Repetitive Natriuresis and Blood Pressure
Long-term Calcium Entry Blockade with Isradipine

LARS ROMER KRUSELL, LENNART TANG JESPERSEN, ANITA SCHMITZ,
KLAAUS THOMSEN, AND OLE LEDERBALLE PEDERSEN

SUMMARY The long-term effects (3.5 months) of a new calcium entry blocker of the 1,4-dihydropyridine class, isradipine (PN 200-110), on renal hemodynamics and excretional parameters were investigated in 10 essential hypertensive subjects (World Health Organization Classes I and II). Blood pressure and renal vascular resistance fell significantly (p < 0.001), and a slight increase in glomerular filtration rate and renal plasma flow was seen (p < 0.05). Output of fluid from the proximal tubules, measured as clearance of lithium and uric acid, increased significantly (p < 0.01 and p < 0.05, respectively), and a compensatory increase in absolute reabsorption of sodium beyond the proximal tubular level accompanied by an increase in clearance of potassium was noted. A 40% increase in the resultant clearance of sodium (p < 0.01) and an increase in diuresis (p < 0.05) followed the morning dose of isradipine after 3.5 months of treatment. Changes in blood pressure were significantly correlated with changes in absolute proximal reabsorption of sodium (r = 0.81), excretion of sodium (r = -0.64), and diuresis (r = -0.80). Thus, the natriuretic properties of calcium entry blockers may be more important for the long-term antihypertensive effect than the vasodilator effect per se. A model for renal sodium handling following treatment with calcium entry blockers was proposed. Although a causal relationship is not implied, isradipine induced a sustained, repetitive postdose effect on proximal fluid output, net natriuresis, and diuresis, that was intimately related to the long-term blood pressure-regulating response. (Hypertension 10: 577-581, 1987)

Key Words • hypertension • calcium entry blockade • isradipine • sodium excretion • lithium clearance • proximal tubule • uric acid

THE ability of calcium entry blockers to produce natriuresis and diuresis has been demonstrated in several short-term studies, whereas the clinical impact of this effect on blood pressure (BP) regulation following long-term treatment has been subject to debate. To our knowledge, a net effect beyond 10 days of treatment with a calcium entry blocker on sodium homeostasis has not been reported.1-5 Therefore, the present study was undertaken to investigate the long-term effects of a new dihydropyridine derivative (isradipine, PN 200-110) with respect to renal hemodynamics and excretional parameters in subjects with essential hypertension (World Health Organization Classes I and II).

Subjects and Methods
We studied 10 subjects with essential hypertension who had a diastolic BP (DBP) exceeding 100 mm Hg on repeated measurements (Table 1). Secondary hypertension was excluded by standard investigations. After a 4-week single-blind placebo period, the subjects received isradipine, 5 mg b.i.d. At weekly visits the dose was increased (from 10 to 15 to 20 mg b.i.d.) unless a DBP less than 90 mm Hg was achieved or limiting side effects occurred. The renal investigations were performed 2 to 3 hours after the usual morning dose after 3.5 months of active therapy.

All subjects were drug-free. Proteinuria was absent. No cardiovascular damage or other diseases were present. The subjects gave informed consent to enter the study, which was approved by the local ethical committee.

Procedure
At 2200 on the evening before the study, 16 mmol of lithium carbonate was given orally. The procedure was ambulatory, and the subjects arrived at the laboratory at 0800 after an overnight fast. To ensure urinary flow rate the subjects were given 200 ml of tap water every 20 minutes for 2 hours before and during the measuring procedure. The subjects were examined in the su-
Renal Handling of Sodium and Water

The following parameters of renal water and sodium handling were calculated using the lithium clearance method:

1. Absolute rate of proximal reabsorption of isotonic fluid: GFR—liothalamate clearance (in ml/min).
2. Absolute rate of proximal reabsorption of sodium: (GFR—liothalamate clearance) x serum sodium concentration (in \( \mu \text{mol/min} \)).
3. Fractional proximal escape of sodium: lithium clearance/GFR.
4. Absolute distal reabsorption of sodium: lithium clearance—sodium clearance (in \( \mu \text{mol/min} \)).
5. Fractional distal escape of sodium: sodium clearance/lithium clearance.
6. Absolute distal reabsorption of water: lithium clearance—urinary flow rate (in ml/min).
7. Fractional distal escape of water: urinary flow rate/lithium clearance.

Statistical Calculations

Two-way analysis of variance was employed to evaluate differences among the three placebo periods and the three corresponding periods after 3.5 months of treatment. Results are given as means ± SD in the text and as means ± SEM in the figures. Linear regression analysis was employed for statistical evaluation of the relationship between changes in parameters.

Results

Hemodynamics

Isradipine significantly reduced systolic BP (SBP) and DBP \((p<0.001)\), and heart rate increased slightly \((p<0.05)\) after 3.5 months of treatment (mean dose, 8.75 ± 3.75 mg b.i.d.; see Table 1). RPF was significantly increased from baseline measurement \((p<0.05)\) at the follow-up investigation. The filtration fraction remained unchanged. Renal vascular resistance was significantly reduced \((p<0.001)\). GFR, measured as liothalamate clearance, showed a minor, but significant increase, whereas creatinine clearance was unchanged.

Renal Handling of Sodium and Water

A 40% mean increase in sodium clearance was present at the second investigation \((p<0.01)\; \text{see Table 1}.\) Clearances of lithium and uric acid were also enhanced significantly compared with placebo values \((p<0.01)\). Urometric flow rate rose \((p<0.05)\), and fractional excretion of uric acid (uric acid clearance/liothalamate clearance) was augmented. No significant changes were seen in fractional and absolute proximal

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pretreatment ((n=10))</th>
<th>Posttreatment ((n=10))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>6:4</td>
<td>--</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>49.1 ± 5.8</td>
<td>--</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.4 ± 19.8</td>
<td>76.0 ± 18.5</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>180.4 ± 13.3</td>
<td>153.4 ± 18.3*</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>110.4 ± 7.7</td>
<td>95.5 ± 9.0*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68 ± 7</td>
<td>74 ± 13†</td>
</tr>
<tr>
<td>Renal plasma flow (ml/min)</td>
<td>391 ± 59</td>
<td>428 ± 91†</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>0.248 ± 0.031</td>
<td>0.244 ± 0.030</td>
</tr>
<tr>
<td>Renal vascular resistance (mm Hg-min/L)</td>
<td>197 ± 30</td>
<td>154 ± 43*</td>
</tr>
<tr>
<td>Glomerular filtration rate (ml/min)</td>
<td>97 ± 18</td>
<td>103 ± 22†</td>
</tr>
<tr>
<td>C_0/C - 100%</td>
<td>103 ± 30</td>
<td>100 ± 36</td>
</tr>
<tr>
<td>C_Na (ml/min)</td>
<td>2.0 ± 0.4</td>
<td>2.8 ± 1.1†</td>
</tr>
<tr>
<td>V (ml/min)</td>
<td>10.5 ± 1.8</td>
<td>12.1 ± 3.4†</td>
</tr>
<tr>
<td>Proximal fluid output (ml/min)</td>
<td>30.2 ± 8.0</td>
<td>33.2 ± 9.4†</td>
</tr>
<tr>
<td>Uric acid clearance</td>
<td>11.0 ± 2.9</td>
<td>13.3 ± 3.0‡</td>
</tr>
<tr>
<td>Fractional proximal escape</td>
<td>31.3% ± 7.1</td>
<td>32.5% ± 8.7</td>
</tr>
<tr>
<td>C_u/C_Li</td>
<td>11.7% ± 3.1</td>
<td>13.2% ± 3.4‡</td>
</tr>
<tr>
<td>Absolute proximal reabsorption (mmol/min)§</td>
<td>9.3 ± 2.0</td>
<td>9.8 ± 0.8</td>
</tr>
<tr>
<td>Fractional distal escape</td>
<td>C_Na/C_Li</td>
<td>6.7% ± 1.4</td>
</tr>
<tr>
<td>V/C_Li</td>
<td>3.7 ± 0.9</td>
<td>3.9 ± 1.1</td>
</tr>
<tr>
<td>Absolute distal reabsorption (C_Li—C_Na) (\mu\text{mol/min})</td>
<td>3937 ± 1069</td>
<td>4277 ± 1239†</td>
</tr>
<tr>
<td>C_Li—V (ml/min)</td>
<td>19.7 ± 8.0</td>
<td>20.3 ± 9.4</td>
</tr>
<tr>
<td>C_K (ml/min)</td>
<td>17.8 ± 3.6</td>
<td>22.4 ± 8.0†</td>
</tr>
</tbody>
</table>

Values are means ± SD before and after 3.5 months of treatment with isradipine (PN 200-110). C_Na = Na clearance; V = urinary flow rate; C_Li = Li clearance; C_u = uric acid clearance; S Na = serum Na concentration; C_K = K clearance. *p<0.001, †p<0.05, ‡p<0.01, compared with pretreatment values. §Measured as \( (C_0 - C_Li) \times S Na \).
reabsorption of sodium and water (see Table 1). Fractional distal escape of sodium increased ($p<0.01$), and absolute distal reabsorption of sodium increased ($p<0.05$; see Table 1). No significant relationship between changes in renal vascular resistance and clearance of uric acid or fractional excretion of uric acid was present. Clearance of potassium increased significantly ($p<0.01$), whereas no significant changes were seen in serum potassium (from 4.2 to 4.0 mmol/L), uric acid (from 0.31 to 0.29 mmol/L), sodium (from 140 to 139 mmol/L) or creatinine (from 84 to 84 $\mu$mol/L) concentration.

The BP response obtained after 3.5 months of treatment with isradipine was intimately related to the percent change in absolute reabsorption of sodium in the proximal tubule and to the percent change in sodium clearance and urinary flow rate (Table 2 and Figures 1–3).

Side effects were reported by four subjects. Two had slight ankle edema, one complained of transient postdose palpitations, and one reported passing postdose flushing.

Discussion

Despite the pronounced hemodynamic changes following short-term calcium entry blockade, normally, no changes are seen in GFR. Also, most long-term studies have indicated that calcium blockade induces no changes in GFR. However, in one study, Bauer et al. found a significant increase in GFR in patients selected with a low GFR at baseline. In the present study, GFR, as measured by iothalamate clearance, increased slightly.

RPF has been shown to be either unaffected or increased following short-term calcium entry blockade. Long-term treatment does not seem to affect this parameter, not even long-term treatment with a vasoselective calcium entry blocker. In the present series, isradipine induced a significant increase of RPF after 3.5 months of treatment.

Although urinary 24-hour excretion of sodium is not increased when measured after about 1 week of treatment with calcium entry blockers, a negative sodium balance within the first days is obtained with verapamil, felodipine, and nitrendipine treatment. Following antihypertensive treatment with nicardipine for 2 months in humans, Young et al. observed unaltered excretion of sodium within 5 hours after the morning dose and a concomitant increase in diuresis. Similarly, Chaignon et al. found no postdose increase in natriuresis following only 6 days of treatment with nicardipine. When fractional excretion of sodium was measured after a single dose of felodipine, the prompt increment in excretion of sodium was followed by a decrement in excretion, resulting in an unchanged net 24-hour excretion. A similar antinatriuresis was seen following a short-term dose of nicardipine, resulting in a net unchanged excretion of sodium within the first 6

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**Table 2. Relationship Between Changes in BP and Changes in Sodium Clearance, Urinary Flow Rate, and Absolute Rate of Proximal Sodium Reabsorption in 10 Hypertensive Subjects Treated with Isradipine for 3.5 Months**

<table>
<thead>
<tr>
<th>Variable</th>
<th>$C_{Na} (%)$</th>
<th>$V (%)$</th>
<th>$APR_{Na} (%)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>-0.64*</td>
<td>-0.80†</td>
<td>0.85†</td>
</tr>
<tr>
<td>DBP</td>
<td>-0.59</td>
<td>-0.76†</td>
<td>0.69*</td>
</tr>
<tr>
<td>Mean BP</td>
<td>-0.64*</td>
<td>-0.80†</td>
<td>0.81†</td>
</tr>
</tbody>
</table>

$C_{Na} = \text{Na clearance; } V = \text{urinary flow rate; } APR_{Na} = \text{absolute rate of proximal Na reabsorption}.$

* $p<0.05$, † $p<0.01$, compared with baseline.
hours after dose. Thus, the acute antinatriuresis following acute “nonspecific” vasodilatation, which is believed to be mediated by the degree of hemodynamic change, seems initially to be counterbalanced or even overridden by the specific natriuretic action of calcium entry blockers on the proximal tubular reabsorption of sodium (Figure 4). This effect might be due to an ability of calcium entry blockers to blunt the antinatriuretic effects of intrarenal angiotensin II. In contrast to other vasodilators employed for long-term antihypertensive treatment, calcium entry blockers do not seem to cause expansion of extracellular volume, even in a subgroup of patients with ankle edema.

In the present study there was a significant increase in sodium clearance and urinary flow rate 2 to 3 hours after the morning dose, even after 3.5 months of treatment (see Table 1). This finding suggests a sustained postdose natriuretic or diuretic effect, possibly outbalanced by a counteracting sodium-retaining state during the subsequent hours, resulting in a net unchanged 24-hour excretion. Isradipine induced an increased outflow of fluid from the proximal tubules, although no change in the rate of absolute proximal reabsorption of sodium was seen for the group as a whole. Nevertheless, there was a significant relationship between the degree of changes in absolute rate of proximal sodium reabsorption and changes in SBP, MBP, and DBP (see Table 2 and Figure 1). This finding suggests that the long-term antihypertensive efficacy of isradipine is determined by the ability of the drug to prevent an increase in the absolute rate of proximal sodium reabsorption on the one hand and the ability of the patient to counterbalance this effect on the other. The observed changes in distal tubular handling of sodium are in agreement with the results seen following short-term calcium entry blockade. We noted an increase in absolute distal reabsorption but a fall in the relative reabsorption of sodium. In argument against a direct pharmacological effect on the distal reabsorption, this action could be ascribed to an incapacity of compensatory mechanisms of the distal tubules to overcome the increased delivery from the proximal segments. On the contrary, if the distal tubules are capable of reacting with a full compensatory reabsorption, without regarding the amount of delivery from the proximal segment, an inhibitory effect on the distal tubules could be claimed.

The relation between renal sodium and water handling in regulation of BP is further emphasized by the demonstrated significant relationship between the changes in BP and the changes in sodium clearance and urinary flow rate (see Table 2 and Figures 2 and 3). Although a poor parameter for volume expansion, no increase in mean body weight was seen during the study.

The acute uricosuric effect of calcium entry blockers also suggests a proximal tubular effect. Following 8 weeks of treatment with felodipine in essential hypertensive subjects, Hulthén et al. demonstrated a significant reduction in serum uric acid and an increased fractional 24-hour excretion of uric acid. The present study showed a slight, nonsignificant fall in serum uric acid but a significant increase in uric acid
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clearance and fractional clearance of uric acid in the hours after the morning dose of isradipine, probably following the biphasic pattern proposed for the sodium excretion (see Figure 4). In contrast, conventional antihypertensive regimens, including diuretics and β-blockers, tend to induce uric acid retention and even gout. 26, 27 Hyperuricemia is more prevalent in the hypertensive population than in normotensive subjects. Although uric acid is more likely to be a marker of hypertensive vascular involvement than a risk factor per se, 10, 28 the uricosuric action of calcium entry blockers may represent an added advantage in the treatment of hypertension.

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