Lack of Beta-adrenoreceptor Hypersensitivity After Abrupt Withdrawal of Long-term Therapy with Oxprenolol

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SUMMARY The possibility of β-adrenoreceptor hypersensitivity after abrupt withdrawal of long-term therapy (8–18 months) with the slow-release (SR) formulation of oxprenolol (160–320 mg/day) was assessed in six patients with uncomplicated essential hypertension. The chronotropic dose 25 of isoproterenol (the dose that increases the resting heart rate by 25 beats/min), plasma concentration of catecholamines, triiodothyronin and thyroxin, plasma renin activity and aldosterone, hemoglobin, hematocrit and oxyhemoglobin dissociation were measured on the last day of oxprenolol SR intake and 1, 2, 3, 6 and 13 days after abrupt replacement by identical placebo tablets. The chronotropic dose 25 of isoproterenol (μg/m²), which was greater than 25.6 in all patients on the last day of oxprenolol SR, fell to 4.83 ± 2.03 on the second day and to 3.50 on the third day after its abrupt withdrawal and reached a minimal value on the thirteenth day (2.78 ± 0.30). Throughout the study, plasma concentrations of catecholamines, triiodothyronin and thyroxin and oxyhemoglobin dissociation remained unchanged. Plasma renin activity and plasma aldosterone, which were suppressed during oxprenolol administration, rose significantly during placebo, coinciding with a significant fall in hematocrit and hemoglobin. No major subjective symptoms were reported by the patients. Thus, hypersensitivity of β-adrenoreceptor-mediated responses was not demonstrated after sudden withdrawal of oxprenolol SR.

THE SUDDEN WITHDRAWAL of long-term therapy with β-adrenoreceptor-blocking agents in patients with coronary artery disease can exacerbate angina pectoris,1–9 which may progress to myocardial infarction and sudden death.5, 10 Abrupt β-blocker withdrawal in hypertensive patients is associated with palpitations, headaches, tremor, sweating and malaise.10–15 Such events and symptoms could result from recurrence of suppressed symptoms after cessation of effective therapy,16, 17 from progression of underlying disease,18 or from a rebound phenomenon or supersensitivity response to abrupt drug withdrawal.5, 6, 11, 13, 15

Several mechanisms18, 20 have been proposed to explain this withdrawal phenomenon, such as hypersensitivity of the adrenoreceptors and β-adrenoreceptor-mediated responses,19, 21 a reactive increase of sympathetic nerve activity,11 increased production of triiodothyronin10 and reduced oxyhemoglobin dissociation.22, 23 Withdrawal symptoms have been described, mostly as individual case reports, to occur with propranolol1, 9, 12, 13, 15 and timolol,18 which are noncardioselective, and with atenolol14 and metoprolol,15, 18 which are cardioselective. No controlled study has been performed regarding the effect of sudden withdrawal of oxprenolol, a widely used compound that differs in its pharmacologic properties from the abovementioned β-blockers, in that oxprenolol contains intrinsic sympathomimetic activity.24 We investigated whether the abrupt withdrawal of long-term administration of the slow-release (SR) formulation of oxprenolol25 would lead to a phenomenon compatible with a supersensitivity syndrome.

Patients and Methods

Six patients (five males and one female), ages 27–53 years (mean 41 years), with essential hypertension (World Health Organization stages I and II) whose blood pressure had been well controlled with oxprenolol SR therapy (160–320 mg/day, mean 187 mg/ day) for 8–18 months, were investigated. None had clinical or electrocardiographic evidence of coronary artery disease. Five patients were classified as normal-renin and one as a high-renin type; low-renin patients were excluded because their β-adrenoreceptor responsiveness may be reduced.27 Endocrine disorders were excluded in all patients; the female patient did not take estrogen-containing contraceptive pills. All patients gave informed consent.

The daily dose of oxprenolol SR was substituted with identical placebo tablets in a single-blind fashion. Investigations were performed on the last day of oxprenolol SR therapy (day 0) and thereafter on days 1, 2, 3, 6 and 13 of placebo therapy. Measurements were taken between 8:00 and 10:00 a.m., i.e., 2 hours after taking oxprenolol SR or placebo and after the patient had been recumbent for 30 minutes after insertion of an indwelling venous cannula for repetitive blood sampling. These measurements included five subsequent
measurements of blood pressure and heart rate and boluses of the chronotropic dose 25 of isoproterenol (CD25) (i.e., the dose, corrected for body surface area, that increased resting heart rate by 25 beats/min, a method described earlier\textsuperscript{28, 29} and adopted in our laboratory\textsuperscript{30}). Confirmation of cardiac β-adrenoceptor blockade was the purpose of determining the CD25 on day 0. To adhere to the same timing on day 0 as on subsequent days, and to avoid a change in receptor density that might occur with exposure of greater concentrations of the agonist,\textsuperscript{31} CD25 values greater than 25.6 μg/m\textsuperscript{2} of isoproterenol were considered to reflect adequate blockade of β adrenoreceptors. Preliminary studies done in these patients revealed CD25 values of 102.4–204.8 μg/m\textsuperscript{2} with the same treatment. Plasma norepinephrine and epinephrine concentrations were measured by the radioenzymatic technique.\textsuperscript{32} Blood for triiodothyronin (T3) and thyroxin (T4) was drawn twice at a 30-minute interval to account for cyclic variations in the plasma level of these hormones\textsuperscript{33} and was measured by radioenzymatic methods. To assess the reactive increase in the previously suppressed renin-aldosterone system and the attendant volemia, plasma renin activity,\textsuperscript{34} plasma aldosterone\textsuperscript{35} and hemoglobin and hematocrit were measured. Oxyhemoglobin dissociation was assessed by establishing oxygen-binding curves of whole blood;\textsuperscript{36} erythrocyte 2,3-diphosphoglycerate (2,3-DPG) was measured using a test kit (Böhringer Mannheim) determining stoichiometric oxidation of reduced nicotinamide adenine dinucleotide.\textsuperscript{37} Oxprenolol plasma levels were measured by a new double isotope procedure (Riess W: unpublished methods).

At each visit the patient was assessed by general routine inquiry and with the aid of a structured analog scale patients’ self-assessment questionnaire that listed 49 symptoms pertaining to common complaints in hypertensive patients and β-blocker-related side effects in particular. Values are given as mean ± SEM. For statistical significance a paired t test was used. The p values refer to differences vs day 0 unless specified.

**Results**

All patients showed adequate cardiac β blockade (i.e., CD25 > 25.6 μg/m\textsuperscript{2}) on the last day of oxprenolol SR therapy (day 0) in the presence of a plasma oxprenolol concentration lying within the therapeutic range (678 ± 131 ng/g plasma). The CD25 fell rapidly, to 8.23 ± 2.08 on day 1 and to 4.83 ± 2.03 on day 2 after withdrawal of oxprenolol SR. Therefore, the curve flattened, with the lowest mean value of 2.78 ± 0.30 on day 13. In no instance was there evidence for supranormal values of β-adrenoreceptor sensitivity to isoproterenol (fig. 1, table 1). The oxprenolol plasma concentrations were 19.7 ± 7.01 ng/g 24 hours after withdrawal of oxprenolol SR and remained undetectable (< 5 ng/g plasma) (fig. 1).

Plasma norepinephrine and epinephrine concentrations remained constant throughout the withdrawal period, as did the results of T3 and T4 (table 2).

Oxygen pressure (PO\textsubscript{2}) at 50% saturation of hemoglobin with oxygen was within the normal range during oxprenolol SR therapy and did not change during placebo administration. Similarly, erythrocyte 2,3-DPG content did not change after withdrawal of oxprenolol SR (table 2).

Systolic and diastolic pressure increased significantly (p < 0.05) 24 hours after abrupt cessation of oxprenolol SR, but heart rate did not increase until the second day of placebo administration (p < 0.005). Thereafter, blood pressure remained elevated at about the same level for the rest of the study.

Plasma renin activity and plasma aldosterone values were low on the last day of oxprenolol SR therapy (1.53 ± 0.3 ng/ml/hour and 7.77 ± 0.905 ng%, respectively (fig. 2). Both rose sharply 24 hours after withdrawal of β blockade remaining elevated for the first 48 hours, while a gradual but significant fall in hematocrit (p < 0.005) and hemoglobin (p < 0.01) (table 1) reached a maximum on day 3. This coincided with a transient fall in plasma renin and aldosterone, followed by a further rise on day 6. Finally, on day 13, hematocrit and hemoglobin were below and plasma renin activity (p < 0.05) and aldosterone above the values obtained at the last day of oxprenolol SR therapy.

None of the patients complained of untoward symptoms during the study. On the self-assessment questionnaire, two patients indicated a moderate degree of headache and some palpitations after discontinuing oxprenolol SR. While on the active drug, one patient indicated depressed mood and insomnia and one cold fingers; these symptoms improved during placebo therapy.
TABLE 1. Blood Pressure, Heart Rate, Chronotropic Dose 25 of Isoproterenol and Hemoglobin in Hypertensive Patients After Abrupt Withdrawal of Slow Oxprenolol Therapy

<table>
<thead>
<tr>
<th></th>
<th>On oxprenolol</th>
<th>Days after withdrawal of oxprenolol therapy</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>133.3 ± 5.90</td>
<td>144.1 ± 7.27†</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>92.1 ± 3.30</td>
<td>98.5 ± 2.87†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>60.5 ± 2.38</td>
<td>61.2 ± 2.82</td>
</tr>
<tr>
<td>CD25 (µg/m²)</td>
<td>&gt; 25.6</td>
<td>8.23 ± 2.081</td>
</tr>
<tr>
<td>Hemoglobin (g%)</td>
<td>14.53 ± 0.512</td>
<td>14.38 ± 0.503</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
Values vs day 0:
* p < 0.01;
† p < 0.05;
‡ p < 0.005.
Values vs day 1:
§ p < 0.01.
¶ p < 0.05.

Abbreviations: BP = blood pressure; CD25 = chronotropic dose 25 of isoproterenol.

Discussion

Up to 13 days after abrupt withdrawal of long-term treatment with oxprenolol SR, there was no evidence of hypersensitivity of cardiac β-adrenoreceptors to isoproterenol bolus injections. Neither plasma catecholamines nor thyroid hormones increased. This is in accord with the paucity of the patients' subjective symptoms after withdrawal of β-blockade.

Our results differ from some observations after sudden withdrawal of propranolol. Boudoulas et al. demonstrated a hypersensitivity to isoproterenol 24-48 hours after the withdrawal of a daily dose of 160 mg propranolol given for 2 days to six normal subjects. Nattel et al. reported transient hypersensitivity to isoproterenol 2-13 days after abrupt cessation of 3 months of antihypertensive therapy with propranolol in nine patients. Total plasma catecholamines also increased slightly, relating to some extent to the complaints of those patients who had isoproterenol hypersensitivity. However, in that study, median values for plasma catecholamine levels were already higher, presumably because of baroreflex activation resulting from the β-blocker-induced fall in cardiac output, than those found 2 weeks after stopping propranolol; thus, the increase during withdrawal was comparatively small.

Pantano and Lee found no evidence for hypersensitivity in 21 healthy subjects for 4 days after abrupt cessation of 15 days of propranolol (120-160 mg/day). Similarly, Lindenfeld et al. who measured several hemodynamic, hematologic, metabolic changes.

TABLE 2. Thyroid Function Tests, Plasma Catecholamines, Oxyhemoglobin Dissociation and Erythrocyte 2,3-Diphosphoglycerate in Six Hypertensive Patients After Abrupt Withdrawal of Slow Oxprenolol Therapy

<table>
<thead>
<tr>
<th></th>
<th>On oxprenolol</th>
<th>Days after withdrawal of oxprenolol therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Plasma T3 (ng/ml)</td>
<td>1.13 ± 0.077</td>
<td>1.17 ± 0.054</td>
</tr>
<tr>
<td>Plasma T4 (ng/100 ml)</td>
<td>6.6 ± 0.29</td>
<td>6.6 ± 0.32</td>
</tr>
<tr>
<td>Plasma epinephrine (pg/ml)</td>
<td>44.7 ± 17.02</td>
<td>40.0 ± 13.80</td>
</tr>
<tr>
<td>Plasma nor-epinephrine (pg/ml)</td>
<td>365 ± 110.1</td>
<td>353 ± 86.3</td>
</tr>
<tr>
<td>Oxyhemoglobin dissociation (p 50; mm Hg)</td>
<td>26.7 ± 0.2</td>
<td>26.3 ± 0.4</td>
</tr>
<tr>
<td>Red cell 2,3-D.P.G. (n = 5) (µmol/ml)</td>
<td>4.41 ± 0.14</td>
<td>4.75 ± 0.22</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
None of the changes reached statistical significance.
Abbreviations: T3 = triiodothyronin; T4 = thyroxin.
vent a reactive increase in the number of β receptors.\textsuperscript{31, 44, 46} Differences in the results of various studies also could be accounted for by differences in methods or in the pharmacokinetic characteristics of the β blockers\textsuperscript{46} and the duration of their cardiovascular action.\textsuperscript{25, 26, 47}

However, the half-life in plasma of oxprenolol is shorter than that in most other β blockers,\textsuperscript{46} so it is less likely that the absence of a withdrawal syndrome may be due to the pharmacokinetic characteristics of this drug.

In the search for further mechanisms for the withdrawal syndrome, Kristensen et al.\textsuperscript{19} found an increase in serum free T3 that they attributed to the removal of a propranolol-induced inhibition of the mono- deiodination of T4 and T3.\textsuperscript{44} Although with oxprenolol SR, T3 values increased slightly but not significantly, this pattern was not observed consistently in any individual patient.

The present study also shows that removal of β blockade results in a significant increase in plasma renin activity and plasma aldosterone, with subsequent sodium volume retention indicated by a concomitant fall in hematocrit and hemoglobin. This sodium volume expansion may help to prevent a reactive increase in sympathetic activity. Moreover, increased extracellular volume, together with an increase in heart rate, contribute to the rise in blood pressure after cessation of antihypertensive therapy with β blockers.

Discontinuation of propranolol therapy in patients with coronary artery disease has been reported to result in a shift to the left\textsuperscript{29} of the previously favorably altered oxyhemoglobin dissociation curve, and may thus contribute to the withdrawal syndrome.\textsuperscript{18} Although the effect of β blockers on the oxyhemoglobin dissociation curve is controversial,\textsuperscript{46-48} the fact that it remained unchanged in our study during the withdrawal of oxprenolol therapy gives at least assurance that myocardial oxygen delivery is not jeopardized by an altered oxyhemoglobin dissociation at a time when oxygen demand may be increased due to a greater left ventricular work.

In conclusion, a hypersensitivity syndrome was not demonstrable in our study with oxprenolol SR. This feature may be of clinical relevance in patients with coronary artery disease, in whom even a slight yet transient hypersensitivity could alter the balance between oxygen delivery and consumption.

**Acknowledgment**

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**References**


**FIGURE 2.** Change in hematocrit, resting plasma renin activity and aldosterone after abrupt withdrawal of long-term antihypertensive therapy with slow-release oxprenolol (mean ± SEM). Plasma renin and aldosterone were suppressed during oxprenolol therapy (filled circles). They increased after discontinuation of oxprenolol (open circles), paralleled by a decrease in hematocrit.

A and endocrine variables in normal subjects and in patients with angina pectoris before, during and up to 6 days after abrupt withdrawal after 2 weeks of propranolol administration, could not demonstrate hypersensitivity to β-adrenoreceptor-mediated responses; nor did they observe any significant change in plasma epinephrine, norepinephrine or dopamine β-hydroxylase before, during or after propranolol.

Maling and Dollery\textsuperscript{41} found no increase in plasma norepinephrine after discontinuation of long-term antihypertensive therapy with propranolol; nor did Lederballe-Pedersen et al.\textsuperscript{42} after cessation of metoprolol treatment. Therefore, it is unlikely that sudden withdrawal of therapy with these β blockers leads to a transient and excessive increase in sympathetic activity. Hence, in cases that demonstrate a propranolol withdrawal syndrome, this appears to be due to increased β-adrenoreceptor sensitivity.\textsuperscript{11, 21} Aarons et al.\textsuperscript{43} suggested that β-adrenorezeptor-mediated hypersensitivity may be attributed to an increase in β-adrenoreceptor density during propranolol treatment that persists for several days after its discontinuation. Thus, a β blocker that contains intrinsic sympathomimetic activity, like oxprenolol, could be less likely to cause a hypersensitivity state because constant receptor stimulation due to the presence of intrinsic sympathomimetic activity may pre-
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