left jugular vein, left atrial appendage and aorta. Studies began three weeks after surgery, when vital signs were normal and no evidence of infection was present. Dogs were trained to lie quietly in a sling without anesthesia or sedation.

Recordings of left ventricular pressure and the first derivative of left ventricular pressure were inscribed on a Beckman RM oscillograph and an Ampex PR 2200 magnetic tape recorder. Left ventricular pressure was obtained from the solid state transducer, which has a natural frequency in excess of 3,000 Hz. Sensitivity did not change during implantation, and correction for small amounts of day-to-day drift was made by assuming that, during resting controls, left ventricular end-diastolic pressure equaled mean left atrial pressure, measured via the implanted catheter with a Statham P23Db manometer.9 The left ventricular pressure was differentiated by an active resistance-capacitance network that decreased three db at 100 Hz.

Plasma free fatty acids (FFAs) were measured by
the method of Trout et al.\textsuperscript{10} In this modification of Dole's titrimetric procedure,\textsuperscript{11} lactic acid and phospholipids are extracted before titration of heptane aliquots to provide improved specificity. The plasma was processed immediately after blood was drawn. Values were expressed as μEq of FFA per liter of plasma. Plasma propranolol levels were measured by the method of Shand et al.\textsuperscript{11}

Experimental Protocol

To evaluate the FFA response, epinephrine at 1.0 μg/kg/min was infused for 5 minutes into the jugular catheter with a Harvard infusion pump. Heparinized arterial blood samples were drawn before and at 6, 8, 10, 15 and 20 minutes after the infusion began.

When heart rate had returned to pre-epinephrine levels, the hemodynamic response to an isoproterenol challenge was evaluated. Resting heart rate and dP/dt max were measured and isoproterenol was infused at a rate of 0.02 μg/kg/min. At the end of a 5-minute infusion period, at which time a steady state was present, the hemodynamic response was recorded. Immediately following this first infusion, a second infusion of isoproterenol (0.04 μg/kg/min) was started and hemodynamic recordings were repeated at the end of 5 minutes.

Data was collected on each dog on three separate days before administration of medication. All measurements were made in the morning, with the animals in a fasting state. After these baseline studies had been obtained, six male dogs were given 40 mg tablets of propranolol orally three times per day (8 a.m., 4 p.m. and 12 midnight) for four weeks. The dose of propranolol in dogs (approximately 6 mg/kg) was selected to simulate high clinical dosages in patients. Four dogs (two males and two females) received placebo tablets on an identical time schedule. The effectiveness of beta adrenergic blockade was assessed midway through the drug administration period by challenging each animal with epinephrine and isoproterenol in exactly the same manner as the baseline measurements. In one experimental dog the serum propranolol concentration was measured 90 minutes after the morning medication was given, during the third week of drug administration.\textsuperscript{12}

The hemodynamic and FFA responses to catecholamine challenges were repeated 24 hours, 72 hours, 96 hours (propranolol group only) and one week after the medication was discontinued. In each animal, baseline values and results during or after propranolol administration were compared using a paired Student $t$ test.

Results

1. Premedication Responses

Figure 1 shows the mean and standard error for heart rate and dP/dt max in all measurements in all 10 dogs at rest and during infusions of isoproterenol. With the low dose of isoproterenol (0.02 μg/kg/min) the mean increase over the resting value in heart rate was 26 beats/min and with the high dose (0.04 μg/kg/min) was 54 beats/min. Mean dP/dt max increased by 489 mm Hg/sec with the low dose and 1195 mm Hg/sec with the high dose. There were no apparent differences in responses between control and experimental dogs or between male and female control dogs.

The rise in FFAs following a 5-minute infusion of epinephrine (1.0 μg/kg/min) is shown in figure 2. The peak response, which occurred 10 minutes from the beginning of infusion, was 45% above the resting FFA value. The relatively large standard error noted for these values is the result of higher FFA levels found in two female dogs used in this study. The two female animals had higher resting FFA levels (998 vs 646 μEq/l) and a greater response (54% vs 43%) to the epinephrine infusion than the eight males. Although a sex difference in FFA responses has not been cited previously in dogs, it has been observed in human studies in which FFA is measured.\textsuperscript{13} By chance, the two females were both included in the placebo group.
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2. Responses of Placebo Group During Medication and Postmedication Periods

The placebo group consisted of four dogs, two males and two females. Figure 3 shows the heart rate and dP/dt max response to isoproterenol during each experimental period. There were no apparent differences in the individual or group responses between values early in the course of the study (premedication) and later (medication and postmedication periods).

The mean FFA response of the placebo group to the five epinephrine challenges is shown in figure 4. The shaded area represents the standard error of values obtained for the three premedication measurements. Again, the response found during placebo administration and after its withdrawal was similar to the FFA response noted during the premedication period.

3. Responses of the Experimental Group During the Medication Period

The serum level of propranolol measured 1 1/2 hours after the morning dose midway through the medication period was 453 ng/ml in the dog in which the level was measured. The heart rate and dP/dt max values in the experimental group during the isoproterenol challenges are shown in figure 5. After two weeks of
therapy, the resting heart rate was 16 beats/min below that found during the premedication period ($P < 0.05$). When challenged with isoproterenol, the heart rate of the treated group increased only 1 beat/min at a low dose and 11 beats/min with the high dose. The heart rates at both doses were significantly less ($P < 0.05$) than those noted before propranolol was administered. Furthermore, propranolol reduced dP/dt max at rest by 10% of the premedication value and significantly attenuated ($P < 0.05$) the responses to the isoproterenol infusions.

Figure 6 illustrates the FFA response of the propranolol group to the various epinephrine challenges. The shaded area outlines the standard error of the mean of the three premedication challenges. Treatment with propranolol abolished the FFA response; there were significant reductions at 6, 8, 10, 15 and 20 minutes after infusion of epinephrine began.

4. Responses of the Experimental Group During the Postmedication Period

There were no consistent or statistically significant changes in left ventricular end-diastolic or left ventricular peak systolic pressures when the premedication levels were compared with postmedication levels. For example, peak systolic pressures at rest, during the low dose infusion of isoproterenol and during the high dose infusion of isoproterenol were $126 \pm 6$ (SEM), $132 \pm 6$ and $135 \pm 7$ mm Hg, respectively, pre-propranolol, and $118 \pm 14$, $129 \pm 12$ and $136 \pm 15$ mm Hg 72 hours post-propranolol. Because of the lack of evidence of substantial changes in preload or afterload, dP/dt max was assumed to reflect the contractile state of the myocardium.

Twenty-four hours after propranolol was stopped, the heart rate during both rates of isoproterenol infusion and dP/dt max at the lower rate of isoproterenol infusion were significantly less than premedication levels (fig. 5). At the higher rate of isoproterenol infusion, dP/dt in most dogs was well below the premedication level, but because of wide variation, this difference was not statistically significant. However, fatty acids at 24 hours did not differ consistently from premedication levels (fig. 6).

At 72 hours, 96 hours and seven days after propranolol, there were no differences from the premedication levels in heart rate or dP/dt max either at rest or during isoproterenol infusions. There was a tendency for FFAs to exceed premedication levels during epinephrine challenge at 72 hours, but this was not statistically significant. There was no elevation of FFAs during epinephrine at 96 hours or seven days. The only statistically significant change in FFAs was a slight reduction in the resting value at 96 hours (fig. 6).

Discussion

The purpose of our study was to ascertain whether abrupt termination of prolonged beta adrenergic blockade with propranolol resulted in a greater than normal sensitivity to catecholamines during the withdrawal period. Such a mechanism could explain clinical reports of exacerbation of symptoms in patients with coronary artery disease whose therapeutic doses of propranolol have been suddenly discontinued.17

Increasing doses of isoproterenol, a potent beta
receptor agonist, result in linear increases in heart rate and $dP/dt$ max, an index of myocardial contractile force. Therefore, repeated measurements of these parameters at fixed doses of isoproterenol given under identical conditions would be expected to provide a reliable means of assessing cardiac sensitivity to catecholamines.

Epinephrine mobilizes FFAs from adipose tissue, causing sharp transient rises in plasma levels in both the dog and in man. This effect appears to be mediated entirely by beta adrenergic receptors. Accordingly, measurement of plasma FFAs during infusion of epinephrine in a dose which causes minimal hemodynamic effects is a sensitive means of detecting alterations in generalized beta receptor-mediated catecholamine effects.

Since during the medication period both hemodynamic and FFA responses were completely or almost completely abolished in the experimental group, there is evidence that an effective level of beta

**FREE FATTY ACIDS**

![Graph showing free fatty acids levels](image)
blockade was attained. Twenty-four hours after propranolol was stopped the FFA responses to epinephrine had returned to premedication levels but the hemodynamic response to isoproterenol closely resembled values obtained during the medication period.

The half-time of single doses of oral propranolol is reported to be approximately 45 minutes in the dog and 2½ hours in man. Therefore, substantial residual cardiac effects of beta blockade persisted at 24 hours after withdrawal when blood levels of propranolol should have been low or undetectable. Paterson et al. have reported an attenuated heart rate response to isoproterenol 24 hours after cessation of a two- or three-day course of oral propranolol in human subjects. Propranolol tends to concentrate in the heart and certain other organs and substantial quantities of either the drug or an active metabolite may persist in myocardial tissue after it has been cleared from the blood and other organs. Alternatively, the effects of competitive inhibition by the drug in this particular organ may result in continued inability of the receptor, or the cyclic AMP system, which is presumably activated by the receptor, to respond to catecholamines for some time after the drug has been metabolized. Twenty-four hours after withdrawal, when many of the clinical cases of "propranolol rebound" became manifest, there was still significantly diminished responsiveness to beta adrenergic stimulation in the heart.

Subsequent to the 24-hour tests, all responses to epinephrine and isoproterenol were similar to the premedication responses. Since residual beta blockade as long as one week after the drug has been stopped is highly unlikely, any tendency to a supernormal response to beta receptor agonists should have been detected between 24 hours and one week of withdrawal. Therefore, according to our data, there is no evidence that abrupt withdrawal from propranolol is associated with development of greater than normal sensitivity to catecholamines.

Our results differ from those of Boudoulas et al. This group reported an increase in the duration of electromechanical systole 24–48 hours after propranolol withdrawal in six normal humans. However, the duration of the propranolol therapy was only two days at 160 mg/day p.o. and there were no controls to assess the day-to-day variation in the measurements. Although species variation cannot be excluded, the four-week course of propranolol we used more closely approximates the usual clinical setting and measurements of max Dp/dt and FFAs are likely to be more sensitive than measurement of duration of systole for assessment of beta adrenergic effects.

In view of our findings, it would seem unlikely that the clinical cases described in the literature in which serious complications occurred when propranolol was suddenly discontinued were due to an exaggerated response to endogenous catecholamine stimulation of the heart. Progression of the disease during propranolol therapy or an increased level of physical or emotional stress during withdrawal as compared with the premedication situation are possible explanations for the clinical observations reported.

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References

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