Mechanism of Propranolol Withdrawal Phenomena

STAN NATTEL, M.D., ROBERT E. RANNO, M.D., and GLEN VAN LOON, M.D.

SUMMARY Nine patients on chronic treatment with propranolol for essential hypertension for 3 months or longer were studied after abrupt discontinuation of the drug. Each patient demonstrated transient supersensitivity to the chronotropic effects of isoproterenol, beginning 2–6 days (median 4 days) after propranolol withdrawal, lasting for 3–13 days (median 6 days), with the maximum sensitivity on day 6. A significantly lower dose of isoproterenol was necessary to increase heart rate 25 beats/min on day 6 (median dose 1.2 μg, range 0.3–3.4 μg) compared with after day 14, when sensitivity had stabilized (median dose 2.3 μg, range 1.4–7.6 μg). Six patients had transient symptoms (headache, chest pain, palpitations and sweating) after abrupt propranolol withdrawal, coinciding with supersensitivity to isoproterenol in five. Transient increases in plasma catecholamines and blood pressures and sustained increases in heart rate occurred during the period of isoproterenol supersensitivity in most patients, and may have contributed to symptoms noted. The delayed onset and potentially long duration of β-adrenergic supersensitivity after abrupt propranolol withdrawal have important clinical implications.

WORSENING OF ANGINA, myocardial infarction and ventricular dysrhythmias have been observed after abrupt discontinuation of propranolol in patients with coronary artery disease. Abrupt withdrawal of β-blocking drugs in patients with hypertension has resulted in transient symptoms, including malaise, headache, sweating and palpitations. Several mechanisms have been proposed to explain these phenomena. Persistently increased levels of physical activity and changes in the renin-angiotensin system or in the oxyhemoglobin dissociation curve have been postulated, but their role has not been tested. The importance of transient increases in platelet aggregation, which have been shown to occur after abrupt propranolol withdrawal, is unknown. Although increases in plasma catecholamine concentrations could explain some of the phenomena, such changes have not been demonstrated. Denervation supersensitivity to catecholamines after chronic β blockade may be another mechanism. Evidence for the latter hypothesis was presented by Boudoulas et al. in a study of normal volunteers after 2 days of propranolol administration. No data are available on the participation of such a mechanism among patients with cardiovascular disease in whom chronic propranolol therapy has been discontinued abruptly. The risks of abrupt propranolol withdrawal and of isoproterenol administration to test β-adrenergic sensitivity preclude such a study among patients receiving propranolol for the treatment of angina. Patients on propranolol therapy for hypertension, however, are similar in age to those with coronary disease. In the absence of a history of angina, discontinuation of propranolol is often abrupt in these patients. This investigation was designed to study changes in cardiac β-adrenergic responsiveness and plasma catecholamines after abrupt withdrawal of chronic propranolol therapy in patients with essential hypertension.

Materials and Methods

Nine patients on chronic therapy (longer than 3 months) with propranolol for mild-to-moderate essential hypertension constituted the study population (table 1). Eight males and one female, median age 48 years (range 26–79 years), were taking a median daily propranolol dose of 240 mg (range 160–320 mg). Previous anti-hypertensive therapy consisted only of thiazide diuretics taken by seven patients, who continued taking them throughout the study. None of the study patients had historical or ECG evidence of coronary artery disease. All patients gave informed consent before the trial. The studies were conducted on an outpatient basis. Patients were studied initially 3 hours after their last dose of propranolol, on day 0. Studies were subsequently conducted at the same time of the day, on days 2, 4, 6, 9 and 14 after propranolol withdrawal and at approximately three 1-week intervals thereafter. Patients refrained from tobacco and caffeine-containing beverages for at least 12 hours before each study. On each study day the following protocol was observed:

1) A brief history was taken using a symptom check-list to elicit complaints possibly related to propranolol withdrawal.
2) A 19-gauge butterfly needle was inserted into an antecubital vein, after which a 12-lead ECG was recorded.
3) After 30 minutes of bed rest in a quiet room, blood was drawn from the indwelling catheter for subsequent assay of plasma catecholamines.
4) Blood pressure was measured three times by sphygmomanometer, with diastolic pressure defined by the disappearance of Korotkoff sounds.
5) The heart rate changes produced by small incremental bolus doses of isoproterenol were measured.
to obtain an index of cardiac β-adrenergic sensitivity. Before each dose of isoproterenol, baseline heart rate was obtained by measuring the two shortest RR intervals on the resting ECG. Isoproterenol 200 μg/ml (Winthrop) was used, with 20 μg/ml and 2 μg/ml solutions obtained by serial 1:10 dilutions in normal saline. Each bolus dose of isoproterenol was administered by rapid intravenous push and followed immediately by a rapid infusion of 5% dextrose solution.

The logarithm of each isoproterenol dose was then plotted against the resulting change in heart rate, to obtain a log dose-response curve by the method of Cleaveland, Rangno and Shand. A minimum of three points was obtained and fitted by linear least-squares regression. (The regressions had a median value for r = 0.98, range 0.89–0.99 and the lines were not different for parallelism). The isoproterenol dose required to produce an increase in heart rate of 25 beats/min was obtained from this line of best fit. This chronotropic dose necessary to increase heart rate 25 beats/min will be referred to as the isoproterenol CD25. Increased β-adrenergic sensitivity would thus be indicated by a decreased isoproterenol CD25, as less isoproterenol would be needed to produce the same heart rate change. Total plasma catecholamines were measured in all patients by a radiometric assay. Samples of three patients were also subjected to separation assay of plasma norepinephrine, epinephrine, and dopamine concentrations by a radioenzymatic method. The sensitivity of these assays is about 10–20 pg/ml and the reproducibility variation is less than ± 10%. Heart rate was calculated as the mean rate from all the baseline values during each isoproterenol test. Study of a given patient was terminated when the isoproterenol CD25 values on three successive study days were within 15% of one another at least 2 weeks after discontinuation of propranolol therapy. The median of the CD25 values on these days was termed the “stable CD25”, reflecting β-adrenergic sensitivity off propranolol. Similarly, the median of plasma catecholamines, heart rate, and arterial pressure on these days were termed “stable catecholamines,” “stable heart rate” and “stable blood pressure,” respectively.

Analysis of Data

We used nonparametric (or distribution-independent) statistics to analyze all our data. The reasons for this were: 1) the relatively small number of patients studied, 2) apparently skewed distribution of the stable CD25’s, and 3) the unknown effect of interventions (such as withdrawal of propranolol) on the characteristics of the distribution of parameters measured. Parametric statistics depend on a normal sample distribution, which for the above reasons we could not assume. Therefore, grouping of data was expressed using the median rather than mean as a measure of central tendency, and range to express the degree of variability in measurements. Changes in all measurements over time were analyzed using the Friedman nonparametric analysis of variance with multiple comparison and one-tailed probability. The significance of correlation regressions was tested by two-way analysis of variance.

Results

Isoproterenol CD25 Values

All patients had a similar pattern of response to isoproterenol after the abrupt withdrawal of propranolol as measured by the CD25 (table 2), with a large CD25 value just after the last dose, a period with small CD25 values and a longer period with intermediate values. The last three CD25 values observed more than 14 days after propranolol withdrawal were shown to be stable for each patient after analysis of variance indicated the individual values were not different from each other (p > 0.98). These values represented the patient’s β-adrenergic sensitivity to isoproterenol off propranolol. On day 0 (3 hours after the last dose of propranolol) all CD25 values were very large, confirming appreciable bioavailability and pharmacological effect of propranolol in these patients. Intercurrent differences in CD25 values on day 0 could not be explained by differences in size of the ingested dose of propranolol. On day 2, CD25 values were greater than the median stable CD25 values in 7 of 9 patients, suggesting persistent β blockade. On day 2, two CD25 values and on days 4, 6 and 9, all but one value were less than the stable CD25 values, indicating increased β-adrenergic sensitivity to isoproterenol. CD25 values on day 6 were significantly less than stable values after day 14 (p < 0.05). By day 14, CD25 values approached or were identical to the mean stable CD25 values in all but patients 4 and 6. The average time course for changes in β-adrenergic sensitivity can be seen in figure 1, where CD25 values are plotted as the median for all patients. The period of increased β-adrenergic sensitivity (i.e., decreased CD25 values compared with stable values) is between days 4 and 9, with the lowest median value on the sixth day after propranolol withdrawal. For each patient, supersensitivity began at an average of 4 days (range

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Daily dose of propranolol (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>79</td>
<td>M</td>
<td>320</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>M</td>
<td>320</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>M</td>
<td>320</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>M</td>
<td>240</td>
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<tr>
<td>5</td>
<td>45</td>
<td>F</td>
<td>160</td>
</tr>
<tr>
<td>6</td>
<td>48</td>
<td>M</td>
<td>160</td>
</tr>
<tr>
<td>7</td>
<td>64</td>
<td>M</td>
<td>240</td>
</tr>
<tr>
<td>8</td>
<td>37</td>
<td>M</td>
<td>240</td>
</tr>
<tr>
<td>9</td>
<td>62</td>
<td>M</td>
<td>320</td>
</tr>
<tr>
<td>Median</td>
<td>48</td>
<td></td>
<td>240</td>
</tr>
</tbody>
</table>

TABLE 1. Patient Characteristics and Propranolol Dose
2-6 days) and lasted for 6 days (range 3-13 days) after propranolol withdrawal.

Plasma Catecholamines

Total plasma catecholamine values (pg/ml) after propranolol withdrawal are shown in table 3. Because of spoiled samples, only days 0, 6 and 14 for patients 1 to 8 could be compared by nonparametric analysis of variance. Total plasma catecholamines on days 0 and 6 and 14 were different (p < 0.02). Values on day 6 were significantly greater than on day 14 (p < 0.02). Values on days 0 and 6 were not different (p > 0.2). The average time course and magnitude of changes in total plasma catecholamines after propranolol withdrawal are shown in figure 1, where values are plotted as the median for all patients on all study days. The time relationship of these changes to those of the CD25 values shows that plasma catecholamines were increased 3 hours after the last dose of propranolol and remained increased during the period of maximum β-adrenergic sensitivity to propranolol. An inverse relationship was obtained between the increases in plasma catecholamines and the decreases in CD25 values (Ft, 36 = 4.32; p < 0.05). Norepinephrine was the major component of the total plasma catecholamines in samples of the three patients for which separation analysis could be performed.

Heart Rate and Blood Pressure

The average time course of changes in heart rate and blood pressures after propranolol withdrawal is shown in table 4 and figure 2. Lowest heart rate values in all patients were observed on day 0, 3 hours after the last dose of propranolol. Within 2 days, heart rates in all patients had increased to values that were not different from heart rates after 14 days, when the stable CD25 values were recorded. Heart rates on day 0 were substantially lower than heart rates after day 2 (p < 0.001).

Changes in arterial pressure after propranolol withdrawal were more variable among patients (table 4, fig. 2). Six patients had transient increases in systolic and diastolic pressures, one had a sustained increase and two had sustained decreases. When assessed for the group as a whole, there was a significant difference in systolic pressures only (p < 0.05). This difference was attributable to higher systolic pressures on day 6 (median 149 mm Hg) compared with day 0 (median 140, p < 0.05). When assessed for the six patients who showed transient increases in pressure, both systolic and diastolic pressures were greater on day 6 compared with day 0 (p < 0.05) and compared with pressures after day 14 (p < 0.05). All of these transient increases in arterial pressure were coincident with the period of increased β-adrenergic sensitivity and persistently increased total plasma catecholamines (figs. 1 and 2). There was a direct relationship between systolic blood pressures and total plasma catecholamines. (Ft, 45 = 8.96; p < 0.01).

Clinical Symptoms

Transient symptoms after propranolol withdrawal were described by six patients (table 5). All of these
symptoms were otherwise unexplained, had not previously been experienced by the patient, and were self-limited. In five of these patients, symptoms were limited to the period of increased β-adrenergic sensitivity. ECGs were unchanged after abrupt propranolol withdrawal in eight patients. Patient 7 developed generalized T-wave flattening unassociated with chest pain during peak β-adrenergic sensitivity. His ECGs were normal while on propranolol and after propranolol withdrawal when β sensitivity had stabilized. Two additional patients had headaches in association with blood pressure increases. These resolved when their blood pressure was controlled after the trial was concluded.

There were no apparent differences in changes after propranolol withdrawal between patients taking thiazide diuretics and those not on medication.

**Discussion**

We have shown that sudden withdrawal of propranolol after chronic administration is followed by transient supersensitivity to the chronotropic effects of isoproterenol. The time course of these phenomena with respect to onset, peak and duration was much longer in our patients than reported by Boudoulas et al.17 after 48 hours of propranolol therapy in normal volunteers. This discrepancy is probably the result of the longer duration of propranolol therapy (longer than 3 months) after

### Table 4. Heart Rate and Arterial Pressures (Median and Range) on Days After Propranolol Withdrawal

<table>
<thead>
<tr>
<th>Day</th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heart rate*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>55 (48-70)</td>
<td>77 (68-91)</td>
<td>72 (64-100)</td>
<td>74 (62-113)</td>
<td>73 (63-113)</td>
<td>75 (64-116)</td>
<td>78 (60-105)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systolic pressure†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>140 (97-159)</td>
<td>146 (109-214)</td>
<td>157 (130-179)</td>
<td>149 (128-180)</td>
<td>147 (110-183)</td>
<td>144 (111-171)</td>
<td>140 (112-180)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diastolic pressure‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>87 (74-100)</td>
<td>93 (84-115)</td>
<td>95 (80-105)</td>
<td>95 (84-107)</td>
<td>94 (80-106)</td>
<td>91 (79-107)</td>
<td>89 (79-120)</td>
<td></td>
</tr>
</tbody>
</table>

*Significant changes occurred from—days 0 to > 14 (p < 0.001), with difference due to day 0 being less than all other days (p < 0.001).
†Significant changes occurred from—days 0 to > 14 (p < 0.05) with difference being due to day 6 being greater than day 0 (p < 0.05).
‡Days 0 to > 14—No significant change. When assessed for 6 patients with transient increases in pressure (patients no. 1, 2, 3, 4, 7 and 8), both systolic and diastolic pressures were greater on day 6 compared with day 0 (p < 0.05) and compared with days after day 14 (p < 0.05).
withdrawal in our patients. Our findings of \( \beta \)-adrenergic supersensitivity after propranolol withdrawal are supported by Kunos et al. from their data in hypertensive rats.\(^{22} \) However, the phenomenon was not demonstrated in dogs after chronic administration of propranolol was abruptly discontinued.\(^{23} \)

The delay to the onset of supersensitivity is somewhat puzzling, given the short elimination half-life of propranolol of 3.4–6 hours.\(^{24} \) However, others have shown persistence of cardiovascular effects in patients 72 hours after the discontinuation of propranolol,\(^{25} \) and dissociation between the rate of clearance of propranolol from blood and the slower disappearance of its effects.\(^{26} \) In vitro studies have shown continued effects of propranolol despite exhaustive rinse perfusion in isolated hearts of rats sacrificed 72 hours after discontinuation of chronic propranolol therapy.\(^{27} \) The persistent effects of propranolol may be due to tightly bound drug in a deep compartment that includes cardiac \( \beta \) receptors.

The mechanism of \( \beta \)-adrenergic supersensitivity after chronic \( \beta \) blockade may be similar to that seen after chronic preganglionic sympathetic denervation.\(^{28} \) In all systems tested thus far, supersensitivity to \( \beta \) agonists has been associated with an increase in \( \beta \)-receptor concentration.\(^{29} \) Glaubiger and Lefkowitz have recently shown increases in \( \beta \)-receptor concentrations in the hearts of rats chronically treated with propranolol.\(^{30} \)

The time course of changes in \( \beta \)-adrenergic sensitivity after propranolol withdrawal have important implications. Our data suggest that coronary events related to \( \beta \)-adrenergic supersensitivity after abrupt withdrawal could occur long after the last dose of propranolol. The more extensive reviews in the literature describe coronary events “up to 2 weeks” after abrupt withdrawal,\(^{1,2} \) and as late as 21 days after withdrawal.\(^{3} \) The frequency of coronary events over time after abrupt propranolol withdrawal is carefully described in only one of these series,\(^{4} \) and appears to follow a bimodal distribution (fig. 3). Patients experiencing such events very soon (i.e., within 2 days) after propranolol withdrawal are likely to be critically

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**TABLE 5.** **Transient Symptoms After Withdrawal Noted Among Nine Patients Withdrawn Abruptly From Propranolol**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Symptom</th>
<th>Time after withdrawal (days)</th>
<th>Isoproterenol CD(<em>{50}) (% of stable CD(</em>{50}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Anxiety</td>
<td>4</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>Tremulousness</td>
<td>1–2</td>
<td>113–76</td>
</tr>
<tr>
<td>5</td>
<td>Headache</td>
<td>6</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>Headache</td>
<td>4–8</td>
<td>64–58</td>
</tr>
<tr>
<td>7</td>
<td>Headache</td>
<td>6</td>
<td>51</td>
</tr>
<tr>
<td>9</td>
<td>Chest pain, sweating, “heavy breathing” (1/2) hr</td>
<td>5</td>
<td>76</td>
</tr>
</tbody>
</table>

---

**FIGURE 2.** Comparison of time course for heart rate (median) and arterial pressures (medians) after propranolol withdrawal.
dependent on a propranolol-induced reduction in cardiac work to diminish myocardial oxygen requirements. These patients would probably have experienced their coronary event upon propranolol withdrawal irrespective of how gradually the dose was tapered. A second group of patients experienced their coronary events 4–7 days after propranolol withdrawal. This corresponds to the period of maximal β-adrenergic supersensitivity in our patients (fig. 1), and may be the result of a true rebound phenomenon. This suggests that gradual tapering of propranolol over less than 1 week might not effectively prevent the rebound phenomena. In keeping with this, we have reported cases in which typical "rebound" coronary syndromes occurred despite gradual discontinuation of propranolol over less than 1 week.\textsuperscript{31} This is consistent with our recent demonstration that tapered withdrawal of propranolol over 6–9 days did not prevent β-adrenergic supersensitivity in two of three patients.\textsuperscript{32} Our data indicate that 14 days of tapering before propranolol withdrawal may be necessary to prevent β-adrenergic supersensitivity (and possibly "rebound" symptoms). Studies in progress seem to substantiate such an approach.

Increase in plasma catecholamine concentrations in patients during chronic β blockade has been observed,\textsuperscript{33–38} but the changes that occur after abrupt withdrawal of β-blocking drugs have not been studied. The increase in catecholamines associated with β blockade may simply be part of a reflex response to a decrease in cardiac output and blood pressure or may relate to some unknown effect of these drugs on rate of release or degradation of catecholamines. The apparent further increase in plasma catecholamines that occurs along with maximal β-adrenergic sensitivity is interesting. Increases in endogenous catecholamines usually decrease responsiveness to exogenous catecholamines.\textsuperscript{36} Thus, the presence of demonstrable increases in responsiveness to an exogenous β agonist such as isoproterenol, despite increased circulating catecholamines, may be all the more important. Furthermore, the coincidence of these changes suggests that β-adrenergic supersensitivity resulted in either increased release or decreased destruction of norepinephrine. There is considerable evidence for pre-synaptic β receptors on peripheral sympathetic nerves, stimulation of which results in increased noradrenaline release by the nerve terminal.\textsuperscript{37} Blockade of these receptors may be a mechanism of the antihypertensive effect of propranolol.\textsuperscript{37} On the other hand, supersensitivity of these receptors after abrupt propranolol withdrawal could result in an increase in noradrenaline release at peripheral sympathetic nerve endings, explaining the transient increases in both plasma catecholamines and blood pressure that we noted.

The reason for the transient increases in blood pressure in some of our patients after propranolol withdrawal is unclear. Alpha-adrenergic supersensitivity does not appear to occur after abrupt propranolol withdrawal (Rangno RE: unpublished data). The correlation of mean arterial pressure with total plasma catecholamines suggests that increases in either norepinephrine release at sympathetic nerve terminals or circulating norepinephrine concentrations played an important role in the blood pressure changes noted.

Our patients with essential hypertension did not have known coronary artery disease. Although ethical considerations precluded such a study in patients with angina or arrhythmia, it is likely that they would experience similar changes in β-adrenergic sensitivity after abrupt propranolol withdrawal. We studied the chronotropic response to isoproterenol as an index of β-adrenergic sensitivity. The role of supersensitivity to other potential effects of β agonists (such as increased inotropy, effects on platelet function and the central nervous system) has not been established.
We have demonstrated increased sensitivity to the chronotropic effects of β agonists after abrupt propranolol withdrawal. This is probably the major mechanism of clinically observed withdrawal syndromes. Increases in plasma catecholamine concentrations and transient increases in blood pressure may play a contributing role in some patients. Gradual withdrawal of propranolol may prevent some of these symptoms, but gradual dose reduction over a short period (less than 1 week) may not be of value.

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References

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