Effect of Nifedipine on Renal Function in Patients with Essential Hypertension

GARRY P. REAMS, ANN HAMORY, ALISA LAU, AND JOHN H. BAUER

SUMMARY Twenty-six essential hypertensive patients were entered into a protocol to assess the blood pressure and renal effects of the dihydropyridine calcium antagonist nifedipine (30–120 mg/day given in divided doses) administered for 4 weeks. Nifedipine monotherapy effectively lowered blood pressure in 73% of the patients. Glomerular filtration rate and effective renal plasma flow were increased 13.3 and 19.6%, respectively. The filtration fraction and urinary albumin excretion remained unchanged. Renal vascular resistance was markedly reduced (25.2%). Changes observed in renal function were independent of the patients’ initial glomerular filtration rate. Furthermore, there was no correlation between the systemic and renal effects of nifedipine monotherapy. Patients with a poor systemic blood pressure response exhibited increases in both glomerular filtration rate (+13%) and effective renal plasma flow (+20%), changes comparable with increases in glomerular filtration rate (+13%) and effective renal plasma flow (+19%) observed in patients achieving a goal blood pressure response (diastolic blood pressure ≤90 mm Hg, or a ≥10 mm Hg decrease in diastolic blood pressure, or both). These results suggest that nifedipine monotherapy has the potential to improve renal function abnormalities encountered in the essential hypertensive state independently of its effect on systemic blood pressure. (Hypertension 11: 452–456, 1988)

Key Words • calcium antagonism • glomerular filtration rate • effective renal plasma flow • blood pressure

CALCIUM channel antagonists represent a heterogeneous group of drugs. They share a common pharmacological property, interference of calcium flux through voltage-sensitive channels. Although the systemic effects of calcium channel antagonists are generally well known, their renal effects are only now being characterized.1,2 The potential role for calcium antagonists to reverse or prevent the pathophysiological progression of hypertensive renal disease or to attenuate the progression of chronic renal disease is unknown.

We have previously reported on the renal effects of the benzothiazepine calcium antagonist diltiazem3,4 and the dihydropyridine calcium antagonist amiodipine.5 These studies suggested that calcium antagonists have the potential to enhance effective renal plasma flow (ERPF) and renal blood flow, to preserve or improve glomerular filtration rate (GFR), and to lower renal vascular resistance. We now report on the short-term renal effects of the dihydropyridine calcium antagonist nifedipine. Our results suggest that renal function abnormalities encountered in the essential hypertensive state may be improved by nifedipine independently of its systemic blood pressure effect.

Patients and Methods

Twenty-six patients with essential hypertension were selected for this prospective study. To be included, each patient had to maintain a mean 5-minute recumbent diastolic blood pressure (fifth phase) between 95 and 114 mm Hg following withdrawal of prior drug therapy and during 2 to 4 weeks of placebo therapy. The diagnosis of essential hypertension was established by history and physical examination and by the absence of clinical findings suggestive of a secondary form of hypertension. Excluded from the study were patients with a history or clinical or laboratory findings of moderate to severe cardiomegaly, congestive heart failure, recent myocardial infarction, second- or third-degree heart block, overt diabetes mellitus, or Grade 3 or 4 Keith-Wagener hypertensive retinopathy, as well as patients who were nonadherent to drug therapy (as monitored by count of returned tablets).
Informed consent was obtained according to the principles of the Declaration of Helsinki. All studies were approved by the University of Missouri Health Sciences Center Committee for Research Involving Human Subjects.

Protocol

A standard mercury sphygmomanometer was used to record systolic (first phase) and diastolic (fifth phase) blood pressure. Three pressures were recorded after the patient had been supine for 5 minutes and standing for 3 minutes. The three pressures were averaged to give a mean representation of the patient's blood pressure. The mean heart rate, measured in beats per minute, was obtained after each blood pressure measurement.

Following a 2- to 4-week baseline placebo period, patients with recumbent diastolic blood pressure between 95 and 114 mm Hg were treated with nifedipine monotherapy. The drug was titrated each week (from 10 to 20 to 30 mg, to a maximum of 40 mg, administered 3 times a day) to achieve a goal blood pressure response (defined as a recumbent diastolic blood pressure ≤90 mm Hg, or a ≥10 mm Hg decrement in diastolic blood pressure, or both). All renal function studies were performed following the placebo run-in period and following 4 weeks of nifedipine monotherapy.

Serum and Urine Electrolyte Determinations

Serum and urine electrolytes were determined by ion selective electrode (Beckman Instrument, Brea, CA, USA). The 24-hour urine electrolyte determinations were expressed as milliequivalents per gram of creatinine to normalize for accuracy of collection.

Renal Function

Timed renal clearances were performed as previously described by Bauer et al.6,7 Patients were hydrated (20 ml of tap water/kg body weight) to achieve a urine specific gravity below 1.010. GFR was determined by three parameters. Creatinine clearance was determined in all patients. In addition, paired inulin clearances were determined in six of the 26 patients, and paired 99mTc-diethylenetriamine pentaacetic acid (DTPA) clearances were determined in the remaining 20 patients. The 99mTc-DTPA clearances were performed because of a shortage of inulin experienced during the clinical trial. ERPF was determined by p-aminohippurate (PAH) clearance. 99mTc-DTPA clearance was determined using a single injection technique.8 Specifically, a 2-μCi bolus was administered intravenously. Priming doses of inulin and PAH were administered to obtain a plasma inulin concentration of approximately 20 mg/dl and a plasma PAH concentration of approximately 2 mg/dl. Subsequently, sustaining infusions of inulin (rate depending on the estimated level of GFR) and PAH (rate depending on the estimated level of ERPF) were administered to maintain the initial plasma concentrations of inulin and PAH. Three timed urine collections (spontaneous voidings) were made at 25- to 40-minute intervals following a 45-minute equilibration period. Plasma was obtained between each urine collection. The specific activity of 99mTc-DTPA in plasma and urine was assayed by gamma counter. Plasma and urine were assayed for inulin, PAH, and creatinine as previously described.6,7 Urinary albumin excretion was determined on the three timed urine collections using a double-antibody iodine-125 radioimmunoassay technique (Diagnostic Products, Los Angeles, CA, USA). Results were expressed as the mean of the three determinations.

Calculations

Clearances of inulin or 99mTc-DTPA, PAH and creatinine were calculated as (urine concentration/plasma concentration) x urine flow rate (ml/min) and corrected for body surface area (1.73 m²). All results were expressed as single mean values of triplicate determinations for each patient. In our laboratory, the correlation between inulin and 99mTc-DTPA clearances, performed simultaneously in 24 hypertensive subjects, has an r value of 0.919 (p < 0.001). Filtration fraction was calculated as inulin clearance/PAH clearance or 99mTc-DTPA clearance/PAH clearance and was expressed as a percentage of PAH clearance. Renal blood flow was calculated from PAH clearance by using the peripheral venous hematocrit and assuming 74% renal extraction of PAH.9 To our knowledge, the effect of nifedipine on the renal extraction of PAH is unknown. To the degree that nifedipine may affect the extraction of PAH, our results may underestimate the magnitude of the change in ERPF/renal blood flow. Renal vascular resistance (dyn·sec·cm⁻²/1.73 m²) was calculated as (mean arterial pressure [MAP; mm Hg]/renal blood flow [ml/min/1.73 m²]) x 80,000. MAP was calculated as one third of the pulse pressure plus the diastolic pressure.

Data Analysis

Data were analyzed for the entire group. In addition, data were segregated into two additional subpopulations: 1) patients who achieved a goal blood pressure response (supine diastolic blood pressure ≤90 mm Hg, or a ≥10 mm Hg decrement in diastolic blood pressure, or both) versus those who did not achieve a goal blood pressure, and 2) patients with initial impaired renal function (GFR ≤80 ml/min/1.73 m²) versus those patients with normal renal function (GFR > 80 ml/min/1.73 m²). All data were expressed as means ± 1 SD and were analyzed by paired r test. A difference was considered statistically significant at a p level below 0.05.

Results

Patient Characteristics, Drug Dosages, and Estimated Sodium Intake

Twenty-six patients with essential hypertension (22 men, 4 women; mean age, 54 years; range, 32–70 years; mean duration of hypertension, 9.4 years; range, 0–30 years) received a mean nifedipine dose of 57.7 mg (range, 30–120 mg; given in 3 divided doses...
per day) to achieve goal blood pressure response. All patients were advised to follow a no-added-salt diet.

The patients as a group excreted 181 mEq of sodium/day, following 2 to 4 weeks of placebo therapy (assessed by 24-hour urine collection). Mean sodium excretion for the group following 4 weeks of nifedipine monotherapy was 162 mEq of sodium/day. These data suggest that the patients as a group consumed from 3.7 to 4.1 g of dietary sodium/24 hr during the study period.

**Blood Pressure and Pulse Response to Therapy**

Mean blood pressure responses in the recumbent and upright position are shown in Table 1. Nineteen of 26 subjects (73%) achieved a goal blood pressure response with nifedipine monotherapy. There were no significant postural changes in blood pressure. Heart rate was not increased.

**Serum and Urine Electrolyte and Protein Excretion Response to Therapy**

There were no significant differences following 4 weeks of nifedipine monotherapy in the urinary excretion of sodium (end of placebo period, 148 ± 47 mEq/g creatinine; end of nifedipine therapy, 143 ± 60 mEq/g creatinine), potassium (end of placebo period, 52 ± 19 mEq/g creatinine; end of nifedipine therapy, 50 ± 17 mEq/g creatinine), or creatinine (end of placebo period, 1.22 ± 0.37 g; end of nifedipine therapy, 1.17 ± 0.40 g). Serum sodium and potassium concentrations were unchanged (end of placebo period, 135 ± 3 and 3.9 ± 0.2 mEq/L, respectively; end of nifedipine therapy, 136 ± 3 and 3.8 ± 0.3 mEq/L, respectively).

**Renal Function Response to Drug Therapy**

Individual data for GFR and ERPF for all subjects are shown in Figure 1. The mean data for all subjects are given in Table 2. There was a significant increase (+13.3%) in GFR (assessed by inulin or 99mTc-DTPA clearance) and in ERPF/renal blood flow (+19.6%/20.1%) for the total group following nifedipine monotherapy. The filtration fraction was unchanged. There was a 25.2% mean decrease in renal vascular resistance. There was no change in urinary albumin excretion.

**TABLE 1.** Systemic Hemodynamic Response to Nifedipine Monotherapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (4 wk)</th>
<th>Nifedipine (4 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recumbent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>159 ± 16</td>
<td>141 ± 9*</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>101 ± 6</td>
<td>88 ± 7*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>75 ± 9</td>
<td>78 ± 9</td>
</tr>
<tr>
<td><strong>Upright</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>149 ± 16</td>
<td>134 ± 11*</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>100 ± 9</td>
<td>86 ± 6*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>83 ± 8</td>
<td>85 ± 9</td>
</tr>
</tbody>
</table>

Values are means ± SD of 26 subjects.

* *p < 0.001, compared with placebo values.

**Table 2.** Renal Function and Hemodynamic Response to Nifedipine Monotherapy (All Subjects)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (4 wk)</th>
<th>Nifedipine (4 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>120 ± 8</td>
<td>106 ± 6*</td>
</tr>
<tr>
<td>Pcr (mg/dl)</td>
<td>1.0 ± 0.1</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>Ccr (ml/min/1.73 m²)</td>
<td>103 ± 21</td>
<td>107 ± 22</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²)†</td>
<td>90 ± 25</td>
<td>102 ± 30†</td>
</tr>
<tr>
<td>ERPF (ml/min/1.73 m²)†</td>
<td>358 ± 83</td>
<td>428 ± 96*</td>
</tr>
<tr>
<td>FF (%)†</td>
<td>25.5 ± 5.1</td>
<td>24.3 ± 5.9</td>
</tr>
<tr>
<td>RBF (ml/min/1.73 m²)†</td>
<td>835 ± 205</td>
<td>1003 ± 223*</td>
</tr>
<tr>
<td>RVR (dyne-sec-cm⁻²/ 1.73 m²)</td>
<td>11.9 ± 2.9</td>
<td>8.9 ± 2.1*</td>
</tr>
<tr>
<td>UAE (µg/min)</td>
<td>25.8 ± 7.0</td>
<td>24.1 ± 65.1UAE</td>
</tr>
</tbody>
</table>

Values are means ± SD of 26 subjects except as otherwise noted.

Pcr = plasma creatinine; Ccr = clearance of creatinine; GFR = glomerular filtration rate by either paired inulin or 99mTc-DTPA clearances; ERPF = effective renal plasma flow by p-aminohippurate clearance; FF = filtration fraction; RBF = renal blood flow; RVR = renal vascular resistance; UAE = urinary albumin excretion.

*p = 0.001, †p = 0.025, compared with placebo values.

n = 25; one subject's initial p-aminohippurate clearance was not technically valid due to an elevated plasma p-aminohippurate concentration.
and tachycardia. These patients were not included in the data analysis.

Discussion

Nifedipine monotherapy was effective in controlling blood pressure in essential hypertensive patients consuming an estimated 3.7 to 4.1 g of sodium/day. We found no clinically significant alterations in serum sodium or potassium concentrations. We did observe significant increases in GFR (+13%) and ERPF (+20%) and a significant decrease in renal vascular resistance (−25%). The filtration fraction and urinary albumin excretion were unchanged.

The subgroup of patients achieving goal blood pressure with nifedipine monotherapy demonstrated a 13% increase in GFR and a 19% increase in ERPF. Unexpectedly, the subgroup of patients not achieving a significant reduction in blood pressure demonstrated similar mean increases in GFR (+13%) and ERPF (+20%). Those essential hypertensive patients whose initial GFR was impaired (GFR ≤ 80 ml/min/1.73 m²) demonstrated an improvement in GFR (+18%) and ERPF (+23%) following nifedipine monotherapy. Those patients whose initial GFR was normal (GFR > 80 ml/min/1.73 m²) likewise demonstrated improvement in GFR (+11%) and ERPF (+18%) following nifedipine monotherapy. We have reported previously that essential hypertensive patients who have the most impaired renal function demonstrate the greatest renal response to calcium antagonism. Our results with nifedipine monotherapy are consistent with this prior observation.

Our renal function results with the short-term oral administration of nifedipine are similar to those reported by Klutsch et al. using intravenous nifedipine administration, and by Tsunoda et al., using a single 20-mg nifedipine capsule. However, they contrast with the results reported by Olivari et al. and Leonetti et al., using a single 10-mg oral dose of nifedipine, Guazzi et al., using oral nifedipine (10 mg q.i.d.) administration for 1 week, and Bruun et al., using a mean 51 mg/day oral dose of nifedipine for 12 weeks. The differing results may be related in part to the lower oral doses of nifedipine used in some of these studies or to the sensitivity of clearance techniques employed, or to both. The single injection technique used by Bruun et al. determine GFR (51Cr-EDTA) from samples of blood alone, using a compartmental analysis. Such a technique has not been found to be an adequate substitute for standard urinary clearance determinations when compared with inulin clearance. Also, to our knowledge our prospective evaluation of 26 patients is the largest number of patients studied, compared with all prior clinical trials assessing the renal response to nifedipine monotherapy.

Our short-term renal effects of nifedipine monotherapy are similar to those we have reported previously with the dihydropyridine calcium antagonist amlodipine. Indeed, the percent increases in GFR and ERPF with nifedipine monotherapy were identical to those
observed with short-term amlodipine monotherapy (+13% increase in GFR; +19% increase in ERPF). The ability of calcium channel antagonists to prevent an increase in cytosol-ionized calcium would be expected to decrease the sensitivity of the renal vasculature to both angiotensin II and norepinephrine. Several investigators have demonstrated that diltiazem, nifedipine, nitrendipine, and verapamil attenuate the intrarenal effects of exogenously administered angiotensin II and norepinephrine.\(^1\)\(^-\)\(^2\) Since the filtration fraction was unchanged in this study and in our previous studies with calcium antagonists,\(^3\)\(^-\)\(^4\) we believe the increase in GFR and ERPF may be related predominantly to a decrease in afferent arteriolar resistance. However, we cannot exclude the possibility of a reversal of the direct effect of angiotensin II or norepinephrine on the glomerulus (mesangium) or efferent arteriolar resistance, or both.

Our observation that the essential hypertensive patients, who were unresponsive to the systemic blood pressure-lowering effect of nifedipine, were responsive to the renal effects of nifedipine was not anticipated. There was no correlation between nifedipine's blood pressure-lowering effect and its renal effect (change in GFR vs change in MAP, \(r = 0.267, p > 0.1\); change in ERPF vs change in MAP, \(r = 0.08, p > 0.1\)). There appears to be dissociation between the systemic and renal effects of calcium antagonism.

We conclude that nifedipine is an effective antihypertensive drug when given as monotherapy for the treatment of mild to moderate hypertension. It was less well tolerated compared with other calcium antagonist monotherapies studied in our laboratory. Only 10 of the 19 patients achieving goal blood pressure elected to remain on a regimen of nifedipine monotherapy for prolonged blood pressure control. Short-term renal function, however, was improved. If calcium antagonism predominately decreases preglomerular (afferent) arteriolar resistance, without a decrease in postglomerular (efferent) arteriolar resistance, glomerular capillary pressure may increase, potentially accelerating hemodynamic glomerular injury.\(^18\)\(^-\)\(^21\) However, urinary albumin excretion, a marker of glomerular injury, was unchanged. If calcium antagonists can be demonstrated experimentally to reduce both preglomerular and postglomerular arteriolar resistance (i.e., to maintain a normal glomerular capillary pressure), they may be expected to provide long-term renal protection. Clearly, long-term clinical studies will be required to determine if these short-term renal responses to nifedipine monotherapy are sustained or have the potential to modify the clinical course of hypertensive nephrosclerosis.

Acknowledgments

The authors express their appreciation for the technical assistance of Richard Lumpkin and Evelyn Monzon and the secretarial skills of Jo Ann Snell.

References

Effect of nifedipine on renal function in patients with essential hypertension.
G P Reams, A Hamory, A Lau and J H Bauer

*Hypertension*. 1988;11:452-456
doi: 10.1161/01.HYP.11.5.452

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/11/5/452