Summary

In essential hypertension, the blood pressure is variable, with large changes occurring in response to variations in physical and emotional stimuli. Patients given placebo tablets often have short-lived decreases in blood pressure. Placebo-controlled studies are essential for the proper evaluation of antihypertensive drugs. In longer term studies in mild hypertension, many patients given placebos have substantial decreases in blood pressure, often to normal levels, a finding that makes a period of observation desirable before commencing active treatment. Patients given placebos also have a high incidence of symptomatic side effects. (Hypertension 5 (supp III): III-3-III-4, 1983)

Key Words • blood pressure • variability • antihypertensive drugs • side effects • placebo

Continuous recording of blood pressure over extended periods of time reveals that, in both normotensive and hypertensive individuals, both systolic and diastolic pressures vary substantially depending on the ambient circumstances. The variability of the blood pressure appeared to be greater in hypertensive patients than in normal subjects.

Alam and Smirk described the measurement of basal blood pressure, which consisted of emotional desensitization to the procedure of blood pressure measurements by repeating the measurements regularly and monotonously under very quiet conditions. The pressures so recorded were defined as the "basal blood pressure." "Casual blood pressures" were the pressures of the same individuals measured in a routine clinical setting, and the difference between the two was called the "supplemental pressure," which is the variable or labile part of the blood pressure dependent on the state of metabolic, physical, and emotional activity at the time of measuring the blood pressure. This variable component of blood pressure is often extremely large, and differences of 60 to 80 mm Hg in systolic, and 20 to 40 mm Hg in diastolic, pressures may be obtained between the casual and basal pressures.

These considerations have a number of implications for the diagnosis of hypertension, and are even more crucial when evaluation of the effects of treatment are being considered.

Use of placebo-controlled studies in the evaluation of antihypertensive drugs is thus mandatory. In short-term studies, a double-blind technique of evaluating antihypertensive drugs can usually demonstrate that active drugs lower blood pressure more than placebos. Since such studies usually involve the sequential administration of active and placebo drugs to the same individuals, a major difficulty with the placebo response, namely, differences between individuals, is avoided.

In large epidemiological studies of the effects of treatment on the incidence of complications of hypertension, separate groups of actively treated and placebo-treated individuals have to be used. In the Australian Therapeutic Trial in Mild Hypertension,3 blood pressures fell from the time of entry into the study in both actively treated and placebo groups, with a somewhat greater drop in the active than placebo group. The initial diastolic blood pressures averaged between 95 and 109 mm Hg. The changes in blood pressure that occurred over 3 years of observation in 1408 subjects who took placebos are shown in table 1.

Table 1. Status of Placebo Group at 3 Years

<table>
<thead>
<tr>
<th>Trial endpoints</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP above 110 mm Hg</td>
<td>172</td>
<td>12.2</td>
</tr>
<tr>
<td>DBP 95-109 mm Hg</td>
<td>450</td>
<td>32.5</td>
</tr>
<tr>
<td>DBP below 95 mm Hg</td>
<td>669</td>
<td>47.7</td>
</tr>
<tr>
<td>Total</td>
<td>1408</td>
<td>100</td>
</tr>
</tbody>
</table>

The data is from the Australian Therapeutic Trial in Mild Hypertension. Numbers and percentages of individuals who had experienced trial endpoints and those with various levels of blood pressure at the end of 3 years observation are indicated.
TABLE 2. Incidence of Reported Side Effects of Drug Treatment in a Group of Patients in the Australian Therapeutic Trial in Mild Hypertension

<table>
<thead>
<tr>
<th>Treatment category</th>
<th>Sleepiness (%)</th>
<th>Depression (%)</th>
<th>Nocturia (%)</th>
<th>Impotence (%)</th>
<th>Failed ejaculation (%)</th>
<th>Sore gritty eyes (%)</th>
<th>Skin rash (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>38 M, 36 F</td>
<td>17 M, 31 F</td>
<td>90 M, 61 F</td>
<td>39 M</td>
<td>17 M</td>
<td>48 M, 26 F</td>
<td>28 F, 17 F</td>
</tr>
<tr>
<td>Placebo</td>
<td>48 M, 12 F</td>
<td>20 M, 11 F</td>
<td>103 M, 49 F</td>
<td>27 M</td>
<td>10 M</td>
<td>45 M, 32 F</td>
<td>33 F, 11 F</td>
</tr>
<tr>
<td>No tablets</td>
<td>10 M, 8 F</td>
<td>8 M, 5 F</td>
<td>33 M, 21 F</td>
<td>15 M</td>
<td>7 M</td>
<td>20 M, 11 F</td>
<td>10 F, 4 F</td>
</tr>
<tr>
<td>Nonstudy</td>
<td>7 M, 13 F</td>
<td>7 M, 10 F</td>
<td>39 M, 46 F</td>
<td>13 M</td>
<td>7 M</td>
<td>19 M, 17 F</td>
<td>6 F, 8 F</td>
</tr>
</tbody>
</table>

Active means patients taking active drugs and placebo means those taking placebos. Those taking no tablets were also being observed in the study and the nonstudy group were randomly selected from the population at large.

Thus, almost half the patients initially defined as having mild hypertension on the basis of six blood pressure measurements, averaged over a period of about 4 weeks, experienced a drop in blood pressure to nonhypertensive levels over a 3-year period. The largest drop occurred within the first few months of observation. Significantly, the incidence of trial endpoints was lowest in those patients whose blood pressures fell below 95 mm Hg in both the active and placebo-treated groups. This finding makes a period of observation desirable before active treatment is commenced.

Finally, a comment needs to be made concerning the incidence of side effects commonly attributed to drugs in a group of patients taking placebos. These data, reported by Bauer and colleagues, were also derived from the Australian Therapeutic Trial (table 2).

The data indicate that there was surprisingly little difference between the incidence of side effects as reported on a questionnaire between patients taking active and placebo tablets. Interestingly, a group of patients not taking tablets, and a group of randomly selected age-matched members of the Australian population, had almost as high an incidence of symptomatic side effects as those taking tablets.

References
Response to placebo treatment in hypertension.
A E Doyle

Hypertension. 1983;5:III3
doi: 10.1161/01.HYP.5.5_Pt_2.III3

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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