Renal Effects of Diltiazem in Primary Hypertension

SOBHA SUNDERRAJAN, GARRY REAMS, AND JOHN H. BAUER

SUMMARY Although the calcium channel blocker diltiazem has been shown to be an effective antihypertensive agent, its effect on renal function, salt and water excretion, and body fluid composition has not been well characterized in patients with primary hypertension. Therefore, these parameters were prospectively studied in 18 subjects with primary hypertension after placebo and 8 weeks of diltiazem monotherapy. Diltiazem monotherapy was confirmed to be an effective antihypertensive agent. Although mean arterial pressure was reduced from 121 to 108 mm Hg, diltiazem had no overall effect on glomerular filtration rate, renal plasma blood flow, salt and water excretion, or body fluid composition. Renal vascular resistance, however, was decreased. In subjects with pretreatment glomerular filtration rates of 80 ml/min/1.73 m² or less, diltiazem therapy was associated with marked improvement in glomerular filtration rate (48%) and effective renal plasma flow (36%). Since the filtration fraction was unchanged, changes in glomerular filtration rate may have been related to the attenuated intrarenal effects of angiotensin II or norepinephrine, or both.

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KEY WORDS • diltiazem • hypertension • glomerular filtration • renal plasma flow • calcium antagonists

THE calcium channel blocker diltiazem has been shown to be an effective antihypertensive agent in patients with primary hypertension1-4; however, its effect on renal function has not been well characterized. Short-term studies in animals have demonstrated diltiazem-induced dose-dependent increases in glomerular filtration rate (GFR) and effective renal plasma flow (ERPF).5-8 Studies in patients with primary or secondary renal disease (with and without hypertension) have suggested that chronic oral diltiazem therapy (dose ranges, 30-120 mg/day for 1 week to 3 months) tended to increase GFR and ERPF; the latter demonstrated the greatest and most consistent change.5-12 Conversely, short-term oral administration of diltiazem (30-60 mg) to patients with arteriosclerotic cardiovascular disease or chronic congestive heart failure (with or without hypertension) has failed to demonstrate a consistent effect on either GFR or ERPF.13-14

Although use of diltiazem reportedly has been associated with a low incidence of swelling or edema formation,15 its effect on the renal excretion of salt and water or on body fluid composition has not been well characterized. Short-term studies in both animals and humans have demonstrated that diltiazem administration produces prompt increases in urinary sodium excretion and urine flow rate.5, 12-14, 16, 17 Long-term studies in humans, however, of dosages ranging to 360 mg/day, have failed to demonstrate any diltiazem-induced change in either serum electrolyte levels or fluid retention, as evidenced by edema or weight gain.18, 19 Therefore, the current prospective study attempted to evaluate the short-term (8 weeks) effects of diltiazem monotherapy on renal function, salt and water excretion, and body fluid composition in patients with primary hypertension.

Subjects and Methods

Eighteen hypertensive men (mean age, 54 years; mean duration of documented hypertension, 9 years) were selected for the study. To be included in the protocol all subjects had to have supine diastolic blood pressures greater than 95 mm Hg on two successive occasions and subsequently had to maintain a supine diastolic blood pressure greater than 95 mm Hg while receiving placebo (2-4 weeks). Informed consent was obtained from all subjects according to the principles of the Declaration of Helsinki. All studies were approved by the Harry S. Truman Memorial Veterans Hospital and the University of Missouri (joint committee for research involving human subjects).

A standard mercury sphygmomanometer was used
to record systolic (first phase) and diastolic (fifth phase) blood pressure. The subjects' blood pressure and heart rate were recorded after 10 minutes in a supine position and 5 minutes of standing. Average recordings of three measurements were then determined. Mean arterial pressure was calculated as diastolic pressure plus one third pulse pressure.

After 2 to 4 weeks of placebo therapy, a 24-hour urine collection was obtained on the day before the clinic visit. On the day of the clinic visit, volume studies were performed with subjects in the recumbent position from 0800 to 1100. After a light lunch, timed clearances were performed on the recumbent subjects from 1230 to 1600. Subjects were then begun on diltiazem and the dosage was titrated during biweekly visits. Dosage initially was 120 mg b.i.d. and was increased to a maximum of 240 mg b.i.d. to achieve a sustained reduction in the diastolic pressure to below 90 mm Hg. After 8 weeks of diltiazem monotherapy, 24-hour urine collection, volume studies, and timed clearances were repeated.

Simultaneous volume studies were performed as described by Bauer et al. Radioactive isotopes and average dosages used were as follows: erythrocytes labeled with sodium chromate Cr 51, 10 μCi (for red blood cell mass); human serum albumin labeled with sodium iodide I 125, 5 μCi (for plasma volume); sodium sulfate S 35, 75 μCi (for extracellular fluid); and tritiated water, 90 μCi (for total body water). Total blood volume was calculated by adding red blood cell mass and plasma volume. Intracellular fluid volume was calculated by subtracting extracellular fluid from total body water. All volumes were expressed in absolute units (liters) since each subject served as his own control. Peripheral venous hematocrit readings were determined by the microhematocrit technique. Cumulative radiation exposure for each study period was estimated to be less than 100 mrad.

Renal function studies were performed as previously described. Following hydration (20 ml of tap water per kilogram of body weight; urine specific gravity < 1.010), priming doses of inulin (10% solution purified inulin) and p-aminohippurate (20% solution PAH) were administered to obtain a plasma inulin concentration of approximately 2 mg/dl and a plasma PAH concentration of approximately 2 mg/dl. Subsequently, a sustaining infusion of inulin (rate depending on the estimated level of GFR) and PAH (rate depending on the estimated level of ERPF) was administered to maintain initial plasma concentrations of inulin and PAH. Three timed urine collections (spontaneous voidings) were made at approximately 30- to 40-minute intervals following a 90-minute equilibration period and evidence of good urine flow (75 ml/min). Plasma was obtained between the first and second and the second and third urine collections; a steady state concentration of both inulin and PAH was indicated by a concentration difference of less than 10% between sample collections.

Plasma and urine were assayed for the following: creatinine, according to the method of Bonsnes and Taussky; inulin, according to the method of Walser et al.; PAH, according to the method of Smith et al.; osmolality, by freezing point depression; and sodium, potassium, chloride, and total CO2 content, by autoanalyzer techniques.

Clearances of creatinine, inulin, PAH, sodium, potassium, and osmolality were calculated as (urine concentration/plasma concentration) x urine flow rate (in ml/min) and were corrected for body surface area (1.73 m²). Since there were no significant differences in urine flow rate or clearances from one collection period to another, all results were expressed as single mean values of the triplicate determinations for each subject.

Filtration fraction was calculated as inulin clearance/PAH clearance and was expressed as a percent of PAH clearance. Renal blood flow was calculated from PAH clearance by using the peripheral venous hematocrit reading and assuming 74% extraction of aminohippurate. Renal vascular resistance was calculated as (mean arterial pressure/renal blood flow) x 80,000 (in dyn·sec·cm⁻⁵/1.73 m²). Fractional sodium and potassium excretion were calculated as sodium clearance/inulin clearance and potassium clearance/inulin clearance. Free water clearance was calculated as urine flow rate minus osmolality clearance. The 24-hour urine determinations for sodium and potassium were expressed as milliequivalents per gram of creatinine to normalize for accuracy of the 24-hour urinary collection. Data were analyzed by paired Student's t test. A difference was considered statistically significant when p was less than 0.05.

**Results**

Short-term diltiazem monotherapy significantly reduced both recumbent and upright systolic and diastolic blood pressure in 16 of the 18 hypertensive subjects (Table 1). Seven subjects required 120 mg of diltiazem, twice daily to achieve blood pressure control; four required 180 mg twice daily, and five required 240 mg twice daily. Two subjects failed to achieve a diastolic pressure below 90 mm Hg on the maximum dosage allowed (240 mg b.i.d.). Heart rate was reduced significantly from 78 to 71 beats/min only when the subjects were in the recumbent position.

<table>
<thead>
<tr>
<th>Position</th>
<th>Placebo (4 wk)</th>
<th>Diltiazem (8 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recumbent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>163 ± 6</td>
<td>149 ± 7*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>101 ± 1</td>
<td>88 ± 2†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>78 ± 3</td>
<td>71 ± 2‡</td>
</tr>
<tr>
<td>Upright</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>157 ± 6</td>
<td>138 ± 7*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>99 ± 2</td>
<td>85 ± 2†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>83 ± 3</td>
<td>79 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SEM. *p < 0.005, †p < 0.0005, ‡p < 0.025, compared with placebo values.
Diltiazem monotherapy had no significant effect on serum electrolyte levels. Mean (± SEM) serum sodium level was 141 ± 1 mEq/L before and 142 ± 1 mEq/L after therapy. Serum potassium level was 4.0 ± 0.1 mEq/L before and after therapy. Serum chloride level was 104 ± 1 mEq/L before and 103 ± 1 mEq/L after therapy. Total CO₂ content was 27 ± 1 mEq/L before and 29 ± 1 mEq/L after therapy. Diltiazem monotherapy was not associated with a significant effect on either 24-hour urinary sodium excretion (114 ± 8 mEq/g creatinine during placebo treatment vs 98 ± 12 mEq/g creatinine during drug therapy) or 24-hour urinary potassium excretion (38 ± 4 mEq/g creatinine during placebo treatment vs 39 ± 4 mEq/g creatinine during drug therapy).

Although diltiazem monotherapy reduced mean arterial pressure from 121 to 108 mm Hg in the 18 hypertensive subjects, it had no overall effect on creatinine clearance, inulin clearance, ERPF, or renal blood flow (Table 2). Filtration fraction was unchanged, while renal vascular resistance was reduced significantly.

In subjects whose GFR (by inulin clearance) was 80 ml/min/1.73 m² or less during placebo therapy, diltiazem significantly increased GFR, as assessed by both creatinine and inulin clearance, and ERPF without significantly altering the filtration fraction (Table 3). Individual data on GFR and ERPF for the eight subjects with impaired renal function are shown in Figure 1.

In subjects whose GFR was greater than 80 ml/min/1.73 m² during placebo therapy, diltiazem had no significant effect on the creatinine clearance, ERPF, or the filtration fraction (Table 3). Inulin clearance, however, was decreased from 116 to 93 ml/min/1.73 m².

### Table 2. Effects of Diltiazem on Renal Function, Renal Hemodynamics, and Salt and Water Excretion in 18 Hypertensive Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (4 wk)</th>
<th>Diltiazem (8 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>121 ± 2</td>
<td>108 ± 3*</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>87 ± 5</td>
<td>93 ± 4</td>
</tr>
<tr>
<td>Inulin</td>
<td>91 ± 8</td>
<td>91 ± 4</td>
</tr>
<tr>
<td>PAH</td>
<td>336 ± 29</td>
<td>362 ± 23</td>
</tr>
<tr>
<td>Free water</td>
<td>8.6 ± 1.3</td>
<td>8.8 ± 1.0</td>
</tr>
<tr>
<td>Filtration fraction (%)</td>
<td>27.6 ± 1.4</td>
<td>26.4 ± 1.9</td>
</tr>
<tr>
<td>RBF (ml/min/1.73 m²)</td>
<td>840 ± 71</td>
<td>870 ± 54</td>
</tr>
<tr>
<td>RVR (dyne sec/cm²/1.73 m²) × 10³</td>
<td>13.5 ± 1.6</td>
<td>10.5 ± 0.6§</td>
</tr>
<tr>
<td>( FE_{Na} ) (%)</td>
<td>1.5 ± 0.3</td>
<td>1.2 ± 0.2$</td>
</tr>
<tr>
<td>( FE_{K} ) (%)</td>
<td>12.7 ± 1.7</td>
<td>13.3 ± 1.3</td>
</tr>
<tr>
<td>Urine flow rate (ml/min)</td>
<td>11.2 ± 1.5</td>
<td>11.2 ± 1.0</td>
</tr>
</tbody>
</table>

Values are means ± SEM. MAP = mean arterial pressure; PAH = p-aminohippurate; RBF = renal blood flow; RVR = renal vascular resistance; \( FE_{Na} \) = fractional excretion of sodium; \( FE_{K} \) = fractional excretion of potassium.

\*p < 0.0005, \$p < 0.05, compared with placebo values.
\†Glomerular filtration rate; \$effective renal plasma flow.

### Table 3. Differential Effects of Diltiazem on Renal Function, Hemodynamics, and Fractional Sodium Excretion in Eight Hypertensive Subjects with Low Inulin Clearance and 10 with Normal Inulin Clearance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (4 wk)</th>
<th>Diltiazem (8 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low clearance group*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>119 ± 2</td>
<td>105 ± 3†</td>
</tr>
<tr>
<td>( C_{PAH} ) (ml/min/1.73 m²)</td>
<td>76 ± 4</td>
<td>92 ± 5</td>
</tr>
<tr>
<td>( C_{IN} ) (ml/min/1.73 m²)</td>
<td>60 ± 6</td>
<td>89 ± 6†</td>
</tr>
<tr>
<td>( C_{PAH} ) (ml/min/1.73 m²)</td>
<td>250 ± 31</td>
<td>339 ± 21§</td>
</tr>
<tr>
<td>Filtration fraction (%)</td>
<td>25.0 ± 1.9</td>
<td>26.8 ± 2.2</td>
</tr>
<tr>
<td>( FE_{Na} ) (%)</td>
<td>2.3 ± 0.5</td>
<td>1.5 ± 0.4†</td>
</tr>
</tbody>
</table>

Normal clearance group|| initial GFR > 80 ml/min/1.73 m².

Values are means ± SEM. Filtration fraction = \([C_{IN}/C_{PAH}]\) × 100.

\*Initial glomerular filtration rate (GFR) ≤ 80 ml/min/1.73 m².
\‖Initial GFR > 80 ml/min/1.73 m².

\†p < 0.005, \$p < 0.05, \$p < 0.01, compared with placebo values.

Fractional sodium excretion was decreased from 1.6 to 1.2% only in those subjects whose renal function was initially impaired (see Tables 2 and 3). Diltiazem monotherapy had no effect on the fractional excretion of potassium, urine flow rate, free water clearance, body weight, plasma volume, red blood cell mass, total blood volume, extracellular fluid space, intracellular fluid space, or total body water (Table 4).

### Discussion

Diltiazem monotherapy, in dosages ranging from 240 to 480 mg/day for 8 weeks, effectively reduced both systolic and diastolic blood pressures in 16 of 18 subjects with primary hypertension. Although mean arterial pressure decreased from 121 to 108 mm Hg, renal function and hemodynamics were not altered significantly, except for a 22% decrease in renal vascular resistance. Eight subjects with pretreatment (placebo) inulin clearance of 80 ml/min/1.73 m² or less exhibited marked increases in ERPF (36%) and GFR, as assessed by both inulin clearance (48%) and creatinine clearance (21%).

At least two pharmacological mechanisms potentially could account for the observed increase in GFR and ERPF following diltiazem therapy: 1) reversal of angiotensin II-induced vasoconstriction (mesangium and/or efferent arteriolar tone) and 2) reversal of norepinephrine-induced vasoconstriction (mesangium and/or afferent arteriolar tone). The ability of calcium entry...
blockers to prevent an increase in cytosol-ionized calcium would be expected to decrease the sensitivity of the renal vasculature and the mesangium to both angiotensin II and norepinephrine. Indeed, several investigators have reported that diltiazem or verapamil, or both drugs attenuate the intrarenal effects of both exogenously administered angiotensin II and norepinephrine. Additionally, both of these drugs may differentially affect α-adrenergic receptors; both drugs have been reported to preferentially antagonize post-synaptic (voltage-dependent calcium channel) α₂-adrenergic receptor-mediated vasoconstriction. Selective interference with the vasoconstrictor action of norepinephrine on the afferent arteriole (suggesting greater density of α₂-adrenergic receptors), while leaving intact its action on the efferent arteriole (suggesting a greater density of α₁-adrenergic receptors), would be expected to increase GFR.

Our observation that GFR increased in hypertensive subjects with initially impaired filtration, without an associated increase in the filtration fraction supports a differential effect of norepinephrine on the renal vasculature. However, we cannot exclude the possibility of a reversal of the direct effect of angiotensin II or norepinephrine on the glomerulus (mesangium). Reversal of angiotensin II–mediated efferent arteriolar vasoconstriction would be expected to enhance ERPF disproportionately, decreasing the filtration fraction; this effect was not observed. The pathophysiology of the observed decrease in inulin clearance in hypertensive subjects with pretreatment normal renal function is unclear. Both creatinine clearance and ERPF, however, were unchanged.

The acute intravenous administration of nifedipine has been reported to markedly increase GFR and renal blood flow in patients with primary hypertension, whereas these same parameters were not altered significantly in normotensive subjects and patients with chronic glomerulonephritis. Similar findings have been reported following 1 week of oral nicardipine therapy: creatinine clearance increased markedly in hypertensive patients, whereas it was not significantly altered in normotensive subjects. These observations, in addition to ours, suggest that patients who have primary hypertension with mild to moderate renal impairment have reversible alterations in renal vascular or mesangial tone that is modulated, in part, by changes in intracellular calcium concentration.

Although diltiazem has been observed to induce an acute natriuresis and diuresis, it has not been reported to have a clinically important sustained effect on salt and water excretion, as evidenced by edema or weight gain. Although we found that fractional sodium excretion decreased, this decrease was restricted to subjects with initially impaired renal function and may simply reflect down-regulation of sodium homeostatic mechanisms resulting from the associated increase in GFR. The fact that we found no alteration in serum and urine electrolyte levels, potassium excretion, urine flow rate, free water clearance, body weight, or body fluid composition supports clinical observations that diltiazem monotherapy has no net effect on sodium homeostasis. However, anecdotal case reports do attest to the potential for diltiazem to produce edema. Of 18 subjects who entered our study, one experienced severe bilateral pitting leg edema and had to be withdrawn from the study. This subject showed a 1.2-kg net weight gain; although his plasma volume was unchanged (3.4 L before and after therapy), his extracellular fluid volume increased from 13.1 to 16.3 L. The frequency of and mechanisms for this potential side effect are unclear.

We conclude that diltiazem is an effective antihypertensive drug when given as monotherapy for the treatment of mild to moderate hypertension. Since renal function is either unchanged or improved, and sodium and volume expansion does not usually occur, diltiazem can be expected to assume a permanent role as first-step therapy in the treatment of hypertensive diseases.

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