Comparison of First-Line Antihypertensive Drugs by a Randomized Cross-Over Method
—A Preliminary Report—

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The present study was undertaken to compare the effects of first-line antihypertensive drugs in Japanese patients. Four antihypertensive drugs were studied: trichlormethiazide (TCT), nifedipine retard (NIF), atenolol (ATN), and enalapril malate (ENP). Thirty-eight patients (16 men and 22 women; age, 53.3±8.8 years, mean±SD) were enrolled in the study. After a control period of 2 to 4 weeks, the four drugs were administered according to a randomized, cross-over design, the duration of each treatment period being 8 to 12 weeks. The initial dose of each drug was increased until blood pressure (BP) fell to less than 150/90 mmHg. The maximum doses of TCT, NIF, ATN, and ENP were 4, 40, 50, and 20 mg/day, respectively. The protocol was completed in 25 of the 38 patients. The BPs (SBP/DBP) at the end of each period were 168±3 (mean±SEM)/105±1 (control), 149±4/98±2 (TCT), 138±3/89±2 (NIF), 151±4/94±2 (ATN), and 152±4/97±2 mmHg (ENP). The BP during NIF treatment was significantly lower than during the other treatments. This finding suggests that the calcium antagonist had a greater hypotensive effect than the other first-line antihypertensive drugs studied. The subjects seem to more closely resemble black rather than white populations with respect to their response to antihypertensive treatment. (Hypertens Res 1995; 18: 303-305)

Key Words: antihypertensive drugs, genetic difference, calcium antagonists

Two principal guidelines for the management of mild hypertension recommend the use of diuretics, β-blockers, calcium antagonists, and angiotensin-converting-enzyme inhibitors (ACEI) as initial drug therapy (1, 2). If the response to the initial therapy is inadequate after a one- to three-month interval, there are three options for subsequent therapy: increase the dose of the first drug if it is below the recommended maximum daily dosage; add an agent from another class; or discontinue the initial drug and substitute a drug from another class. Substitution of the initial drug by a drug of another class seems to be preferable to addition, since single-drug therapy simplifies treatment and avoids useless drug administration (3). This treatment strategy is based on the contention that the mechanisms or causes of hypertension differ from one patient to another, and that the derangement of blood pressure should be corrected by the most appropriate drug. Antihypertensive drugs are usually selected empirically; however, rationales for the selection of antihypertensive drugs have been proposed. Reid (4) has suggested that genetic differences should be considered, because black people seem to be more sensitive to diuretics and calcium antagonists than white. Two recent, prospective studies (5, 6) undertaken to compare antihypertensive drugs have produced contradictory results. The Treatment of Mild Hypertension Study (TOMHS) showed no difference in antihypertensive effects among five first-line drugs: chlorthalidone, acebutolol, doxazosin mesylate, amloidipine malate, and enalapril malate (5). The Veterans Affairs Cooperative Study Group (6), on the other hand, concluded that treatment with a calcium antagonist (diltiazem) produced the highest rate of success. Moreover, “race” and age were shown to have an appreciable influence on the response to single-drug therapy. Calcium antagonists had the greatest antihypertensive effects in blacks, captopril in younger whites, and atenolol in older whites. In Japanese hypertensive patients, however, there have been few comparative studies of multiple antihypertensive drugs. Previous studies (5, 6), in which antihypertensive drugs of only one class were given to individual patients, required a large number of patients. Although the overall number of patients is reduced by within-patient comparison of multiple drugs, only a few studies (7, 8) have used

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such a protocol. Roberts et al. (7) compared the hypotensive effects of captopril and several $\beta$-blockers by giving these drugs to the same patient according to a randomized cross-over design. Here, we report the results of a study in which antihypertensive drugs of four classes were given to the same patients according to the protocol described by Roberts et al. (7).

**Subjects and Methods**

Thirty-eight patients (16 men and 22 women; age, 53.3 ± 8.8 yr, mean ± SD) with mild or moderate essential hypertension were enrolled from among patients who were seen for the first time at the Hypertension Outpatient Clinic of the National Cardiovascular Center Hospital. The patients were in World Health Organization stage I or II and showed no cardiovascular complications due to hypertension other than high voltages in the electrocardiogram. The patients were enrolled if blood pressure (BP) in the diastolic phase was greater than 95 mmHg and less than 114 mmHg after a 4-week wash-out period, during which any previous antihypertensive drugs were discontinued. Before enrollment, informed consent was obtained from all patients. BP was measured, with a mercury sphygmomanometer, three times with the patients in a sitting position, and the mean value was used for later analysis. BP was measured on two different days during the wash-out period, and during which any previous antihypertensive drugs were discontinued. Before enrollment, informed consent was obtained from all patients. BP was measured, with a mercury sphygmomanometer, three times with the patients in a sitting position, and the mean value was used for later analysis. BP was measured on two different days during the wash-out period, and the mean value of these measurements was regarded as the control BP. Blood samples were taken for the measurement of plasma renin activity and plasma aldosterone concentration and for blood chemistry. Laboratory data suggested that liver and kidney functions were normal in all subjects. Secondary hypertension was excluded on the basis of history, physical examinations, and laboratory data. After the control period, trichlormethiazide (TCT), nifedipine retard (NIF), atenolol (ATN), and enalapril malate (ENP) were administered sequentially in different orders of the four drugs. There are 24 orders by which the four drugs can be administered to the same patient. One or two patients were randomly assigned to receive each of these 24 orders. The treatment period for each of the drugs was 8-12 weeks. The BPs of the patients were measured every 4 weeks. The doses of the drugs followed usual clinical recommendations. TCT was begun at 2 mg once daily and increased to 4 mg if BP was not less than 150/90 mmHg after 4 weeks, treatment with the lower dose. NIF was begun at 20 mg/d (10 mg twice daily) and similarly increased to 40 mg/d. ATN was begun at 25 mg/d (once daily) and increased to 50 mg/d. ENP was begun at 5 mg (once daily) and increased to 20 mg/d (10 mg twice daily). The BPs at the end of each treatment period were used for analysis. The BPs were compared among the control period and the four treatment periods.

The results are expressed as mean ± SE. The effects of antihypertensive drugs on BPs were examined with an analysis of variance (ANOVA) for repeated measurements. If a significant ($p < 0.05$) $F$ ratio was obtained, Fisher’s protected least significant difference test was used to locate significant differences.

**Results**

Of the 38 patients enrolled in this study, 13 dropped out: 7 due to transfer to other hospitals or to non-compliance, 3 because of a rise in BP after switching to other drugs from NIF, and 3 because of side effects (sinoatrial block due to ATN in 1, drug eruption due to ENP in 1, and palpitation due to NIF in 1). The responses to all four antihypertensive drugs were thus evaluated in the remaining 25 patients, who complied with the protocol requirements. The dose was increased in 25 patients receiving TCT, 15 receiving NIF, 17 receiving ATN, and 18 receiving ENP. The goal BP, less than 150/90 mmHg, was attained in 6, 11, 4, and 2 patients while receiving TCT, NIF, ATN, and ENP, respectively. The BP in each period is shown in Table 1. The BPs during antihypertensive treatment were significantly lower than that in the control period, with NIF reducing BP to a greater extent than the other antihypertensive drugs.

**Discussion**

As stated above, two principal guidelines for the treatment of mild hypertension recommend four or five agents as first-line antihypertensive therapy, assuming that the hypotensive effects of these drugs are similar (1, 2). The TOMHS (4) confirmed that the effects of five antihypertensive drugs were equivalent, while the Veterans Affairs Cooperative Study Group (5) concluded that treatment with a calcium antagonist (diltiazem) produced the highest success rate. Further, “race” and age had appreciable effects on the response to single-drug therapy for hypertension. Diltiazem had the highest response rate in blacks, captopril in younger whites, and atenolol in older whites. Our data in Japanese

<table>
<thead>
<tr>
<th>SBP (mmHg)</th>
<th>Control</th>
<th>Trichlormethiazide</th>
<th>Nifedipine retard</th>
<th>Atenolol</th>
<th>Enalapril</th>
</tr>
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<tbody>
<tr>
<td>168 ± 3</td>
<td>149 ± 4$^{ab}$</td>
<td>138 ± 3$^a$</td>
<td>151 ± 4$^{ac}$</td>
<td>152 ± 4$^{ac}$</td>
<td></td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>105 ± 1</td>
<td>98 ± 2$^{ac}$</td>
<td>89 ± 2$^a$</td>
<td>94 ± 2$^{ab}$</td>
<td>97 ± 2$^{ac}$</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>126 ± 1</td>
<td>115 ± 2$^{ac}$</td>
<td>105 ± 2$^a$</td>
<td>113 ± 2$^{ac}$</td>
<td>115 ± 2$^{ac}$</td>
</tr>
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Values represent the mean ± SE in 25 patients. SBP = systolic blood pressure, DBP = diastolic blood pressure, MBP = mean blood pressure. a: $p<0.01$ (vs control), b: $p<0.05$, c: $p<0.01$ (vs nifedipine).
patients showed that another calcium antagonist, nifedipine, reduced BP to the greatest extent, as compared with the other antihypertensive drugs tested. Attwood et al. (8) compared the antihypertensive effects of atenolol, lisinopril, and nifedipine in a study employing a randomized crossover design. They found greater falls in blood pressure with lisinopril and atenolol than with nifedipine. Although the “race” of the patients was not mentioned, the geographic area of the study suggests that the majority of the study population was white. A large, controlled, prospective study (the GLANT study) recently performed in Japan (9) compared the effectiveness of treatment in two groups, one receiving various calcium antagonists and the other the ACEI delapril. BP reduction was greater in the group receiving the calcium antagonists than in the group receiving the ACEI. Consistent with the results of our study, the GLANT study suggested that the spectrum of response to antihypertensive drug therapy in the Japanese resembled that in black rather than in white populations.

A possible drawback of our study was the assumption that the control BP was same for all four first-line antihypertensive drugs. It is conceivable that control BP may have been different since BP may decrease without drug therapy. According to the Veterans Affairs Cooperative Groups Study, however, the decrease in BP during a period of about one year of placebo treatment was only 4-5 mmHg, and the value was similar for subgroups divided according to age and “race” (6). Attwood’s study (8) showed no difference in BP during control periods placed prior to each of three successive treatment periods. In the TOMHS (5), in which the patients were treated actively by non-pharmacological methods, the decrease in BP in the placebo group was greater than 4-5 mmHg. Since no active intervention employing non-pharmacological treatment was undertaken in our study, the variation in the provisional control BP is estimated to be within 4-5 mmHg, which is rather small, as compared to the reduction in BP produced by antihypertensive drugs. Moreover, the protocol was designed to compare BP levels among patients receiving antihypertensive drugs and not to compare the degree of BP reduction from the control period.

In summary, the patients in this study seem to more closely resemble black rather than white populations with respect to their response to antihypertensive drugs. In terms of lowering BP, a calcium antagonist may be most effective in Japanese patients. However, additional strictly controlled studies are required for precise comparison of the antihypertensive effects of different drugs.

References