Comparison of Two Calcium Blockers on Hemodynamics, Left Ventricular Mass, and Coronary Vasodilatory in Advanced Hypertension


Dihydropyridine and nondihydropyridine calcium channel blockers (CCB) differ in pharmacologic characteristics. Few clinical studies distinguish effects of CCB as monotherapy. We conducted a comprehensive comparison of two CCB on patients with moderate to severe hypertension. Thirty patients with pretreatment diastolic blood pressures $\geq 100$ mm Hg were randomly assigned to either nifedipine–GITS or verapamil-SR. Dose titration achieved a diastolic blood pressure of $\leq 95$ mm Hg or a decrease of $\geq 15$ mm Hg over 4 weeks. Clinic blood pressure (BP), 24-h ambulatory BP, exercise BP, left ventricular mass, systolic and diastolic function by echocardiography, and coronary flow reserve by split-dose thallium-201 imaging with adenosine were assessed at baseline, end of titration, 3 months and 6 months of treatment. Plasma renin activity, atrial natriuretic peptide, norepinephrine, and epinephrine were assayed. Both drugs caused similar reductions in clinic and 24-h ambulatory BP and similar reductions in left ventricular mass index. Compared to nifedipine–GITS, verapamil-SR produced a significantly lower resting and peak exercise heart rate. Nifedipine–GITS elicited a lower peak exercise systolic BP. At end titration nifedipine–GITS produced lower plasma atrial natriuretic peptide levels, no longer apparent by 6 months. Plasma norepinephrine was lower with verapamil-SR, also at end titration and at 3 months, but not at 6 months. Plasma epinephrine and plasma renin activity were unchanged by either drug. There was no difference for systolic or diastolic left ventricular function or coronary flow reserve between the two treatments. Once daily nifedipine–GITS and verapamil-SR are equally effective for reduction of arterial pressure in moderate to severe hypertension. Differences in their hemodynamic profiles and neuroendocrine responses are consistent with preclinical pharmacologic characteristics. The clinical implications of their similarities and differences remain to be fully evaluated in outcome studies. Am J Hypertens 2001;14:231–240 © 2001 American Journal of Hypertension, Ltd.

Key Words: Hypertension, calcium channel antagonists, hypertrophy, coronary microcirculation.

Received March 16, 2000. Accepted August 1, 2000.
From the Sections of Hypertension & Nuclear Cardiology (JAD, LRK, AG, AG, KM, RG, MJH, JM, RAP), The Zena and Michael A. Wiener Cardiovascular Institute, The Mount Sinai Medical Center, New York, New York; and Division of Cardiology (NC), Lenox Hill Hospital, New York, New York.

This research was supported by a grant from Pfizer Laboratories Inc. New York, NY.
Address correspondence and reprint requests to Dr. Joseph A. Diamond, Cardiovascular Institute, The Mount Sinai Medical Center, Box 1030, One Gustave L. Levy Place, New York, NY 10029-6574; e-mail: joseph.diamond@mssm.edu

The calcium channel blockers (CCB) nifedipine and verapamil have become widely used for treatment of systemic hypertension, either as single agents or in combination with other drug classes.¹ Both nifedipine and verapamil are “slow” calcium L-channel entry blockers, but differ from each other with regard to their sites of action in cardiac or vascular tissues. Previous pharmacologic studies have established that nifedipine (the prototype dihydropyridine) is predominantly a coronary and systemic vasodilator with minimal effects on myocardial conduction or contractile tissue, whereas verapamil (a phenylalkylamine) has negative cardiac chronotropic and inotropic effects and impairs AV nodal conduction. Either drug is effective as monotherapy for hypertension.² ³ However, there has been no direct comparison of these two agents with regard to many of their actions related to sustained effects on systemic hemodynamics and neuroendocrine systems. This study was designed to compare the
effects of these two distinct CCB as single drug treatment in moderate to severe hypertension on blood pressure (BP), heart rate (HR), rest and exercise hemodynamics, left ventricular (LV) mass, systolic and diastolic function, estimated coronary flow reserve (CFR), and several vasoactive hormones.

Methods
Entry Criteria
The study enrolled asymptomatic hypertensive patients referred with an average sitting diastolic blood pressure (DBP) ≥100 mm Hg, ≤130 mm Hg (either never treated or on ineffective antihypertensive medications). Patients were excluded from the study if they had a previous history of cardiac disease (ischemic or other), evidence of segmental wall motion abnormality on an echocardiogram, renal disease, neurologic disorder, insulin-dependent diabetes mellitus, secondary hypertension, substance abuse, obesity (>50% above ideal body weight), or a creatinine >2.0 mg/dL.

Entry and Placebo Phase
Antihypertensive medications (for subjects entering on therapy) were slowly withdrawn before entering the study. Upon entry, each patient was started on placebo. Blood pressures were confirmed after 2 weeks of treatment with placebo. During medication withdrawal and placebo periods, the patients were seen every second to third day for physical examination, BP determination, and evaluation for symptoms. Patients were removed from the study in the drug withdrawal/placebo phase and treated if the DBP exceeded 130 mm Hg, if it was <100 mm Hg on any visit, or if symptoms attributable to hypertension developed.

Randomization and Treatment Phase
After completion of the placebo phase, the patients were randomized to receive either 30 mg of nifedipine–GITS per day or 240 mg of verapamil-SR per day. All investigators and other persons involved with patient care or any other aspect of the study were completely blinded to assigned medication. A research nurse, unaware of clinical status of the subjects, dispensed medication and performed pill counts. After randomization, patients were seen on a weekly basis for the first month. Medication doses were increased to maintain DBP ≤95 mm Hg or to achieve at least ≥15 mm Hg decrease in DBP on the maximal recommended medication dose. The dose of nifedipine–GITS was increased by 30-mg increments to a maximum of 120 mg per day. The dose of verapamil-SR was increased by 120-mg increments to a maximum of 240 mg twice daily. Because the first dose increment for verapamil-SR introduced twice daily dosing (240 mg in the morning and 120 mg in the evening), all patients on nifedipine–GITS who were titrated above the starting dose received active medication in the morning and placebo in the evening. This was done to maintain proper blinding to medication. Treatment was maintained at that dose level for the remainder of the 6 months of the study. Patients who did not reach this goal by the end of the titration period were withdrawn from the study and treated with the appropriate antihypertensive regimen to achieve adequate BP control. During each patient visit, resting BP and HR were recorded after subjects were seated for 5 min and repeated two additional times, 3 min apart. The three readings were then averaged. The patient was instructed the day before these visits not to take the morning dose of medication until completion of the visit. Thus, measures were made during period of trough plasma drug levels.

While on placebo, patients underwent 24-h ambulatory BP monitoring, two-dimensional, M-mode, and Doppler echocardiography, bicycle exercise stress testing with gas exchange measurements, and split dose thallium-201 stress/rest perfusion imaging with adenosine-induced coronary vasodilatation. All tests with the exception of the latter were repeated after 1-month titration/treatment and after 3 and 6 months of treatment. The thallium-201 study was only performed after 1-month titration and after 6 months of treatment. No subject participated in any aerobic conditioning program before or during the study.

The protocol was approved before implementation by the Institutional Review Board of the Mount Sinai Medical Center, and informed consent was obtained from all subjects.

Blood Pressure
Monitoring was performed using the SpaceLabs 90202 or 90207 models (SpaceLabs, Redwood, WA). Subjects were monitored on a day chosen for typical weekly activity; most were employed in work outside their home. Recordings were made every 20 min from 6:00 AM to midnight and every 60 min from midnight to 6:00 AM. These times were arbitrarily programmed to define the day and nighttime intervals. There were no night shift workers in this study group. The methodology for ambulatory BP monitoring has been previously reported in detail.4

Exercise Testing
A symptom-limited graded bicycle ergometry test with simultaneous electrocardiogram and gas exchange measurements was performed. Each subject performed 2 min of unloaded exercise followed by increasing work loads, based on age and weight, of 10 to 30 W/min on an electronically braked cycle ergometer (Mijnhardt, St. Paul, MN). Incremental changes of workload were kept constant between placebo phase and treatment phase tests for each subject. Patients were exercised until exhaustion or until chest pain developed. Simultaneous 12-lead electrocardiographic monitoring (Case 12, Marquette, Milwaukee, WS) was performed and BP was recorded every minute by manual sphygmomanometry. Expired gas analysis was performed continuously during the test with a metabolic cart computer (2001 System, Medical Graphics Corp.,
Echocardiography

Determination of LV Mass and LV Systolic Function

Two-dimensional and two-dimensionally guided M-mode echocardiography were performed with an ATL Ultramark 6 scanner (Advanced Technology Laboratories, Inc, Bothell, WA) using a 2.5- or 3.5-MHz transducer according to methodology previously reported.5

To avoid underestimation of LV hypertrophy in obese subjects, LV mass was indexed for height to the 2.7 power.6 Left ventricular hypertrophy was defined as the 95th percentile or above based on gender-specific values of 52 g/m².7 for men, 47 g/m².7 for women based on mass indexed to height to the 2.7 power.7 As noted earlier, patients with regional wall motion abnormalities were excluded from the study. End-systolic stress was calculated according to previously described methods.8 Fractional shortening was directly calculated from the left ventricular internal measurements in systole and diastole.

Doppler Measures of Diastolic Function

Two-dimensionally guided pulsed Doppler interrogation of the LV inflow was measured from the apical two- or four-chamber view. Left ventricular inflow was interrogated between the mitral annulus and the leaflet tips, and recordings of the left ventricular inflow velocity profile were made at the point of maximal velocity of early filling.9 An average of three to five beats were measured from digitized recordings to obtain peak velocity of early LV filling (peak E), peak velocity of late LV filling (peak A), the ratio of late-to-early diastolic inflow (A/E ratio), isovolumetric relaxation time, and the diastolic filling period. An A/E ratio >1 was considered to be abnormal.9

Coronary Flow Reserve

Myocardial uptake measured by the radioactive tracer thallium-201 is related in a linear fashion to myocardial blood flow over a wide range of flows.10 Adenosine has been shown to safely and reliably produce maximal coronary vasodilatation in humans.11 Using these principles, we developed and validated in the canine model a noninvasive method of measuring CFR using split-dose thallium-201 stress/rest perfusion imaging with adenosine induced coronary vasodilatation.12 This technique has previously been described in detail, and has been applied in the assessment of CFR in patients with hypertension.13

Assays

While on placebo, all patients underwent routine blood chemistries, blood cell counts, and urinalysis. To determine the effects of these drugs on neurohormones, blood samples for plasma epinephrine, norepinephrine, and plasma renin activity (PRA) determinations were drawn from an indwelling forearm venous catheter after subjects had been supine for at least 30 min. The techniques used were previously described.14 As a surrogate measure of LV filling pressure, atrial natriuretic peptide (ANP) was assayed.2 Atrial natriuretic peptide was measured from extracted plasma by radioimmunoassay, as previously described.14

Statistical Analysis

Comparisons of the baseline characteristics, hemodynamic, exercise, echocardiographic, and coronary flow parameters between groups was done with the unpaired Student t test. Changes from baseline to treatment were analyzed with the paired Student’s t test. Differences in treatment groups over time were analyzed by repeated measurements analysis of variance using the GLM model with least squares means option (SAS Institute, Cary, NC). Linear regression analyses were performed to compare baseline LV mass with baseline CFR, and to compare both baseline and end treatment fractional shortening with corresponding end-systolic stress values. To assess LV filling, ANP and Doppler mitral early inflow patterns were compared using the Pearson correlation coefficient. A P value of ≤.05 was considered to be statistically significant.

Results

Patient Withdrawal or Removal

Seventy-four patients were considered for entry into this study. Twenty were excluded during the placebo phase for BP outside boundaries for continuing. Twenty-four failed to complete the trial, and thus were not included for analysis because of 1) withdrawal for symptomatic adverse effects, 2) lack of response, and 3) poor compliance. There was no significant difference in the number of discontinued patients between the two groups. Consequently, there were 30 subjects with sufficient data sets for inclusion in analyses. Eighty percent of randomized patients completed the protocol with effective control of BP and no side effects. The baseline characteristics of the study group are listed in Table 1.

Effect of Treatment on Blood Pressure and Heart Rate

By the end of the 4-week monotherapy titration period, and throughout the remaining 5 months of the study, verapamil-SR and nifedipine-GITS produced significant and similar reductions in both systolic and diastolic clinic BP, mean daytime ambulatory BP, and mean nighttime ambulatory BP (P ≤ .01) (Fig. 1A). There were signifi-
cant reductions in peak exercise systolic blood pressure (SBP) ($P \leq .03$) and peak exercise DBP ($P < .01$). However, the decrease in peak exercise SBP was significantly more with nifedipine–GITS than with verapamil-SR ($P = .03$).

Significant reductions in mean 24-h ambulatory HR and peak exercise HR were observed with verapamil-SR by 4 weeks of treatment. No such changes were seen with nifedipine–GITS (Fig. 1B).

Despite differences in peak exercise BP and HR, there were no significant differences in exercise double product, total exercise time, or maximal watts achieved at any phase of the study. The changes in resting and peak exercise BP and HR after 6 months of therapy are summarized in Table 2.

### Left Ventricular Mass

Baseline LV mass is shown in Table 1. Fig. 2 shows that by the end of the 6-month study period, there was a significant and sustained reduction of LV mass in both treatment groups.

### Coronary Flow Reserve

Coronary flow reserve ratios ranged at baseline from $1.5 \pm 0.28$ in the anterior wall to $1.8 \pm 0.27$ in the septum. Despite significant LV mass regression with both drugs, there was no significant change in CFR at any point of the study with either drug. Of note, before treatment, there was a significant inverse linear correlation between LV mass and CFR (Fig. 2), suggesting that CFR is most impaired in those with the largest LV mass. This correlation did not persist after initiation of antihypertensive therapy.

### LV Systolic and Diastolic Function

Fractional shortening did not change with either treatment group over the 6-month treatment period. The relation between fractional shortening and end-systolic stress did not change over the course of treatment, suggesting that LV mass regression with antihypertensive therapy did not adversely affect intrinsic LV contractility.

Mildly abnormal pretreatment Doppler values of diastolic function were observed in these patients. Baseline mitral inflow as measured by A/E ratio was $1.07 \pm 0.29$ ($1.02 \pm 0.19$ verapamil-SR and $1.11 \pm 0.36$ nifedipine–GITS). Isovolumetric relaxation time was mildly prolonged at $122 \pm 29$ msec ($117 \pm 23$ msec verapamil-SR and $128 \pm 33$ msec nifedipine–GITS). The normal range is 70 to 100 msec.$^{15,16}$ Diastolic filling time for these patients was $445 \pm 102$ msec ($458 \pm 118$ msec verapamil-SR and $434 \pm 87$ msec nifedipine–GITS). During the first 3 months of therapy, there was a mild decrease of A/E in both groups (normalization), with mean values $<1.0$. The change did not reach statistical significance, and by 6 months there were no significant changes in any measure of diastolic function.

### Plasma Hormones

Baseline ANP, epinephrine, norepinephrine, and supine PRA are listed in Table 1. As illustrated in Fig. 3, there was a significant decrease in ANP for patients taking nifedipine–GITS at 3 months of therapy. However, the difference was no longer significant by 6 months. There was a significant correlation between ANP and Doppler

---

### Table 1. Patient characteristics after 2 weeks of placebo (mean ± SE)

<table>
<thead>
<tr>
<th></th>
<th>Verapamil-SR ($n = 15$)</th>
<th>Nifedipine–GITS ($n = 15$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 ± 9</td>
<td>46 ± 4</td>
</tr>
<tr>
<td>Sex</td>
<td>10 men, 5 women</td>
<td>9 men, 6 women</td>
</tr>
<tr>
<td>Race</td>
<td>4 White, 4 Black, 7 Hispanic</td>
<td>0 White, 5 Black, 9 Hispanic, 1 Asian</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.4 ± 5</td>
<td>83.2 ± 7.3</td>
</tr>
<tr>
<td>Resting SBP/DBP (mm Hg)</td>
<td>174 ± 19/110 ± 12</td>
<td>167 ± 12/110 ± 8</td>
</tr>
<tr>
<td>Resting 24 hour HR (beats/min)</td>
<td>85 ± 9</td>
<td>84 ± 9</td>
</tr>
<tr>
<td>Anterior wall CFR (ratio)</td>
<td>1.48 ± 0.3</td>
<td>1.59 ± 0.3</td>
</tr>
<tr>
<td>LV Mass (g/m^2.7)*</td>
<td>53 ± 13</td>
<td>58 ± 23</td>
</tr>
<tr>
<td>Number with LVH†</td>
<td>7/15</td>
<td>6/15</td>
</tr>
<tr>
<td>Creatinine (mg/dL)‡</td>
<td>1.1 ± 0.4</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>Epinephrine (ng/mL)</td>
<td>29 ± 17</td>
<td>26 ± 21</td>
</tr>
<tr>
<td>Norepinephrine (ng/mL)</td>
<td>302 ± 185</td>
<td>340 ± 136</td>
</tr>
<tr>
<td>ANP (pg/mL)</td>
<td>25 ± 17</td>
<td>23 ± 10</td>
</tr>
<tr>
<td>PRA (ng/mL/min)</td>
<td>1.2 ± 1</td>
<td>1.0 ± 1</td>
</tr>
</tbody>
</table>

ANP = atrial natriuretic peptide; PRA = plasma renin activity (supine).

* LV mass indexed for height to the 2.7 power.
† LVH defined as ≥ the 95th percentile based on gender specific values of 52 gm/m^2.7 for men, 47 gm/m^2.7 for women based on mass indexed to height to the 2.7 power or 138 gm/m^2 for men, 95 gm/m^2 for women based on mass indexed to height squared. Only one man with LVH based on latter criteria.
‡ Range of creatinine was 0.8–1.3 mg/dL.
peak E (early diastolic inflow) at baseline (Pearson correlation coefficient = 0.5, \( P = .02 \)). This correlation did not persist after treatment for either drug group. There was no significant change in plasma epinephrine with either drug over the 6-month treatment period. There was a significant decrease in plasma norepinephrine for patients taking verapamil-SR for up to 3 months of treatment, with significant differences of plasma levels as compared to the nifedipine–GITS group \( (P < .05) \). However, by 6 months of antihypertensive therapy, there was a return in plasma norepinephrine to baseline levels in both groups (Fig. 3). Pretreatment supine PRA for these patients is listed in Table 1. There was no significant change in PRA with either drug over the 6-month treatment period.

**FIG. 1.** Comparison of verapamil-SR and nifedipine–GITS antihypertensive effects over 6 months of treatment with respect to 24-h blood pressures (BP) (A) and 24-h heart rate (B).
Discussion

Principal Findings

This study confirms that in the majority of randomized patients, both nifedipine-GITS and verapamil-SR are effective monotherapeutic agents (when titrated to high doses) for the control of moderate to severe hypertension. There was significant and sustained 24-h lowering of BP, and significant lowering of exercise BP with no reduction of exercise capacity. Verapamil-SR produced sustained and significantly greater reductions in both resting (24-h ambulatory) and peak exercise HR with significant early, although transient decrease in plasma norepinephrine. Nifedipine–GITS produced more consistent reduction in peak exercise BP. There was early but transient reduction in plasma ANP. Despite the observed differences in hemodynamics and neurohormonal assays, significant and similar regression of LV mass was noted with both agents. Nevertheless, there was no significant change in CFR with either treatment.

Resting and Exercise Hemodynamics

The lowering of HR observed with verapamil-SR may have important implications, particularly in light of the attention CCB have received regarding their influence on fatal and nonfatal myocardial infarctions. There is a growing body of evidence that HR is a powerful independent risk factor for cardiovascular morbidity and mortality. In the patient after myocardial infarction, HR lowering CCB, including verapamil, have been shown to prevent reinfarction and may be particularly beneficial in those who are also hypertensive. In addition to the

FIG. 2. Comparison of verapamil-SR and nifedipine-GITS effects on left ventricular (LV) mass over 6 months of treatment. By the end of the 4-week titration period, there were significant reductions in LV mass (indexed to height and height to the 2.7 power) with both drugs. Linear regression shows a significant inverse correlation between LV mass index and anterior wall coronary flow reserve (CFR) before starting antihypertensive therapy.
direct negative inotropic effect of verapamil, the rate-lowering effect may result in reduced oxygen demand, thus providing a β-blocker-like beneficial action in hypertensive patients who also have coronary artery disease.24

The study design required that the active drug be given twice daily for verapamil-SR, after initial titration, whereas nifedipine could only be given once daily (with placebo used in the evening so as to maintain the blind). This may imply an advantage of verapamil for evening and nighttime blood pressure. On the basis of the manufacturers’ data and other studies, verapamil-SR does not last as long as nifedipine XL and should be dosed twice daily if initial doses are not effective. Plasma drug concentrations of nifedipine XL increase gradually and reach a plateau at approximately 6 h after the first dose. For subsequent doses, relatively constant plasma concentrations at this plateau are maintained with minimal fluctuations over the 24-h dosing interval.25 This is not the case with the sustained release formulation of verapamil. Peak plasma concentrations of verapamil-SR occur approximately 5 h after administration. After repetitive dosing, the half-life ranges from 4.5 to 12 h.26

Both agents produced a significant reduction in peak exercise systolic and diastolic BP. However, reduction of peak exercise BP is more pronounced with nifedipine–GITS than with verapamil-SR. Because the pathophysiology underlying myocardial infarction triggered by heavy physical exertion may be related to BP changes with exertion, lowering exercise BP may be very beneficial.27 A significant reduction of exercise BP occurred by 4 weeks
of antihypertensive therapy and was maintained throughout the 6-month treatment period. Although other studies have shown effective control of exercise BP after 1 year of therapy,28,29 our study demonstrates that maximal effect may occur as early as 4 weeks into therapy with nifedipine–GITS and verapamil-SR.

**LV Mass Regression and Systolic Function**

In addition to the significant hemodynamic improvement, both drugs produced significant regression of LV mass. Left ventricular mass decreased by 15% in patients taking verapamil-SR and 11% in patients taking nifedipine–GITS. This is comparable to the extent of LV mass regression seen after an average of 25 weeks of antihypertensive therapy with angiotensin converting enzyme inhibitors (13.3%), and CCB (9.3%) noted in a comprehensive metaanalysis of double-blind, randomized controlled studies.30

It has not been clearly established whether LV mass regression promotes improved systolic and diastolic function. In this study, there was no significant change in fractional shortening. This is likely because LV systolic function was normal in these patients at the outset of the study. The relation between fractional shortening and end-systolic stress did not change suggesting that intrinsic contractility remained stable during the course of the study. This finding is in accord with our previous study.2

**LV Diastolic Function**

Diastolic function was near-normal at baseline and did not change significantly despite reduction in LV mass. These data are similar to previous studies of hypertensive patients with near-normal baseline diastolic function.31,32

**Coronary Flow Reserve**

Despite effective lowering of 24-h BP and regression of LV mass, there was no observable change in CFR. This is consistent with much of the literature. In a spontaneously hypertensive rat model of renovascular hypertension, long-term treatment with nitrendipine was found to lower BP, reduce LV mass, and increase resting coronary blood flow. However, CFR did not increase.33 A study by Merrill et al34 showed that the increase in left anterior descending coronary artery flow produced in the canine heart with intracoronary infusion of adenosine or by intrinsic reactive hyperemia from transient left anterior descending coronary artery occlusion was significantly attenuated by the concomitant administration of nifedipine. Intravenous administration of diltiazem in humans produces epicardial coronary artery dilatation and increased epicardial coronary blood flow; nevertheless, CFR decreased.35–37 In another study36 of hypertensive patients with microvascular angina and abnormal baseline CFR, there was improvement in CFR after 12 months of treatment with either diltiazem or isradipine.

**Neurohormonal Effects**

Over the 6-month treatment period, there was no detectable activation of either the sympathetic or the renin system in patients on either drug regimen. The stable catecholamine level is probably a reflection of the pharmacologic profile of both long-acting formulations, which produce relatively stable plasma levels over a 24-h period.39–41 Thus, there are relatively minor fluctuations in BP and hence little or no reflex sympathetic activation. This is in contrast to the short-acting formulations, which may have adverse effects in patients with coronary artery disease because of their stimulatory effects on the sympathetic nervous system by way of systemic catecholamine levels. However, we recognize that there was a large standard deviation in the nifedipine–GITS treatment group with respect to heart rate (a surrogate marker of sympathetic activation). Therefore, we may not have had the power to detect a significant change in treatment-dependent neurohumoral activation. Our trial is similar to other clinical trials of CCB in showing little effect on PRA.42,43

By the end of the 6-month treatment period, there was

---

**Table 2. Comparison of the change in BP and HR after a 6-month treatment period, verapamil-SR versus nifedipine–GITS**

<table>
<thead>
<tr>
<th></th>
<th>Verapamil-SR</th>
<th>Nifedipine-GITS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood pressure (mm Hg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ clinic BP</td>
<td>−25 ± 6/−17 ± 3</td>
<td>−21 ± 4/−15 ± 2</td>
</tr>
<tr>
<td>Δ 24 hour BP</td>
<td>−16 ± 3/−13 ± 2</td>
<td>−21 ± 2/−15 ± 2</td>
</tr>
<tr>
<td>Δ day BP</td>
<td>−18 ± 3/−14 ± 2</td>
<td>−22 ± 2/−16 ± 2</td>
</tr>
<tr>
<td>Δ night BP</td>
<td>−11 ± 3/−10 ± 2</td>
<td>−16 ± 3/−10 ± 2</td>
</tr>
<tr>
<td>Δ peak exercise BP†</td>
<td>−15 ± 5/−15 ± 6</td>
<td>−33 ± 6/−14 ± 6*</td>
</tr>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ 24 hour HR</td>
<td>−7 ± 6</td>
<td>+1 ± 10*</td>
</tr>
<tr>
<td>Δ day HR</td>
<td>−8 ± 6</td>
<td>+1 ± 12*</td>
</tr>
<tr>
<td>Δ night HR</td>
<td>−3 ± 8</td>
<td>+1 ± 8*</td>
</tr>
<tr>
<td>Δ peak exercise HR†</td>
<td>−17 ± 12</td>
<td>+0.3 ± 11**</td>
</tr>
</tbody>
</table>

* P < .03, ** P < .0004 for nifedipine–GITS versus verapamil-SR.
† There was no significant difference in double product, total exercise time, or maximal watts achieved for the patient groups.
no significant overall change in plasma ANP for either drug from the baseline level. Unlike a previous study, this relatively young group of hypertensive patients did not have significantly elevated baseline ANP because they were less likely to have developed the chronic manifestations of severe hypertension that lead to elevated ANP (eg, congestive heart failure).

In conclusion, detailed and comprehensive comparison of two different types of calcium channel antagonists nifedipine–GITS and verapamil-SR revealed clinical differences entirely consistent with previously defined pharmacologic characteristics. In a significant number of randomized patients with moderate to severe hypertension, they both produced effective, sustained 24-h lowering of BP. A significantly lower peak exercise BP was achieved with nifedipine–GITS. However, 24-h ambulatory HR and peak exercise HR were lower with verapamil-SR. Despite these hemodynamic differences, there was significant and equivalent regression of LV mass with both agents. However, there was no concurrent change in CFR. With long-term use, there were no significant neurohormonal changes. The observed hemodynamic differences may have clinical relevance for long-term outcomes.

Acknowledgments

We acknowledge the nurse coordinators for this study, Maria Ardeljan, RN, and Arlene Travis, RN.

References


