Intracellular Sodium and the Response to Nitrendipine or Atenolol in African Blacks

JEAN-RENE M'BUYAMBA-KABANGU, BOMPELA LEPIRA, PAUL LUNEN, KALANTANDA TSHIANI, ROBERT FAGARD AND ANTOON AMERY

SUMMARY The relationship between the hypotensive effect of nitrendipine (N), 20 mg/day ($n = 17$), or atenolol (A), 100 mg/day ($n = 17$), and the erythrocyte sodium ([Na$]_i$) and potassium ([K$]_i$) concentrations was investigated in hypertensive African blacks during a randomized double-blind study. After 6 weeks, both treatments significantly reduced supine and standing blood pressures; however, the magnitude of the decrease in supine systolic ($-22.0 \pm 2.0$ vs $-12.1 \pm 3.4$ mm Hg) and diastolic ($-14.1 \pm 1.3$ vs $-7.6 \pm 2.1$ mm Hg) pressures and in standing diastolic pressure ($-16.0 \pm 1.7$ vs $-9.2 \pm 2.0$ mm Hg) was more pronounced ($p<0.05$) in the N-treated than in the A-treated group. Pulse rate, plasma aldosterone, and plasma renin activity were lower ($p<0.05$) in the A-treated patients. Neither treatment had significant influence on [Na$]_i$, [K$]_i$, or ouabain-sensitive sodium efflux. The N-induced changes in supine systolic and diastolic pressure correlated ($p<0.05$) with age ($r = -0.65$ and $r = -0.58$, respectively) and pretreatment plasma renin activity ($r = 0.71$). Multiple regression analysis demonstrated a negative association between prettrial [Na$]_i$ and the change in systolic pressure during N treatment that was independent of age, pretreatment blood pressure, and change in pulse rate. Age and the change in supine pulse rate were also independently correlated with the change in diastolic pressure during N treatment. The results show a greater antihypertensive efficacy of N than A in the patients entered in this study and suggest that a higher intracellular sodium concentration could predict a better hypotensive response to N.

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KEY WORDS • nitrendipine • atenolol • erythrocyte sodium • hypertension • black population

N black as well as in white populations, various abnormalities of circulating blood cell sodium and potassium concentrations and transport systems have been described in patients with essential hypertension. A dissociation between these abnormalities and high blood pressure has been shown, however, by demonstrating similar anomalies in normotensive subjects. Heagerty et al. have suggested that such abnormalities in hypertensive patients should be considered simply as markers of altered membrane handling of calcium. Raised levels of intracellular free calcium have been found in various cells of hypertensive patients, and cytosolic free calcium appears to be the final determinant of arterial tone, and hence, of blood pressure level in the smooth muscle.

Antihypertensive treatment with calcium entry blockers or /-adrenergic receptor blockers was reported to decrease intracellular calcium in red blood cells or platelets from white hypertensive patients while lowering arterial blood pressure. However, the effect of these drugs on cellular sodium concentration and transport in hypertensive white patients has been the subject of controversy. In view of the difference in cellular sodium and potassium concentration and transport between blacks and whites, racial factors could modulate the effect of antihypertensive treatment on cellular sodium metabolism. Therefore, the present work aimed to evaluate the clinical effects of atenolol (A) and nitrendipine (N) in hypertensive black subjects, to examine the action of the two drugs on cellular sodium and potassium concentrations and fluxes using the red blood cell model, and to investi-
gate the relationship between the change in pressure with the two drugs and these red blood cell cationic variables.

**Subjects and Methods**

Thirty-four Zairian subjects with mild to moderate hypertension (18 men and 16 women) gave informed consent and participated in the study. All had probable essential hypertension on the basis of history, physical examination, serum electrolytes, and urinalysis, but further specific investigations for secondary forms of hypertension were not performed. Sixteen subjects had received no previous antihypertensive therapy, whereas 18 had been treated for an average of 3.2 years before entering the run-in period in this study; none had been stabilized with previous therapy.

In all subjects serum creatinine was below 2 mg/dl and serum bilirubin was 1.5 mg/dl or less. No subject had cardiac failure, history or sequelae of cerebrovascular accident, or other major organ damage as a result of hypertension. Other exclusion criteria included insulin-requiring diabetes mellitus, chronic obstructive pulmonary disease, second-degree and third-degree atrioventricular block, and pregnancy.

**Study Design**

A double-blind parallel design with a double-dummy technique was used. The subjects were randomized to receive for 6 weeks either 100 mg of A or 20 mg of N once a day and were seen at the outpatient clinics after 2 and 6 weeks of therapy. This active treatment period was preceded by a 6-week run-in period during which the subjects attended outpatient clinics at 3-week intervals and received in a single-blind fashion two placebo tablets each morning. At each examination on placebo or on active medication, three blood pressure readings were obtained with a standard mercury sphygmomanometer after 3 minutes of relaxation in supine position and after 2 minutes of standing upright. Korotkoff’s sounds I and V were used to characterize systolic and diastolic pressure, respectively. Pulse rate was measured under the same conditions. Body weight was measured in loose clothing without shoes, whereas height was obtained once, during the run in period. All measurements were performed 3 to 5 hours after the morning dose. Compliance with therapy was assessed by tablet count.

**Additional Procedures**

At randomization a chest roentgenogram and a 12-lead electrocardiogram (ECG) were obtained. A venous blood sample was withdrawn with the subjects in the supine position for blood cell count and determination of hemoglobin, hematocrit, serum electrolytes, creatinine, transaminases, uric acid, plasma glucose, plasma renin activity (PRA), aldosterone concentration, erythrocyte concentration of sodium ([Na⁺]) and potassium ([K⁺]), and ouabain-sensitive efflux of sodium. A 24-hour urine collection was obtained in 17 patients, 9 in the A and 8 in the N group and was analyzed for sodium excretion.

At the end of the study a second blood sample for the same hematological and biochemical measurements could be obtained only in 18 patients (8 on A and 10 on N) who first entered the study. These patients were not different from the total group.

**Statistical Analysis**

Statistic methods included paired and unpaired Student’s t tests, chi-square test, and single and multiple regression analyses. Values are expressed as the mean ± SEM. Since the distribution of PRA and plasma aldosterone concentration was positively skewed, logarithmic transformation was applied; therefore, geometric means and range are reported for these variables.

A satisfactory response to therapy was defined as a fall in diastolic pressure of at least 5 mm Hg; the response was considered unsatisfactory when the decrease was less than 5 mm Hg. Left ventricular hypertrophy was defined as a Romhilt-Estes score of 5 points or more on ECG.

**Results**

**Subject Characteristics at Randomization**

At randomization no significant differences were observed between the two treatment groups (Table 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atenolol group (n=17)</th>
<th>Nitrendipine group (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>9:8</td>
<td>9:8</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>43±2</td>
<td>45±3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164±3</td>
<td>162±2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74±4</td>
<td>68±4</td>
</tr>
<tr>
<td>Supine blood pressure (mm Hg)</td>
<td>162±2/102±1</td>
<td>160±2/101±1</td>
</tr>
<tr>
<td>Standing blood pressure (mm Hg)</td>
<td>157±2/102±4</td>
<td>156±3/101±5</td>
</tr>
<tr>
<td>Supine pulse rate (beats/min)</td>
<td>73±3</td>
<td>77±2</td>
</tr>
<tr>
<td>Standing pulse rate (beats/min)</td>
<td>81±3</td>
<td>83±2</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.03±0.27</td>
<td>1.26±0.77</td>
</tr>
<tr>
<td>PRA (ng Ang I/ml/hr)</td>
<td>0.54 (0.14–1.49)</td>
<td>0.54 (0.01–2.01)</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/dl)</td>
<td>20.04 (11.22–40.74)</td>
<td>15.52 (8.89–25.12)</td>
</tr>
<tr>
<td>Urinary Na (mmol/24 hr)</td>
<td>84±9</td>
<td>92±10</td>
</tr>
<tr>
<td>Cardiothoracic ratio</td>
<td>0.48±0.04</td>
<td>0.46±0.04</td>
</tr>
<tr>
<td>Left ventricular hypertrophy on ECG (no. of subjects)</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

**Statistical tests**

Most values are arithmetic means ± SEM. Values for PRA and plasma aldosterone are geometric means with ranges in parentheses. Ang I = angiotensin I.

* Determined in nine subjects from atenolol group and in eight from nitrendipine group.
Clinical Effects of Both Drugs

All randomized subjects completed the double-blind study. After 6 weeks of active therapy, supine and standing systolic and diastolic pressures were significantly reduced in the A-treated ($p < 0.01$) and in the N-treated subjects ($p < 0.001$). The hypotensive effect was more pronounced in the N-treated than in the A-treated group (Figure 1), and the difference was significant ($p < 0.05$) for supine systolic ($-22.2 \pm 2.0$ vs $-12.1 \pm 3.4$ mm Hg) and diastolic ($-14.1 \pm 1.3$ vs $-7.6 \pm 2.1$ mm Hg) pressures and for standing diastolic pressure ($-16.0 \pm 1.7$ vs $-9.2 \pm 2.0$ mm Hg). The number of subjects with a satisfactory response to therapy was greater in the N-treated than in the A-treated group (16 vs 9 patients; $\chi^2 = 5.44; p = 0.02$).

Treatment with A induced a significant fall in supine ($-5.6 \pm 1.7$ beats/min; $p < 0.01$) and standing ($-5.5 \pm 2.3$ beats/min; $p < 0.05$) pulse rates, whereas a slight and nonsignificant acceleration of $2.0 \pm 1.9$ beats/min in supine and $3.1 \pm 2.2$ beats/min in standing pulse rate occurred with N treatment (see Figure 1). Body weight was unchanged in the two groups at the end of the active treatment.

Effect of Therapy on Red Blood Cell Electrolytes and Other Laboratory Measurements

In eight A-treated and 10 N-treated subjects biochemical measurements were obtained at baseline and at the end of the active treatment (Table 2); the two subgroups were comparable for blood pressure and demographic data at baseline. After a 6-week administration of A, PRA tended to decrease ($p = 0.09$) whereas an opposite trend was seen in the N-treated subgroup; the difference between the two treatments was significant ($p < 0.01$). Plasma aldosterone concentration decreased ($p < 0.05$) in the A-treated group, whereas no change ($p > 0.10$) occurred in the N-treated subgroup. Treatment with A or N did not affect erythrocyte [Na], [K], the ouabain-sensitive efflux of sodium (see Table 2), or the other laboratory measurements (data not shown).

Regression Analysis

With the use of single regression analysis, the N-induced but not the A-induced changes in supine

![Figure 1. Change in blood pressure and pulse rate after a 6-week administration of atenolol (O) or nitrendipine (a). Single (p < 0.05) and double (p < 0.01) asterisks indicate the significance of within-group comparisons; the indicated p value compares the two treatment groups. Values are means ± SE.](http://hyper.ahajournals.org/abstracts/11/1/102)

<table>
<thead>
<tr>
<th>Variable</th>
<th>At randomization</th>
<th>After 6-week treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA (ng Ang I/ml/hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.54 (0.14–1.48)</td>
<td>0.49 (0.16–1.31)</td>
</tr>
<tr>
<td>N</td>
<td>0.57 (0.01–2.01)</td>
<td>1.48* (0.54–7.57)</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>20.94 (11.22–40.74)</td>
<td>16.67† (8.99–22.91)</td>
</tr>
<tr>
<td>N</td>
<td>15.10 (8.89–25.12)</td>
<td>17.22* (10.96–33.88)</td>
</tr>
<tr>
<td>Erythrocyte Na concentration (mmol/L cells)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>12.70 ± 1.44</td>
<td>12.30 ± 1.50</td>
</tr>
<tr>
<td>N</td>
<td>11.30 ± 0.83</td>
<td>11.16 ± 0.61</td>
</tr>
<tr>
<td>Erythrocyte K concentration (mmol/L cells)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>90.82 ± 3.69</td>
<td>86.39 ± 1.57</td>
</tr>
<tr>
<td>N</td>
<td>85.65 ± 2.0</td>
<td>85.33 ± 1.5</td>
</tr>
<tr>
<td>Ouabain-sensitive Na efflux (μmol/L cells/hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>1.35 ± 0.13</td>
<td>1.40 ± 0.08</td>
</tr>
<tr>
<td>N</td>
<td>1.39 ± 0.17</td>
<td>1.46 ± 0.22</td>
</tr>
</tbody>
</table>

Values for PRA and plasma aldosterone are geometric means with ranges in parentheses. Other values are arithmetic means ± SEM. Ang I = angiotensin I; A = atenolol; N = nitrendipine.

*p < 0.01, between-group comparison after 6 weeks of active medication.

†p < 0.05, compared with values at randomization.
systolic (Figure 2) and diastolic ($r = -0.58$, $p < 0.05$) blood pressure were correlated negatively with age and positively with the pretreatment PRA ($r = 0.71$, $p < 0.05$ for systolic and diastolic pressures). No significant relationships were observed between the N-induced or the A-induced changes in blood pressure and erythrocyte $[\text{Na}]$, or $[\text{K}]$.

Multiple regression analysis (Table 3) demonstrated a significant inverse relationship between pretrial $[\text{Na}]$, and the change in supine systolic pressure that was independent of age, initial supine systolic blood pressure, and change in pulse rate during N therapy. Also in the N group, age and the change in supine pulse rate yielded significant partial regression coefficients with the change in supine diastolic pressure after adjusting for initial diastolic blood pressure. No combination of two or more independent variables yielded significant partial regression coefficients with the A-induced changes in systolic or diastolic pressure.

**Discussion**

The purpose of the present study was to assess and compare the hypotensive action of monotherapy with A or N in hypertensive African blacks and to investigate its relationship to PRA and $[\text{Na}]$, in this population. The importance of age and other variables as determinants of the antihypertensive effect of both drugs was also examined.

Treatment with N and A induced a significant fall in blood pressure after a 6-week administration; however, the magnitude of blood pressure reduction was more pronounced with the calcium entry blocker than with the $\beta$-adrenergic receptor blocker. About half of the subjects did not have a satisfactory decrease in pressure after A treatment, whereas all but one subject did after N therapy. Since the effect of N peaks about 4 hours after administration, measuring blood pressure 3 to 5 hours after the medication dose could have favored determination of the efficacy of N and exaggerated differences between N and A. Nevertheless, the results confirm our previous observations of a relatively higher potency of N as compared with acebutolol both after a short-term and after a prolonged 40-week follow-up of black natives of Zaire with mild to moderate hypertension. It is thus likely that the reported difference was unrelated to the use of a specific $\beta$-adrenergic receptor blocker. Likewise the less satisfactory response to A agrees with the well-documented poor efficacy of various $\beta$-adrenergic receptor blocking agents in hypertensive blacks when used as monotherapy. In contrast to the current findings, one study has recently reported similar blood pressure reduction after acute oral administration of A (100 mg) and slow-release nifedipine in South African blacks with malignant hypertension and high PRA that could have modulated the antihypertensive response to the administered drugs. It has been shown that $\beta$-adrenergic receptor blockers are more efficient the higher the renin, whereas the opposite is true for calcium entry blockers. The correlation between the change in blood pressure after N treatment and the initial PRA confirms these previous observations.

In multiple regression analysis the change in pressure after N was independently and negatively related to age and initial erythrocyte [Na], and positively cor-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nitrendipine</th>
<th>Atenolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>129.04</td>
<td>71.6</td>
</tr>
<tr>
<td>$r$</td>
<td>0.69%*</td>
<td>0.69%†</td>
</tr>
</tbody>
</table>

In addition to the variables listed in the table, initial PRA, initial erythrocyte K concentration, and the change in body weight were also included as independent variables in the multiple regression analysis. A dash indicates that the variable was not entered in the analysis. $\Delta\text{SBP}$ and $\Delta\text{DBP} =$ change in supine systolic and diastolic blood pressure, respectively. NS = not significant. Symbols indicate the significance of the partial regression coefficients ($^* p < 0.05$, $^† p < 0.001$, $^‡ p < 0.01$).
related to changes in pulse rate, suggesting a greater fall of pressure in older subjects and those with higher [Na], but only a small blood pressure reduction in the subjects reacting to N with marked tachycardia. Several studies, with the exception of one, have also suggested calcium entry blockers to be more effective in the hypertensive patients. The lack of correlation between age and the A-induced changes in blood pressure could be due to the narrower age range of the subjects randomized to this drug in the present study (see Figure 2).

It appears of particular interest that the relationship of the hypotensive response to N treatment with the initial [Na], has been independent of other factors since possible interrelationships between [Na], PRA, age, and pretreatment blood pressure could have been involved. This relationship can be understood on the assumption that high [Na], in hypertensive patients may be linked to increased cellular free calcium.

Nonetheless, in the present study neither A nor N treatment altered [Na], or the ouabain-sensitive sodium efflux, an estimate of the Na+ -K+ pump activity; other pathways for sodium transport were not investigated. Likewise, Ambrosioni et al. found no change in the lymphocyte sodium of hypertensive patients treated with β-adrenergic receptor blockers. However, conflicting results have been reported for subjects taking calcium entry blockers. In normotensive male volunteers given felodipine, the red blood cell sodium concentration and transport remained unchanged. Using oral nifedipine in hypertensive patients, Heagerty et al. observed a significant fall in blood pressure with unchanged leukocyte sodium concentration. By contrast, a significant decrease in [Na], was seen in the leukocyte after verapamil hydrochloride and, more recently, in the erythrocyte after diltiazem. These conflicting results suggest a differential cellular effect of dihydropyridine derivatives as compared with other calcium entry blockers. A decrease in pulse rate after A administration and no significant change after short-term and long-term treatment with dipyridamole-derivative calcium entry blockers are well-documented observations. The absence of acceleration in pulse rate by a drug with arteriolar vasodilator properties is suggestive of a resetting of baroreceptors. In such a context, the positive and independent correlation between the change in pressure after N treatment and change in pulse rate indicates that the reflex sympathetic activation in a particular patient codetermines the degree of antihypertensive response. The reflex sympathetic stimulation was also reflected by the observed trend toward increment of PRA after N; this did not, however, reach a statistical significance.

We conclude that calcium entry blockade with N was more efficient in reducing blood pressure than β-adrenergic receptor blockade with A in the hypertensive blacks entered in this trial. The effectiveness of calcium entry blockade was more pronounced in older subjects and in those subjects with higher pretreatment level of blood pressure or [Na]; the subjects in whom sympathetic reactivity was less blunted had the lowest response.

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