Effects of Beta-Adrenergic Blocking Agents on the Blood Pressure, Plasma Renin Activity and Hemodynamics of Hypertensive Patients

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SUMMARY

Changes in blood pressure, plasma renin activity, and hemodynamic components were studied in 23 patients with essential hypertension treated with oral pindolol or propranolol. These beta-adrenergic blocking agents effectively lowered the blood pressure in the majority of the patients. Although plasma renin activity was not significantly changed, the higher was the pretreatment level, the more it tended to be decreased. Systemic vascular resistance was significantly decreased, while changes in cardiac index and circulating blood volume were variable. Pindolol showed less effect in reducing the heart rate than propranolol. The antihypertensive effect of these drugs had no correlation with the change in plasma renin activity or in any one of hemodynamic components.

Additional Indexing Words:
Essential hypertension Cardiac index Heart rate Circulating blood volume Vascular resistance Pindolol Propranolol

The antihypertensive effect of beta-adrenergic blocking agents was first described in 19641) and has been increasingly in use for the treatment of hypertension. However, no explanation has been established for the mechanism of this antihypertensive action. Tarazi and Dustan2) assumed that a fall in cardiac output would initiate a readaptive change in the vascular system. On the other hand, Bühler et al3) attributed this action to an inhibitory effect on renal renin release. In order to re-evaluate these theories we studied changes in blood pressure and hemodynamics as well as plasma renin level of hypertensive patients receiving beta-adrenergic blocking agents. The results did not support either view.

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Methods

Hypertensive out-patients were given placebo or no medication for at least 2 weeks. Routine examinations including chest X-ray, electrocardiogram, hematology, blood chemistry, urinalysis, PSP excretion, radioisotope renogram and retinal findings were performed. Circulating blood volume, cardiac index and systemic vascular resistance were determined by radiocardiographic analysis.4) Plasma renin activity (PRA) was measured by radioimmunoassay according to the method of Haber et al.5) The patients were under no dietary regimen. The blood sample for PRA was taken around noon after 2-hour bed rest following serum electrolyte analysis under a fasting condition. Then stimulation of renin release was carried out by 2-hour upright position and intravenous administration of 20 mg furosemide. The urinary sodium excretion in 24 hours prior to the PRA determination was more than 100 mEq in most cases, where the variation of sodium balance gives no significant influence on PRA.6) Therefore no correction was made on PRA in regard to the sodium excretion. When the supine PRA was higher than 3.0 ng/ml/hr, the patient was referred to as a high renin patient. Low renin patients were those whose PRA was lower than 0.3 ng/ml/hr at rest and less than 0.5 following the stimulation procedure.

Subjected to this study were 23 patients with no detectable cause of hypertension and with the blood pressure consistently higher than 160 mmHg in systolic and 90 mmHg in diastolic through the control period. Eleven males aged from 31 to 68 years and 12 females from 42 to 62 were included. Retinal findings ranged from class I to III except one class IV case according to Keith-Wagener classification. Most patients had normal renal function while slightly impaired in 4 patients—18 to 22% of PSP excretion in 15 min. No patient had proteinuria, apparent cardiac involvement, cerebrovascular complications, or abnormal serum electrolytes.

Pindolol (15–30 mg/day) was given orally in 3 divided doses to 16 patients (9 males and 7 females). Propranolol was given in the same way to 7 patients (2 males and 5 females). The dose was initiated from 30 mg per day and, when considered ineffective, 30 mg/day was added every 2 weeks. The maximum dose of propranolol was 120 mg/day. Blood pressure and heart rate were read at least every 2 weeks. The examinations done in the control period were repeated between 35th and 84th day of the treatment and the data were compared with the control values. As for the blood pressure and the heart rate, the comparison was made between means of the last 2 values observed in each period.

Student's t-test was applied to the determination of the significance of correlation coefficients, and paired t-test to the comparison of the values before and after the treatment.

Results

I. Blood pressure

Both of systolic and diastolic pressures were significantly lowered after the treatment with either pindolol or propranolol (Table I). Pindolol was effective in 10 cases out of 16 (62.5%) and so was propranolol in 4 cases out of
7 (57.1%), if considered as effective when mean arterial pressure fell more than 10% of the control level. The antihypertensive effect was usually detected in 2 weeks and almost leveled off in 6 weeks. The effect was not related to the initial level of the blood pressure.

Table I. Effects of Beta-Adrenergic Blocking Agents

<table>
<thead>
<tr>
<th></th>
<th>Pindolol</th>
<th>Propranolol</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>control</td>
<td>treated</td>
<td>control</td>
</tr>
<tr>
<td>Blood pressure:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic (mmHg)</td>
<td>177±28</td>
<td>152±31***</td>
<td>178±24</td>
</tr>
<tr>
<td>diastolic (mmHg)</td>
<td>106±10</td>
<td>93±11***</td>
<td>106±12</td>
</tr>
<tr>
<td>mean (mmHg)</td>
<td>130±15</td>
<td>113±17***</td>
<td>130±15</td>
</tr>
<tr>
<td>Heart rate (per minute)</td>
<td>70±11</td>
<td>69±8</td>
<td>66±7</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>1.5±1.5</td>
<td>1.5±2.2</td>
<td>0.7±1.3</td>
</tr>
<tr>
<td>(ng/ml/hr)</td>
<td></td>
<td></td>
<td>1.3±1.5</td>
</tr>
<tr>
<td>Cardiac index (L/min/M²)</td>
<td>3.9±0.9</td>
<td>3.6±0.7</td>
<td>3.6±0.6</td>
</tr>
<tr>
<td>Systemic vascular</td>
<td>2,859±651</td>
<td>2,516±468*</td>
<td>2,996±621</td>
</tr>
<tr>
<td>resistance (dyne·sec·M²·cm⁻⁵)</td>
<td></td>
<td></td>
<td>2,901±200</td>
</tr>
<tr>
<td>Circulating blood</td>
<td>78±12</td>
<td>76±12</td>
<td>73±13</td>
</tr>
<tr>
<td>volume (ml/Kg)</td>
<td></td>
<td></td>
<td>76±12</td>
</tr>
</tbody>
</table>

Values are mean±sd.
* p<0.05, ** p<0.01, *** p<0.001 as compared with control values.

Fig. 1 (Left). Relationship between the control value of heart rate and its decrease following the treatment with pindolol (○) or propranolol (●). Negative value indicates an increase. r=0.658, p<0.01 for pindolol, r=0.972, p<0.001 for propranolol.

Fig. 2 (Right). Relationship between the control value of plasma renin activity and its decrease following the treatment with pindolol (○) or propranolol (●). Negative value indicates an increase. r=0.703, p<0.001.
II. Heart rate
Heart rate was decreased from 66 to 58 with propranolol \((0.05 < p < 0.10)\), while it was not significantly affected with pindolol (Table I). The higher the initial rate, the more it was decreased after the treatment \((r = 0.606, p < 0.01)\). This correlation was observed with either drug (Fig. 1).

III. Plasma renin activity
Changes in plasma renin activity were not statistically significant (Table I). It was decreased in 10 patients and increased in 4. The others showed no detectable change. On the other hand, the decrease in PRA was directly correlated to the pre-treatment level \((r = 0.703, p < 0.001)\) (Fig. 2). However, the antihypertensive effect showed no relation to the pre-treatment renin level or its changes after the treatment (Fig. 3). The beta-adrenergic blocking agents were effective in 2 out of 4 low renin patients, in 11 of 16 normal renin patients and in 1 of 3 high renin patients. One female patient had the highest plasma renin level and papilledema. Her renal function was maintained fairly well: PSP excretion in 15 min was 20% and BUN remained within normal range. Pindolol (30 mg/day) lowered her plasma renin to a normal level in 2 weeks but had no effect on the blood pressure. She was later treated successfully with a combination of alpha-methyldopa, reserpine, and thiazide.

![Fig. 3 (Left). Changes in the blood pressure and plasma renin activity by the treatment with pindolol (○) or propranolol (●). Circles and arrowheads show values before and after the treatment, respectively.

Fig. 4 (Right). Decreases in the blood pressure and cardiac index by the treatment with pindolol (○) or propranolol (●). Negative value indicates an increase. There is no significant correlation.
Fig. 5 (Left). Decreases in the blood pressure and systemic vascular resistance by the treatment with pindolol (○) or propranolol (●). Negative value indicates an increase. There is no significant correlation.

Fig. 6 (Right). Decreases in the blood pressure and circulating blood volume by the treatment with pindolol (○) or propranolol (●). Negative value indicates an increase. There is no significant correlation.

IV. Hemodynamic components (Table I)
Cardiac index and circulating blood volume showed no significant changes. Though the circulating blood volume tended to be decreased in effective cases on pindolol, the opposite was true on propranolol. Systemic vascular resistance was significantly decreased after the treatment (p<0.02). However, no single component changed with any significant correlation to the antihypertensive effect (Fig. 4, 5, and 6). The fall of the blood pressure was attributed to the decrease in systemic vascular resistance in 7 of 14 effective cases, to the decrease in cardiac output in 4, and to the decrease in the both components in 3. The decrease in systemic vascular resistance showed no relation with the change in PRA.

DISCUSSION
The antihypertensive action of beta-adrenergic blocking agents was confirmed in this study. Both of pindolol and propranolol were effective in lowering the blood pressure in the majority of essential hypertensives. Pindolol showed less effect than propranolol in reducing heart rate. This may be attributed to an intrinsic sympathomimetic action of pindolol.7) Differences between pindolol and propranolol in the other effects were not clear in this study probably, at least in part, because of relatively small number of cases on propranolol. Cardiac depressant and hyporeninemic actions of propranolol seem to be generally accepted. Failure in confirming these effects may be
derived from non-existence of high cardiac output patient in the present study and relatively low PRA in the propranolol group. A hyporeninemic action of pindolol was detected in patients with higher PRA. This action of pindolol has been reported, although it was less than that of propranolol\(^8\),\(^9\).

Tarazi and Dustan\(^2\) stated that propranolol depressed cardiac output at first and a readaptation of vascular resistance to this new hemodynamic condition gradually lowered the blood pressure in several months. In our study, however, cardiac output was not significantly altered and the decrease in systemic vascular resistance, if occurred, was detected much earlier. The fall of blood pressure was recognized as early as in 2 weeks. This indicates that their observation could not be applied generally to the mechanism of the antihypertensive action of beta-adrenergic blocking agents. The response of the blood pressure observed in the present study was rather consistent with that described by Bühler et al.\(^3\). They stated that a decrease in PRA is a major component of the antihypertensive action of propranolol and it was more effective in patients with higher pretreatment level of plasma renin. In our study, however, no correlation was found between the antihypertensive effect of beta-adrenergic blocking agents and either of the initial renin level or the change in PRA after the treatment. Although the higher was the initial PRA the more these drugs reduced it, this effect showed no correlation to the decrement of the blood pressure. The antihypertensive effect was not essentially different between low, normal, and high renin groups. In addition, the decrease in systemic vascular resistance could not be attributed to the change in plasma renin level. These findings are compatible with those obtained by some other investigators.\(^9\),\(^10\) It was reported recently that a new cardioselective beta-1-blocker did not lower PRA even though it was antihypertensive.\(^11\) Changes in circulating blood volume appeared to take no part in the antihypertensive action.

Conclusively no single component observed in the present study could explain the antihypertensive mechanism of beta-adrenergic blocking agents. A possibility that these drugs may exhibit their antihypertensive effect through an action on the central nervous system\(^12\) has not been confirmed yet. Whether the blockade of beta-adrenergic receptor is responsible for the antihypertensive effect or some other action of these drugs is involved in it has not been elucidated either.\(^13\) It is also possible that some metabolites of these drugs may exert the antihypertensive action, since the effects of chronic administration of beta-adrenergic blocking agents seem to be considerably different from those of acute intravenous injection.
REFERENCES

12. Lewis PJ, Reid JL, Myers MG, Dollery CT: Central and peripheral actions of antihypertensive drugs. In: Mechanisms of Hypertension, ed by Sambhi MP, Exerpta Medica, Amsterdam, p 356, 1973