Calcium Channel Blockade with Nitrendipine
Effects on Sodium Homeostasis, the Renin-Angiotensin System, and the Sympathetic Nervous System in Humans

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SUMMARY To test the hypothesis that the antihypertensive effect of the calcium channel blocking drug nitrendipine is in part related to natriuresis, we gave 16 subjects (8 normal, 8 hypertensive) placebo for 8 days followed by nitrendipine titrated to 20 mg twice daily for 8 days. The same diet was prepared for each meal for the entire study. Sodium intake was fixed for each subject and averaged 150 mEq/day. All urine was collected every day. Blood was drawn at the end of the placebo and nitrendipine periods for renin, aldosterone, and norepinephrine values. Nitrendipine caused a significant increase \( (p < 0.05) \) in cumulative sodium excretion of 161 mEq over 7 days in the normal subjects and 103 mEq in hypertensive subjects. Potassium excretion was unaffected. In both hypertensive and normal subjects, plasma renin and plasma norepinephrine activity increased significantly \( (p < 0.05) \), while plasma aldosterone levels did not change. Upright systolic blood pressure decreased significantly \( (p < 0.05) \) in both groups, whereas upright diastolic blood pressure decreased only in hypertensive subjects. We conclude that blood pressure lowering effects of this drug may be in part related to natriuresis and that calcium channel blockade may dissociate plasma renin activity from that of aldosterone. (Hypertension 7: 438-442, 1985)

**KEY WORDS** • calcium • calcium channel blockade • nitrendipine • sodium • natriuresis

INTRACELLULAR calcium is pivotal to the development of smooth muscle tone. Not only is the cation the final determinant for the development of tension in vascular smooth muscle, but it also is a regulator of neural, humoral, and other ionic influences on smooth muscle contraction. The ability of certain drugs to inhibit calcium influx into cardiac and smooth muscle cells has been recognized for over a decade; however, the value of these drugs in the treatment of arterial hypertension has only been recently appreciated. Calcium channel blocking drugs, such as verapamil and nifedipine, cause a prompt decrease in blood pressure that is much more pronounced in hypertensive than in normotensive individuals. The primary antihypertensive effect appears related to a decrease in arterial smooth muscle tone. The ubiquitous role of intracellular calcium in the mediation of important cellular activities other than those related to contractile elements, such as the regulation of renin release and the transport of sodium across renal tubular epithelium, raises the possibility that blockade of calcium channels may influence blood pressure by means other than those related to a direct effect on smooth muscle tone. Single dose studies in experimental animals and humans suggest that short-term calcium channel blockade causes natriuresis. Further, the short-term natriuretic effect appears to be more prominent in hypertensive individuals than in normotensive controls. To examine the natriuretic effect of long-term calcium channel blockade in normotensive and hypertensive subjects, we gave nitrendipine to volunteers receiving a controlled diet for 8 days. We monitored the excretion of electrolytes as well as factors that influence their renal excretion. Our data suggest that the chronic blood pressure lowering effects of calcium...
channel blockade with nitrendipine are the result of more than merely direct influences on smooth muscle tone.

**Methods**

The subjects included eight normotensive, healthy volunteers, five men and three women, ranging in age from 19 to 45 years, and eight subjects, four men and four women aged 24 to 39 years, with mild essential hypertension. Mild essential hypertension was defined by their physicians as diastolic blood pressure ranging between 90 and 104 mm Hg without medication. These subjects had had secondary causes of hypertension excluded by their physicians through pertinent roentgenographic and laboratory studies. Patients with a history of stroke, angina pectoris, congestive heart failure, diabetes mellitus, and renal insufficiency were excluded. The protocol was approved by the Indiana University Medical Center Committee for the Protection of Human Subjects and Clinical Research Center Advisory Committee. Informed consent was obtained from each volunteer after detailed explanation of the procedures to be performed.

Before initiation of the protocol, each subject underwent a history and physical examination; baseline hematological, electrolyte levels, and tests of renal function were obtained, as well as electrocardiograms. The hypertensive subjects' blood pressures met inclusion criteria at that visit. Chest roentgenograms were obtained in hypertensive individuals who had not had previous studies in the past 6 months. Hypertensive individuals were withdrawn from their antihypertensive medication for the 2 weeks before the study. Each subject met with the research dietician to plan a menu for the study. The diets were tailored to the tastes of each individual subject as much as possible, but were designed to provide approximately 150 mEq of sodium, 80 mEq of potassium, and 80 g of protein for each subject. Caloric intake was adjusted to the needs of each individual subject. The subjects understood that they would be receiving the same three meals every day for the duration of the study.

For 16 days the subjects received all their meals in the Clinical Research Center; however, they continued to live at home and go about their business as usual. They were given known amounts of distilled water ad libitum. They collected all their urine in 24-hour aliquots daily. Each morning they were weighed after voiding. Blood pressure was obtained while the subjects were in the supine and upright positions by a trained nurse thrice daily before each meal. For 8 days the subjects received a placebo tablet twice daily, which they ingested at 0800 and 2000 hours. On the ninth day, after 2 hours of upright posture, the subjects had blood drawn for determination of creatinine, electrolytes, plasma renin activity (PRA), plasma aldosterone (PA), and plasma norepinephrine (PNE) values. Thereafter, a 3-day titration period of nitrendipine was begun. The protocol called for an initial 5-mg dose with predose and postdose, taken for 3 hours after the dose, supine and standing heart rate and blood pressure measurements. If the decrease in diastolic blood pressure was no greater than 10 mm Hg and if no adverse effects were experienced, the next day's dose was increased to 10 mg and 20 mg respectively. None of the normotensive or hypertensive subjects had adverse effects, and all were titrated to nitrendipine 20 mg twice daily for the remainder of the study. On the morning of the sixteenth day, the final urine collection was terminated and blood was obtained after 2 hours of upright posture. Physical examinations, electrocardiograms, and the initial laboratory studies were repeated.

Sodium and potassium concentrations in urine were measured by an ion-specific electrode method (Beckman Instruments, Fullerton, CA). Serum chemistries were determined by an automated method (Technicon, Tarrytown, NY). The PRA and PA were measured by previously reported radioimmunoassay methods. The PNE was measured by a radioenzymatic technique. The data were analyzed statistically using paired or two-sample t tests as appropriate. The 95% limits of probability were considered significant.

**Results**

Tables 1 and 2 show body weights, creatinine and potassium excretion, and humoral values of the normal and hypertensive subjects. These values were obtained at the end of the placebo period (Day 8) and the end of the nitrendipine period (Day 16). Supine and upright blood pressure values, as well as supine and upright heart rates, are also shown. The means of the three daily determinations were calculated, then the last 4 days of the placebo period were compared with the last 4 days of the nitrendipine period.

In normal subjects, paired t tests identified no change in body weight, creatinine excretion (U_CrV), creatinine clearance (CrCl), potassium excretion (U_KV), PA, or upright diastolic blood pressure. The PRA (p < 0.01) and PNE (p < 0.01) values increased significantly, while upright systolic blood pressure decreased. In hypertensive subjects body weight decreased (p < 0.01), while PRA (p < 0.01) and PNE (p < 0.01) increased. The decrease in body weight is likely to represent drug effect as no significant decrease was observed from the first day of the study to the end of the placebo period. Both upright systolic and diastolic blood pressure decreased as well. The U_CrV, CrCl, U_KV, and PA did not change significantly in either group. Nitrendipine at the doses given failed to influence supine blood pressure or heart rate in either normal or hypertensive subjects.

The influence of nitrendipine on urinary sodium excretion is shown in Figure 1. Basal urinary sodium excretion was calculated as the mean of the last 4 days during the placebo period. Significant natriuresis (p < 0.05) occurred in both normal and hypertensive subjects. The degree of natriuresis was not significantly different in normal and hypertensive subjects. Figure 2 shows the cumulative effects of nitrendipine on sodium homeostasis in the two groups. At the end of 7 days, net sodium decrease amounted to 161 ± 47 mEq in normal and 103 ± 25 mEq in hypertensive subjects. These values were not significantly different.
Discussion

Antihypertensive agents that foster decreased peripheral vascular resistance by inducing vasodilatation are widely and successfully used in the treatment of arterial hypertension; however, tolerance to the hypotensive action of such drugs may develop because of sodium and water retention, unless diuretics are added to the regimen.1-4 Diuretics effectively lower blood pressure and decrease the propensity to sodium and water retention, but engender their own undesirable side effects, such as depletion of the body’s potassium and magnesium stores.5,6 Thus, the development of agents that act by decreasing peripheral vascular tone, but which do not induce sodium and water retention, is important. If such an agent simultaneously facilitated sodium and water elimination by means of a mild diuretic action, decided therapeutic advantages would result.

**TABLE 1. Variables in Normal Subjects Obtained on the Last Day of the Control Period and on the Last Day of Nitrendipine**

<table>
<thead>
<tr>
<th>Value</th>
<th>Control</th>
<th>Nitrendipine</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>67.2 (3.2)</td>
<td>67.0 (3.1)</td>
<td>NS</td>
</tr>
<tr>
<td>UCrV (g/day)</td>
<td>1.52 (0.16)</td>
<td>1.59 (0.17)</td>
<td>NS</td>
</tr>
<tr>
<td>CI Cr (ml/min)</td>
<td>111 (10)</td>
<td>110 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>UKV (mEq/day)</td>
<td>58.4 (5.1)</td>
<td>61.4 (3.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PRA (ng ANG I/ml/3 hr)</td>
<td>7.36 (1.68)</td>
<td>12.11 (1.25)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PA (ng/dl)</td>
<td>13.1 (2.8)</td>
<td>17.1 (2.8)</td>
<td>NS</td>
</tr>
<tr>
<td>PNE (pg/ml)</td>
<td>351 (45)</td>
<td>459 (60)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Upright systolic pressure (mm Hg)</td>
<td>108 (2.7)</td>
<td>103 (1.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Upright diastolic pressure (mm Hg)</td>
<td>76 (1.7)</td>
<td>77 (2.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Supine systolic pressure (mm Hg)</td>
<td>108 (2.5)</td>
<td>109 (2.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Supine diastolic pressure (mm Hg)</td>
<td>68 (2.4)</td>
<td>70 (1.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Upright heart rate (beats/min)</td>
<td>79 (3.2)</td>
<td>82 (3.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Supine heart rate (beats/min)</td>
<td>64 (3.1)</td>
<td>66 (2.9)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are means (SE).

ANG I = angiotensin I; CI Cr = creatinine clearance; NS = not significant; PA = plasma aldosterone concentration; PNE = plasma norepinephrine concentration; PRA = plasma renin activity; UCrV = urinary creatinine excretion; UK V = urinary potassium excretion.

**TABLE 2. Variables in Hypertensive Subjects Obtained on the Last Day of the Control Period and on the Last Day of Nitrendipine**

<table>
<thead>
<tr>
<th>Value</th>
<th>Control</th>
<th>Nitrendipine</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>89.2 (5.7)</td>
<td>87.6 (5.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>UCrV (g/day)</td>
<td>1.72 (0.16)</td>
<td>1.65 (0.17)</td>
<td>NS</td>
</tr>
<tr>
<td>CI Cr (ml/min)</td>
<td>104 (11)</td>
<td>119 (10)</td>
<td>NS</td>
</tr>
<tr>
<td>UKV (mEq/day)</td>
<td>56.0 (6.0)</td>
<td>58.1 (6.4)</td>
<td>NS</td>
</tr>
<tr>
<td>PRA (ng ANG I/ml/3 hr)</td>
<td>6.30 (1.71)</td>
<td>14.52 (2.82)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PA (ng/dl)</td>
<td>12.5 (1.5)</td>
<td>11.6 (2.4)</td>
<td>NS</td>
</tr>
<tr>
<td>PNE (pg/ml)</td>
<td>354 (58)</td>
<td>526 (86)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Upright systolic pressure (mm Hg)</td>
<td>126 (2.7)</td>
<td>119 (4.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Upright diastolic pressure (mm Hg)</td>
<td>90 (1.7)</td>
<td>86 (1.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Supine systolic pressure (mm Hg)</td>
<td>129 (3.2)</td>
<td>127 (3.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Supine diastolic pressure (mm Hg)</td>
<td>84 (2.4)</td>
<td>83 (2.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Upright heart rate (beats/min)</td>
<td>85 (1.5)</td>
<td>86 (0.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Supine heart rate (beats/min)</td>
<td>76 (2.1)</td>
<td>77 (1.2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are means (SE).

ANG I = angiotensin I; CI Cr = creatinine clearance; NS = not significant; PA = plasma aldosterone concentration; PNE = plasma norepinephrine concentration; PRA = plasma renin activity; UCrV = urinary creatinine excretion; UK V = urinary potassium excretion.

Drugs classified as calcium channel blocking agents share the proclivity of reducing blood pressure in hypertensive organisms; however, they vary among themselves in several other properties. These differences may result in entirely different mechanisms of action.5,6 In this regard, verapamil and nifedipine both were shown to lower blood pressure promptly in hypertensive patients after a single dose; however, nifedipine increased PRA and PNE values while verapamil did not.9 Further, nifedipine caused a notable, acute increase in urine volume and sodium excretion that was not observed with verapamil.10 When given for a period of 6 weeks, nifedipine had no consistent influence on renin, aldosterone, and catecholamine levels, even though blood pressure reduction in the hypertensive subjects was maintained.19 An initial increase in activity of the renin and sympathetic nervous system appears to be followed by a subsequent decrease to-
The antihypertensive response to calcium channel blockade is apparently age related; patients with low renin essential hypertension exhibit a more favorable blood pressure reduction than do those with normal or high renin values. Patients with low renin hypertension are older, and hypertension may develop on the basis of relative sodium and water retention. Moreover, some investigators suggest that patients with low renin hypertension may have increased amounts of a material that inhibits Na-K-ATPase in response to an as yet unidentified defect in renal sodium excretion. Although the hypothesis is by no means proved, the resultant effect could be an increased intracellular sodium content of smooth muscle cells, which in turn promotes increased intracellular free calcium concentration, thereby enhancing smooth muscle tone. The increased efficacy of calcium channel blocking drugs in such patients may be related not only to increased vasodilatation caused by a direct effect on vascular smooth muscle, α-adrenergic receptor blockade, angiotensin antagonism, and converting-enzyme inhibition, but also to facilitated natriuresis.

Nitrendipine is a new calcium channel blocking drug belonging to the dihydropyridine group that includes nifedipine. This particular drug features a longer duration of action than other calcium channel inhibitors, and thus may be given only once or twice daily. In experimental animal studies, nitrendipine caused a dose-related lowering in blood pressure in spontaneously hypertensive rats that was greater than the response observed in the control Wistar-Kyoto rat. In addition, nitrendipine promoted a short-term diuresis and natriuresis in the face of a reduction in arterial blood pressure. The natriuretic and diuretic effects were greater in the hypertensive than in the normotensive animals. The possibility that nitrendipine might engender similar responses in humans, and that these effects might be sustained rather than merely short-term, prompted us to perform the present investigation.

The data show that nitrendipine induced a mild but significant natriuretic response in both hypertensive and normal subjects while simultaneously lowering systolic and diastolic upright blood pressure in the hypertensive and systolic upright blood pressure in the normal subjects. As the doses were low and the degree of hypertension was mild, the effects of nitrendipine on blood pressure in this study were modest. Nevertheless, substantial influences on homeostatic systems influencing sodium regulation were observed. The degree of natriuresis is consistent with the weight loss observed in the hypertensive subjects. These data are consistent with the short-term natriuretic responses reported in humans following the administration of nifedipine and suggest that the natriuretic response may be sufficiently sustained to influence blood pressure regulation chronically.

The mechanism of the natriuresis observed in this study is not clear. The glomerular filtration rate was not influenced by nitrendipine. Because renal tubular intracellular calcium is inversely related to sodium reabsorption, calcium channel blockade would be expected to foster sodium reabsorption rather than excretion. Natriuresis may have been engendered by intrarenal vasodilatation. Recently, DiBona and Sawin studied the effect of felodipine on renal sodium handling in rats with micropuncture techniques.
They found that fractional sodium excretion was increased following felodipine administration in the face of decreased blood pressure without change in renal blood flow or glomerular filtration rate. An inhibition of distal tubular sodium and water reabsorption was identified, while potassium absorption and excretion were not affected.

The humoral responses we observed may have occurred in response to modest volume contraction or secondary to decreased peripheral vascular resistance. Increased NE values have been described in response to nifedipine.17 Alternatively, the increased renin release may have been related to a direct effect of nifedipine on juxtaglomerular cells. Intracellular calcium concentration has been shown to influence renin release in an inverse fashion.17 The PA did not increase in response to nifedipine in either normal or hypertensive subjects, even though PRA increased. Recently, Guthrie et al.28 observed that steroidogenesis was impaired in the face of calcium channel blockade. Such dissociation has been observed by others as well.10,19 Moreover, adrenocorticotrophic hormone and angiotensin II-dependent steroidogenesis depend on adequate intracellular calcium concentration and are inhibited by verapamil in vitro30-31 at levels that are also achieved in vivo.28,32 Failure to increase PA values in the face of peripheral vasodilatation may have facilitated the natriurectic responses in our subjects.

In conclusion, our results underscore the multifaceted effects of calcium channel blockade on arterial blood pressure regulation. Mild natriuresis not accompanied by kaliuresis in the face of peripheral vasodilatation may indicate a general role for this class of calcium channel blocking drugs in the management of essential hypertension.

References

Calcium channel blockade with nitrendipine. Effects on sodium homeostasis, the renin-angiotensin system, and the sympathetic nervous system in humans.

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