Time Course of Development of the Antihypertensive Effect of Propranolol

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SUMMARY Ten patients with essential hypertension were hospitalized and treated with placebo, followed by their usual dose of propranolol. Systolic and diastolic blood pressure decreased significantly after the first dose of propranolol, and by the third day of propranolol treatment reached 84% to 92% of the maximum decrease achieved during the 6 days of treatment. Mean maximum falls in blood pressure were 13/12 mm Hg supine and 12/13 mm Hg standing. This development of the decrease in heart rate and blood pressure over 48 hours occurred in parallel with cumulation of propranolol to steady state in plasma. The decrease in diastolic, but not systolic, arterial pressure was directly related to pretreatment blood pressure, but not significantly related to pretreatment plasma renin activity (PRA) or change in PRA. Thus, single doses of propranolol lowered blood pressure in patients with essential hypertension, and with continued therapy, near maximum antihypertensive effects were achieved within 48 hours. (Hypertension 5: 852-857, 1983)

KEY WORDS • beta blocker • hypertension • dose-effect relationships

In 1966, Prichard and Gillam1 stated that “The full hypotensive effect is not usually seen for several weeks after commencement of propranolol therapy . . . .” This belief has persisted, even though the negative chronotropic effect of propranolol is known to develop within hours or days after initiation of therapy, and despite several reports that near maximum effects of propranolol2-3 and other beta blockers4 5 develop within 2 days to 1 week. Because of these questions regarding the time required for the development of the full antihypertensive effect of propranolol and whether the negative chronotropic and antihypertensive effects of propranolol develop in parallel, we designed a study to examine the development of antihypertensive effects of propranolol in patients with essential hypertension. Propranolol has been reported to have a short terminal half-life (3—4 hours,6 which has led to the expectation of fairly rapid cumulation to steady state in plasma. However, we have previously reported that this actually takes 3 to 5 days, so we examined the development of antihypertensive effect in relation to plasma propranolol concentration, and we also measured plasma renin activity (PRA).

Methods

Patient Selection

Ten patients aged 19 to 58 years on chronic propranolol therapy were selected from the General Clinical Research Center Hypertension Clinic at the Medical University of South Carolina. There were six men and four women; four were black and six were caucasian. Each patient had a physical examination, electrocardiogram, chest x-ray, complete blood count, and measurements of electrolytes, creatinine, blood urea nitrogen, and fasting glucose. None had evidence of secondary hypertension.

Study Design

Informed consent was obtained, and patients had all antihypertensive medications discontinued. After several days they were admitted to the General Clinical Research Center for a period of 9 to 12 days. They were placed on an isocaloric diet of 109 mEq sodium and 80 mEq potassium for the duration of the study. Supine and standing blood pressures and 60-second apical heart rate were measured daily at 0800, 1000, 1200, 1400, 1600, 1800, 2000, and 2200 with a standard mercury sphygmomanometer. Phase V of the Korotkoff sounds was considered to represent diastolic pressure.

The patients received placebo for propranolol (Inderal) for from 3 to 6 days while the blood pressure stabilized, and then propranolol for 6 days. Whether placebo or propranolol was being administered was
unknown to the patients and nurses recording blood pressure. The patients were treated with their own previous dose of propranolol (80–320 mg/day) in four equal doses given every 6 hours (0600, 1200, 1800, and 2400). On the last day of placebo treatment, the patients stood for 2 hours, beginning at 0800 (2 hours after the morning dose of placebo). At the end of this period, blood samples were drawn through a previously inserted heparin lock for assay of PRA in nine of the 10 patients. This procedure was repeated on the 1st and 6th days of propranolol treatment. In six of the 10 patients, blood samples for measurement of plasma propranolol concentration were drawn daily at 0800, 2 hours after the morning dose of propranolol.

Measurements and Assays

Blood samples for propranolol were handled and measured by GC-MS as previously described. PRA was measured by radioimmunoassay of the angiotensin I (Al) generated, by the method of Katz and Smith.

Statistics

The patients served as their own controls. Comparisons were made using a program for two-way analysis of variance with interaction and repeated measures design on a Prime computer system. The factors in the analysis of variance were treatment and time. Whether there was an overall difference between drug and placebo treatment was determined from the treatment term. In addition, each day of active drug treatment was compared to the last day of placebo treatment, and individual times after drug administration were compared to the same time of day on the last placebo day, by the method of least significant difference.

The patients received different doses of propranolol, so for each patient the maximum plasma concentration was defined as the mean of the two highest levels. The percentage of that value represented by the level on each day was calculated, and the percentage of maximum plasma concentration for the six patients was averaged on each day.

Similarly, the greatest decrease in each parameter of blood pressure and heart rate was defined as the mean of the two lowest daily mean values for the group minus the value on the last day of placebo treatment. The percentage of maximum decrease was then calculated on each day of propranolol treatment. Values for mean PRA at each time during the study were compared by dependent (paired) t test. All values are shown as means or means ± SEM.

Results

There were significant reductions in both blood pressure and heart rate after the first dose of propranolol (see fig. 1). The greatest decreases in each parameter, by comparison to the same time on the last day of

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**Figure 1.** Effect of the first dose of oral propranolol (20–80 mg) on supine and standing blood pressure and heart rate in 10 patients with essential hypertension. Mean values ± SEM are shown for 2, 4, and 6 hours after the first daily dose of propranolol (•), compared to the same times on the last day of placebo (○). * = p < 0.05; ** = p < 0.01; *** = p < 0.001.
placebo treatment, are shown in Table 1. The changes in each parameter were significant at the 5% level or less.

Blood pressure and heart rate remained quite constant during the last 3 days of placebo treatment (C,.) (see fig. 2). On a daily basis, the time course of the development of the effects on supine and standing values for systolic and diastolic blood pressure and heart rate were indistinguishable. All parameters of blood pressure and heart rate were significantly decreased on the first day of drug treatment compared to the last placebo day (p < 0.05). By the 3rd day of active drug treatment, 84% to 92% of the maximum effect had been achieved in all six parameters. The greatest decreases on any single day from the last day of placebo treatment are shown in Table 2. Overall, compared to placebo treatment by analysis of variance, propranolol reduced each parameter of blood pressure and heart rate, p < 0.0001.

Within the group, changes in supine and standing diastolic blood pressure were directly related to the pretreatment levels (last control day), r = 0.79 and 0.82 respectively, (both p < 0.01) (see fig. 3). Changes in supine and standing mean arterial pressure

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**TABLE 1. Blood Pressure and Heart Rate Effects After The First Dose**

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>Standing</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>SBP (mm Hg)</td>
<td>DBP (mm Hg)</td>
</tr>
<tr>
<td>Lowest value after 1st propranolol dose</td>
<td>126.8±6.5</td>
<td>89.1±4.6</td>
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<tr>
<td>Same time last day of placebo</td>
<td>137.7±5.5</td>
<td>93.8±4.8</td>
</tr>
<tr>
<td>Maximum change</td>
<td>−10.9</td>
<td>−4.7</td>
</tr>
<tr>
<td>Significance</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.

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**FIGURE 2.** Time course of the effects of oral propranolol on supine (Panel A) and standing (Panel B) blood pressure and heart rate in 10 patients with essential hypertension. Mean daily values ± SEM are shown for the last 3 days of placebo treatment and 6 days of treatment with propranolol (80–320 mg/day).
TABLE 2. Blood Pressure and Heart Rate Effects Over 6 Days

<table>
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<tr>
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<th>Supine</th>
<th>Standing</th>
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<tbody>
<tr>
<td></td>
<td>SBP (mm Hg)</td>
<td>DBP (mm Hg)</td>
</tr>
<tr>
<td>Lowest value during propranolol treatment</td>
<td>122.1±4.1</td>
<td>81.9±3.8</td>
</tr>
<tr>
<td>Last day of placebo</td>
<td>135.9±4.7</td>
<td>74.2±4.5</td>
</tr>
<tr>
<td>Maximum change</td>
<td>-13.8</td>
<td>-12.3</td>
</tr>
<tr>
<td>Significance</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
</tr>
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were also directly related to pretreatment values, \( r = 0.75 \) and 0.76 (both \( p < 0.02 \)) respectively, but changes in supine and standing systolic blood pressure were not significantly related to pretreatment pressure, \( r = 0.34 \) and 0.56 respectively (both ns).

PRA in nine patients was 10.0 ± 2.1 ng/ml/hr on the last placebo day, 10.1 ± 5.0 after the first dose of propranolol, and 6.3 ± 2.0 on the 6th day of treatment. The mean 37% decrease from pretreatment to Day 6 did not reach statistical significance. Change in blood pressure was not related to pretreatment PRA or change in PRA.

In the six patients in whom serial plasma propranolol determinations were obtained, steady state plasma concentration was directly related to daily dose, \( r = 0.84, p < 0.05 \). In the individual patients, 97% or more of the steady state plasma concentration was achieved on the 2nd to 5th day (26 to 122 hours after initiation of dosing). Mean plasma levels for the group were 44% of steady state after the first dose and 94% of steady state by the third day of active drug treatment (see fig. 4). Development of the effects on systolic and diastolic blood pressure and heart rate were essentially parallel to cumulation of propranolol in plasma in both the supine and standing positions (see fig. 4).

Discussion

The conclusion of Prichard and Gillam,1 that the antihypertensive effect of propranolol developed over weeks, was based on infrequent observations during an outpatient study. Under more controlled conditions with more frequent observations, several other investigators have shown that the time required for development of the antihypertensive effect of propranolol2 3 and other beta blockers4 5 is 1 week or less. Our study demonstrates that, in a group of known propranolol responsive hypertensive patients, the antihypertensive effect begins with the first dose, and is nearly complete within 48 hours, corresponding to the cumulation of propranolol to steady state in plasma.

The small further fall in arterial pressure during hospitalization in our study, or over a longer period in the study of Prichard and Gillam,1 may or may not represent direct drug effects per se. During our study, a progression of “hospitalization effect” may be responsible for the small further decline in blood pressure. In longer term studies, such as the one of Prichard and Gillam,1 there may be “resetting” of baroreceptors, or relaxation of vascular tone in the peripheral arterial bed due to the decreased pressure, or some other indirect effect of propranolol. That the fall in blood pressure over 6 days in our study is near maximum in these hospitalized patients is supported by the fact that mean pressure for the group decreased to 122/83 mm Hg supine and 119/87 mm Hg standing (average of the two lowest days), leaving little room for a further decrease in blood pressure.

![Figure 3. Relationship between pretreatment arterial pressure (mm Hg) and maximum change in arterial pressure (mm Hg) from the last day of placebo treatment to lowest daily value for supine diastolic (Panel A) and standing diastolic (Panel B). Each point represents an individual patient.](http://hyper.ahajournals.org/)

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The fall that we observed may, however, be due to some interaction of propranolol treatment and hospitalization, and thus the same time course may not occur when propranolol is administered to unrestricted outpatients. Although one cannot necessarily assume that the inpatient results can be extrapolated to results in outpatients, previous studies with similar findings either in outpatients using home blood pressures or outpatients who spent the day in the clinic suggest that a similar time course may occur in outpatients.

Another possible factor in the rate of fall of blood pressure with propranolol is that it may be dose-dependent. Since we used known effective doses, we may have seen a maximum, or near maximum, rate of fall. Had we started with lower doses in each patient, we might have seen a slower rate of fall. Therefore, in clinical practice in outpatients, where doses of propranolol are usually titrated upward, there would generally tend to be a slower rate of fall in blood pressure.

Our finding that the fall in diastolic but not systolic blood pressure was significantly related to pretreatment blood pressure suggests that different mechanisms may be involved in the lowering of diastolic and systolic arterial pressure by propranolol. Previously in our laboratory in normal volunteers, we found that, after an intravenous dose of propranolol, the decrease in systolic pressure was temporally related to the decrease in cardiac output, and the decrease in systolic pressure was seen in all subjects. However, diastolic pressure did not reach its lowest level until 3 hours after the intravenous dose of propranolol (more than 2 hours after the greatest decrease in cardiac output), and the decrease in diastolic pressure was not seen in all subjects. In addition, the decrease in MAP, reflecting primarily the decrease in diastolic pressure, was directly related to change in total peripheral resistance and inversely related to change in cardiac output. If, in fact, different mechanisms are involved in lowering systolic and diastolic blood pressure, they remain to be elucidated.

The positive relationship between pretreatment MAP and change in MAP after propranolol is similar to that reported for minoxidil. Unfortunately, in that study the relationships between pretreatment systolic
and diastolic blood pressure and the changes in those parameters were not reported, and therefore cannot be compared to our findings.

Although there was an absolute decrease in PRA for the group, it did not reach statistical significance because three patients who received daily doses of 80 mg had an increase in PRA. The phenomenon of a small rise in PRA after propranolol administration has been previously described in a small percentage of patients. Apparently in these patients, the decrease in arterial pressure stimulated renin production more than it was inhibited by the relatively low dose of propranolol.

The direct relationship between daily dose and steady state plasma concentration is similar to our previous report. Also, as in our earlier study, the degree of accumulation is greater and the time required for cumulation to steady state plasma concentration (2 to 5 days) is considerably longer than would be expected from the generally reported 3- to 4-hour terminal half-life of propranolol after single doses. This may reflect partial saturation of tissue binding or partial saturation of metabolism as a result of repeated administration.

The similar time course of the cumulation of propranolol to steady state in plasma, and the development of effects on blood pressure (fig. 4), is easier to reconcile than a rapid cumulation of the drug associated with a delayed development of antihypertensive effect, as might be expected if results of separate studies on blood pressure and kinetics were combined. The similar time course of the effects on heart rate and blood pressure (fig. 4) is also different than previously suggested and indicates that, after oral dosing, the mechanisms responsible for the antihypertensive effect of propranolol develop at approximately the same rate as beta blockade.

Conclusions

The antihypertensive and negative chronotropic effects of propranolol are apparent after the first dose and are nearly complete within 48 hours. Temporally this corresponds to cumulation of propranolol to steady state in the plasma. Since most of the antihypertensive effect of propranolol develops within 48 hours in hospitalized patients, titration of dose and response can be accomplished relatively rapidly, rather than allowing several weeks between dosage adjustments as would be necessary if the effect truly required weeks to develop. It cannot be automatically assumed, however, for the reasons mentioned in the discussion, that a similarly rapid development of effect would be seen in out-patients.

Acknowledgments

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