Efficacy of Different Drug Classes Used to Initiate Antihypertensive Treatment in Black Subjects

Results of a Randomized Trial in Johannesburg, South Africa

Pinhas Sareli, MD; Ivelin V. Radevski, MD; Zdravka P. Valtchanova, MD; Elena Libhaber, MSc; Geoffrey P. Candy, MSc; Elly Den Hond, DSc; Carlos Libhaber, MD; Daniel Skudicky, MD; Ji G. Wang, MD; Jan A. Staessen, MD

Background: Thiazides are recommended to initiate antihypertensive drug treatment in black subjects.

Objective: To test the efficacy of this recommendation in a South African black cohort.

Methods: Men and women (N=409), aged 18 to 70 years, with a mean ambulatory daytime diastolic blood pressure between 90 and 114 mm Hg, were randomized to 13 months of open-label treatment starting with the nifedipine gastrointestinal therapeutic system (30 mg/d, n=233), sustained-release verapamil hydrochloride (240 mg/d, n=58), hydrochlorothiazide (12.5 mg/d, n=58), or enalapril maleate (10 mg/d, n=60). If the target of reducing daytime diastolic blood pressure below 90 mm Hg was not attained, the first-line drugs were titrated up and after 2 months other medications were added to the regimen.

Results: While receiving monotherapy (2 months, n=366), the patients' systolic and diastolic decreases in daytime blood pressure averaged 22/14 mm Hg for nifedipine, 17/11 mm Hg for verapamil, 12/8 mm Hg for hydrochlorothiazide, and 5/3 mm Hg for enalapril. At 2 months the blood pressure of more patients treated with nifedipine was controlled: 133 (63.3%, \(P \leq 0.03\)) vs 20 (39.9%) receiving verapamil, 21 (40.4%) receiving hydrochlorothiazide, and 11 (20.8%) receiving enalapril. At 13 months (n=257), more patients \(P<0.001\) continued receiving monotherapy with nifedipine (94/154 [61.0%]) or verapamil (22/35 [62.9%]) than hydrochlorothiazide (10/39 [25.6%]) or enalapril (1/29 [3.4%]). A sustained decrease of left ventricular mass \(P<0.001\) with no between-group differences was achieved at 4 and 13 months.

Conclusions: In contrast to current recommendations, calcium channel blockers are more effective than thiazides as initial treatment in black subjects with hypertension. If treatment is started with thiazides or converting-enzyme inhibitors, combination therapy is more likely to be required to control blood pressure and reduce left ventricular mass.

Arch Intern Med. 2001;161:965-971
PATIENTS AND METHODS

This trial was a randomized, open-label study conducted at the Chris Hani-Baragwanath Hospital, Johannesburg, South Africa from September 1, 1994, through November 30, 1997. The protocol was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand. Black men and women could be enrolled, if they were between the ages of 18 and 70 years and were free of clinically significant cardiovascular or noncardiovascular disorders. Women of reproductive age had to use adequate contraception. All patients gave informed written consent.

To screen patients for hypertension, we measured their sitting diastolic BP 10 times consecutively at 3-minute intervals, using calibrated oscillometric monitors (Dinamap 1846 SX; Critikon Inc, Tampa, Fla). If the mean diastolic BP was 90 mm Hg or higher, the patients underwent 24-hour ambulatory BP monitoring. Oscillometric devices (SpaceLabs 90207; SpaceLabs Inc, Redmond, Wash) were programmed to obtain readings every 15 minutes from 6 AM to 6 PM. Patients whose mean daytime diastolic BP was 90 mm Hg or higher then proceeded to a 2-week placebo run-in period, after which the ambulatory recording was repeated. If on the second set of measurements the mean daytime diastolic BP ranged from 90 to 114 mm Hg and if the count of the returned placebo tablets was within 80% to 120% of the expected number, the patients qualified for enrollment in the study.

Eligible patients were randomized to the nifedipine gastrointestinal therapeutic system (GITS), 30 mg/d, or 1 of 3 available reference treatments starting with verapamil hydrochloride sustained release (SR), 240 mg/d; hydrochlorothiazide, 12.5 mg/d; or enalapril maleate, 10 mg/d; as indicated in the current guidelines. Patients were followed up at monthly intervals for 13 months with the goal being to lower the daytime diastolic BP below 90 mm Hg. The ambulatory BP recordings were systematically repeated at monthly intervals for 4 months and at the final 13-month visit. From the 4-month visit onward, only the patients whose BP remained uncontrolled at a previous visit underwent ambulatory BP monitoring. At baseline and at 4

RESULTS

As shown in Figure 1, of 591 patients enrolled in the placebo run-in phase, 409 patients were randomized. At baseline no statistically significant differences were noted between the patients in the 4 treatment groups (Table 1). The analysis included 366 patients at 2 months, 344 at 4 months, and 257 at 13 months (Table 2). The women in particular had high body mass indices (BMIs) (32.4 [SE, 0.4] kg/m²) compared with the men (26.9 [SE, 0.5] kg/m², P<.001).

At 2 months, monotherapy with nifedipine GITS had lowered the daytime BP more than monotherapy with hydrochlorothiazide or enalapril (Figure 2). The mean systolic and diastolic decreases in the daytime BP at 2 months for the various treatment groups were as follows: 22/14 mm Hg for nifedipine GITS, 17/11 mm Hg for verapamil SR, 12/8 mm Hg for hydrochlorothiazide, and 5/3 mm Hg for enalapril. At 2 months (Figure 3) the BP of significantly more patients treated with nifedipine GITS was controlled: 133 (63.3%, P=.03) vs 20 (39.2%) receiving verapamil SR, vs 21 (40.4%) receiving hydrochlorothiazide, and vs 11 (20.8%) receiving enalapril; BP control while receiving monotherapy was not different among patients randomized to verapamil SR, hydrochlorothiazide, or enalapril (Figure 3). At 2 months the decrease in the mean (SE) daytime heart rate in the verapamil SR–treated group (~5.6 [1.3]/min) was significantly different (P=.02) from the heart rate changes for those receiving nifedipine GITS (~2.7 [0.6]/min), hydrochlorothiazide (~0.5 [1.0]/min), or enalapril (~0.8 [1.2]/min). The heart rate changes among the latter 3 groups were not significantly different. There was no difference in control rates while receiving monotherapy between patients with a higher BMI (>25 kg/m²) and those with a BMI of 25 kg/m² or less throughout the trial period.
At 4 months fewer patients (P < .004) in the nifedipine GITS–treated and verapamil SR–treated groups had required the addition of second-line medication than did those in the hydrochlorothiazide-treated and enalapril-treated groups (Table 2). Similarly, at 13 months (Table 2 and Figure 4), more patients (P < .001) continued to receive monotherapy with nifedipine GITS (94/154 [61.0%]) or verapamil SR (22/35 [62.9%]) than with hydrochlorothiazide.
The major adverse events were myocardial infarction (1 patient) and unstable angina pectoris (1 patient) in the enalapril-treated group; and angioneurotic edema (1 patient) and second-degree atrioventricular block complicated with left ventricular failure (1 patient) in the verapamil SR-treated group; fatal bowel obstruction (1 patient) and grand mal epilepsy (1 patient) in the hydrochlorothiazide-treated group; and angioneurotic edema (5 patients) in the enalapril-treated group. No patient experienced gastrointestinal bleeding.

Table 2. Study Drugs Administered During the Trial

<table>
<thead>
<tr>
<th>Type of Treatment Received</th>
<th>Nifedipine GITS</th>
<th>Verapamil Hydrochloride</th>
<th>Hydrochlorothiazide</th>
<th>Enalapril Maleate</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line drug</td>
<td>201 (100)</td>
<td>51 (100)</td>
<td>480</td>
<td>25</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>143 (71.1)</td>
<td>38 (77.6)</td>
<td>21 (43.7)</td>
<td>11 (23.9)</td>
</tr>
<tr>
<td>With second-line drug</td>
<td>58 (28.9)</td>
<td>11 (22.4)</td>
<td>27 (56.3)</td>
<td>35 (76.1)</td>
</tr>
<tr>
<td>Verapamil hydrochloride</td>
<td>17 (8.5)</td>
<td>120</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Enalapril maleate</td>
<td>18 (9.0)</td>
<td>10</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Reserpine</td>
<td>...</td>
<td>...</td>
<td>27 (56.3)</td>
<td>0.125</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>23 (11.4)</td>
<td>25</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>First-line drug</td>
<td>154 (100)</td>
<td>60</td>
<td>35 (100)</td>
<td>29 (100)</td>
</tr>
<tr>
<td>Monotherapy‡</td>
<td>94 (61.0)</td>
<td>22 (62.9)</td>
<td>10 (25.6)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Second-line drug‡</td>
<td>49 (31.8)</td>
<td>7 (20.0)</td>
<td>18 (46.2)</td>
<td>13 (44.8)</td>
</tr>
<tr>
<td>≥2 Additional drugs‡</td>
<td>60 (39.0)</td>
<td>13 (37.1)</td>
<td>29 (74.4)</td>
<td>28 (96.6)</td>
</tr>
</tbody>
</table>

* Dose is given as the median daily dose in milligrams. GITS indicates gastrointestinal therapeutic system; SR, sustained release; and ellipses, not applicable.
† At 2 months all patients were still receiving randomized monotherapy.
‡ The numbers do not sum because patients could take multiple drugs.

With second-line drug, no patients in either of the other 2 groups.

The major adverse events were myocardial infarction (1 patient) and unstable angina pectoris (1 patient) in the enalapril-treated group; and angioneurotic edema (1 patient) and second-degree atrioventricular block complicated with left ventricular failure (1 patient) in the verapamil SR–treated group; fatal bowel obstruction (1 patient) and grand mal epilepsy (1 patient) in the hydrochlorothiazide-treated group; and angioneurotic edema (5 patients) in the enalapril-treated group. No patient experienced gastrointestinal bleeding.

COMMENT

At 2 months the rate of BP control was higher for the patients receiving nifedipine GITS treatment than for those patients receiving verapamil SR, hydrochlorothiazide, or enalapril. Monotherapy with nifedipine GITS reduced BP significantly more than hydrochlorothiazide and enalapril. At 13 months more patients continued receiving monotherapy with nifedipine GITS or verapamil SR than hydrochlorothiazide or enalapril.

This study must be interpreted within the context of its limitations. Of 409 randomized patients, the numbers lost to follow-up were 32 (7.8%) at 2 months, 45 (11.0%) at 4 months, and 115 (28.1%) at 13 months. The patients enrolled in the trial were recruited from the Soweto district, an urban black community burdened by unemployment (52.9%), shortage of housing, deprivation, social divide, and broken households. These conditions explain why people frequently relocated to find new jobs and why many of our patients withdrew their consent or dropped out of the study. However, the black inhabitants of Soweto are representative of many modern African cities, characterized by a high prevalence and incidence of hypertension.10,11 The patients characteristically also had a high BMI that may be explained by inactivity or by their high-energy, low-protein maize-based diet. Our study had an open-label design, but we used 24-hour ambulatory BP monitoring to determine objectively the eligibility of the patients and to evaluate the effects of treatment. Indeed, ambulatory BP measurements are characterized by high reproducibility, are not subject to digit preference and observer bias, and avoid the transient rise of a patient’s BP in response to the clinic surroundings or the presence of the observer, the so-called white-coat effect.4

To the best of our knowledge, no other study used ambulatory BP monitoring on a large scale in black African patients with hypertension. In a previous single-blind randomized trial (n = 41), we demonstrated that over a 12-week period treatment twice with nifedipine (20-40 mg twice daily) reduced the 24-hour systolic and diastolic BP by 28/17 mm Hg, whereas treatment with captopril (50 mg twice daily) did not change BP (+2/+1 mm Hg).12 Materson and coworkers13,14 randomized I292...
American men with a clinic diastolic BP of 95 to 109 mm Hg to placebo or 1 of the following 6 drugs: hydrochlorothiazide (12.5-50 mg/d), diltiazem SR (120-360 mg/d), atenolol (25-100 mg/d), clonidine (0.2-0.6 mg/d), captopril (25-100 mg/d), or prazosin (4-20 mg/d). This trial included 291 black patients,13,14 aged 21 to 60 years, in whom the nondihydropyridine calcium channel blocker diltiazem after 1 year achieved the best control rate (56.8%),13 defined as a clinic diastolic BP of less than 90 mm Hg. In agreement with our 2 months’ observations, hydrochlorothiazide treatment titrated up from 12.5 to 50 mg/d controlled BP in 41.7% of the black patients.14

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**Figure 2.** Mean daytime (6 AM-6 PM) systolic (A) and diastolic (B) blood pressure at randomization and during follow-up. At 2 months all patients were still receiving monotherapy with the randomized first-line medications; thereafter 1 or more additional drugs could be added to the regimen (see Table 2). n refers to the total number of patients in follow-up. GITS indicates gastrointestinal therapeutic system; SR, sustained release.

**Figure 3.** Proportion of patients whose blood pressure was controlled (mean daytime diastolic blood pressure [DBP] <90 mm Hg) at various stages of follow-up. For further explanation, see Figure 2. n refers to the total number of patients in follow-up. GITS indicates gastrointestinal therapeutic system; SR, sustained release.

**Figure 4.** Proportion of patients who continued receiving monotherapy with randomized first-line medication. The curves represent Kaplan-Meier estimates9 in which the denominator is the number of patients available for analysis at each time point. GITS indicates gastrointestinal therapeutic system; SR, sustained release.
In keeping with other studies, most of our black patients with mild to moderate hypertension required multiple drug treatment to achieve adequate control, especially if treatment was initiated with a thiazide or an ACE inhibitor. Low rates of BP control have been previously documented in black patients with hypertension who were receiving treatment with captopril, enalapril, or hydrochlorothiazide. On balance, the evidence available suggests that ACE inhibitors should not be used as monotherapy in black patients with hypertension, but only in combination with other medications. At 13 months, the addition of hydrochlorothiazide and/or other drugs (nifedipine GITS in 15 of 29 patients) achieved BP control in 79.3% of patients randomized to enalapril treatment. Furthermore, at the end of the study, the addition of reserpine and/or enalapril to hydrochlorothiazide treatment resulted in a control of 66.7%.

Two research groups have suggested that to reduce left ventricular hypertrophy ACE inhibitors would be most efficient. However, a meta-analyst considered only prospective, randomized, and properly controlled comparative studies. This analysis revealed that thiazides, β-blockers, calcium channel blockers, and ACE inhibitors reduced left ventricular mass to the same degree as the other classes statistically combined, and that ACE inhibitors were not superior to calcium channel blockers. Our study showed a significant decrease in left ventricular mass index at 4 months paralleling the decline in BP, with no differences between the treatment groups. This observation suggests that BP control rather than drug class is the predominant factor determining left ventricular mass regression.

CONCLUSIONS

In contrast with the modified South African guidelines, long-acting calcium channel blockers are more effective than thiazides as initial treatment in African blacks with hypertension. Outcome trials in hypertension were largely conducted in white and Asian subjects. Because such information is not yet available for African blacks, the present findings should be subject to further investigation in prospective morbidity and mortality trials in African blacks.

Accepted for publication November 7, 2000.

The Baragwanath Hypertension Ambulatory Monitoring Study was supported by Bayer (Pty) Ltd, Johannesburg.

We gratefully acknowledge the expert assistance of Elizabeth Tshele, RN, and Margaret Hlatshwayo, RN. William H. Birkenhager, MD, Erasmus University, Rotterdam, the Netherlands, provided helpful comments on the manuscript.

Corresponding author: Pinhas Sareli, MD, Department of Cardiology, Chris Hani-Baragwanath Hospital, University of the Witwatersrand, PO Bertsham, Johannesburg 2013, South Africa (e-mail: psareli@iafrica.com).

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