Effects of Chronic Calcium Channel Blockade on Sympathetic Nerve Activity in Hypertension

Christian Binggeli, Roberto Corti, Isabella Sudano, Thomas F. Luscher, Georg Noll

Abstract—The sympathetic nervous system (SNS) is an important regulator of the circulation. Its activity is increased in hypertension and heart failure and adversely affects prognosis. Although certain drugs inhibit SNS, dihydropyridine calcium antagonists may stimulate the system. Phenylalkylamine calcium antagonists such as verapamil have a different pharmacological profile. We therefore tested the hypothesis of whether amlodipine, nifedipine, or verapamil differs in the effects on muscle sympathetic nerve activity (MSA). Forty-three patients (31 men, 12 women) with mild to moderate hypertension were randomly assigned to 1 drug for 8 weeks. Blood pressure, heart rate, and MSA (by microneurography) were measured at baseline and after 8 weeks of treatment. All calcium antagonists led to a similar decrease in blood pressure of 5.0±1.5 to 6.4±1.4 mm Hg at 8 weeks (P<0.001 versus baseline). There were no significant differences in MSA between groups. With amlodipine, MSA averaged 49±3 bursts/min (3 versus baseline); with nifedipine, 48±3 bursts/min (2 versus baseline); and with verapamil, 49±2 bursts/min (all, P=NS). With verapamil, norepinephrine decreased by 4% but tended to increase by about one third with amlodipine or nifedipine (P=NS). Thus, in hypertension slow release forms of verapamil, nifedipine, and amlodipine exert comparable antihypertensive effects and do not change MSA, although there was a trend toward decreased MSA and plasma norepinephrine with verapamil. (Hypertension. 2002;39:892-896.)

Key Words: sympathetic nervous system ■ calcium antagonists

The sympathetic nervous system is an important regulator of cardiovascular homeostasis. Its basal activity is determined by genetic factors, physical activity, and drugs. Sympathetic nerve activity is stimulated by mental stress, cold,1 pain, exercise, and certain disease states. Indeed, essential hypertension2 and particularly accelerated hypertension3 go along with sympathetic activation. As offspring of hypertensive parents exhibit an exaggerated response of muscle sympathetic activity to mental stress,4 the system may be involved in the development of hypertension. The activity of the sympathetic nervous system also is an important determinant of survival. Indeed, in normotensive subjects higher heart rates are associated with a poorer prognosis compared with that of subjects with lower heart rates.5 In heart failure that is associated with markedly increased sympathetic activity in the periphery,6 plasma catecholamines are inversely related to survival.7

Given the regulatory and prognostic importance of the sympathetic nervous system in patients, pharmacotherapy of hypertension and heart failure should aim at reducing its activity. Indeed, it is likely that the prognostic benefits of β-blockers in hypertension, after myocardial infarction, and in heart failure are related to their sympatholytic effects. The effects of calcium antagonists on the sympathetic nervous system remain unclear. When given acutely, both short-acting8,9 and long-acting nifedipine9 activate the sympathetic nervous system, and this could explain the increased morbidity and mortality observed in some trials.10,11 Other types of calcium antagonists such as verapamil might differ from the dihydropyridines, as they do lower heart rate and may also reduce peripheral sympathetic activity.12 However, the effects of calcium antagonists on the sympathetic nervous system during chronic antihypertensive therapy are unknown.

We therefore compared in a prospective, randomized, double-blind study the effects of long-acting verapamil with 2 long-acting dihydropyridines (ie, slow release nifedipine and amlodipine) on the activity of the sympathetic nervous system in patients with essential hypertension.

Methods

Patients

Forty-five patients (31 men, 14 women; all white) with mild to moderate hypertension were initially included. They were screened in the University Hospital, Zurich, Switzerland. The patients were included according to specific inclusion and exclusion criteria. Patients treated with concomitant antihypertensives and those with secondary hypertension, heart failure, and pulmonary or hepatic disease were excluded. All antihypertensives were stopped before screening. All patients entered a placebo phase of 14 days. At the end of the placebo phase, sitting office diastolic blood pressure of 95 to 114 mm Hg was confirmed (Figure 1). Concomitant medication
Experimental Protocol

Antihypertensive drugs were withdrawn at least 5 half-lives before screening. Muscle sympathetic nerve activity (MSA) was measured at the end of a 14-day single-blinded placebo run-in, after confirmation of arterial hypertension and after 8 weeks of double-blinded active treatment. After successful determination of MSA, active treatment started. After 4 weeks, the dose was doubled if diastolic ambulatory blood pressure was ≥90 mmHg (Figure 1). After 8 weeks of treatment, MSA was measured again. All measurements were made at trough. All subjects were studied under the same conditions, ie, in the morning, after fasting, between 9:00 and 11:00 (verapamil) and between 15:00 and 17:00 (amlodipine and nifedipine). All measurements were performed twice, with an interval of 1 minute. If there were more than 20% changes in the electrode position occurred, the experiment was stopped, and the results were discarded.

Hormones and Drug Levels

Plasma norepinephrine and epinephrine were measured using high-performance liquid chromatography. Plasma levels of amlodipine, nifedipine, and verapamil were determined after placebo run-in and at the end of active treatment.

Drugs

Verapamil SR (240 mg), slow-release nifedipine (40 mg), amlodipine (5 mg), and identical placebo capsules were provided by Knoll AG (Ludwigshafen, Germany). The intake of the study medication was in the morning and in the evening throughout the study. Administration of the drugs was twice a day, ie, active drug in the morning and placebo in the evening for verapamil SR and amlodipine, and active drug in the morning and in the evening for nifedipine.

Data Analysis and Statistics

MSA signals were evaluated with the assistance of a program written in Matlab (The Mathworks Inc). The program detects the time of a burst, the amplitude, and the area under the curve. The parameters are given as mean ± values of 1 minute.

The primary parameter of efficacy (MSA) was analyzed using a repeated-measurement model with the factors treatment (verapamil SR, amlodipine, nifedipine), visit, and time of measurement. The tests are 2-sided with an α-correction according Bonferroni-Holm to keep a global-α of 0.05. Secondary endpoints were supine diastolic blood pressure, supine heart rate, and catecholamines. Results are given as mean±SEM.

Results

Demographics

The 3 treatment groups were balanced with respect to age, gender, race, height, and weight. Overall, age at study-entry ranged from 42 to 75 years, with a mean of 58±9 years. Thirty-one patients (69%) were male, and all were white. Body mass index ranged from 20 to 39, with a mean of 27±4 (Table). Two patients (one of the amlodipine group and one of the nifedipine group) dropped out during treatment because of side effects (rash).

Blood Pressure and Heart Rate

Baseline diastolic blood pressure values at the end of the run-in period, pre-CPT, were similar in all groups and averaged 93±2.0 mm Hg with amlodipine, 92.7±2.6 mm Hg with nifedipine, and 97.1±2.2 mm Hg with verapamil. All calcium antagonists led to a similar decrease in blood pressure at 8 weeks. The overall blood pressure reduction (mean of rest and CPT) after treatment averaged −9.5±1.9 mm Hg with amlodipine, −8.2±1.8 mm Hg with nifedipine, and −3.2±1.9 mm Hg with verapamil (Figure 2, top; P=NS). The antihypertensive effect of amlodipine and nifedipine at rest was not significantly better than that of verapamil (verapamil−amlodipine=−2.0 mm Hg; 97.5% confidence interval [CI], −9.1 to 5.0; P=NS. Verapamil−nifedipine=−1.3 mm Hg; 97.5% CI, −8.2 to 5.7; P=NS). However, during CPT amlodipine (verapamil−amlodipine=−10.6 mm Hg; 97.5% CI, −17.7 to −3.4; P=0.001 versus verapamil) and nifedipine (verapamil−nifedipine=−8.7 mm Hg; 97.5% CI, −15.6 to −1.7; P=0.006) were significantly more effective than was verapamil. The CPT-induced increase was thus significantly less pronounced with amlodipine (P=0.01 versus verapamil) and nifedipine (P=0.02 versus verapamil). Supine diastolic blood pressure was more markedly reduced at rest than during CPT, independent of treatment (at rest, −9.3 mm Hg; during stress, −4.6 mm Hg; P=0.008) (Figure 2, bottom).

Resting systolic blood pressure in untreated patients at baseline averaged 165.4±5.6 mm Hg (amlodipine),
Baseline Patient Characteristics at Study Entry

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Amlodipine (n=14)</th>
<th>Nifedipine (n=15)</th>
<th>Verapamil SR (n=14)</th>
<th>Overall (n=43)</th>
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<td>Age, y</td>
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<td>Weight, kg</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
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<td>48.0±2.8</td>
<td>49.3±2.1</td>
<td>...</td>
</tr>
</tbody>
</table>

Values are n or mean±SEM. Values in parenthesis are the range.

163.1±5.5 mm Hg (nifedipine), and 169.4±5.2 mm Hg (verapamil). After 8 weeks of treatment, it was reduced in all groups by 9.1 (nifedipine) to 16.0 mm Hg (amlodipine); P=NS among groups.

Resting heart rate at the end of the run-in period was similar in all groups and averaged 65.1±2.4 bpm with amlodipine, 67.3±3.6 bpm with nifedipine, and 61.4±1.9 bpm with verapamil (P=NS). The overall heart rate reduction (mean of rest and CPT) averaged −3.3±1.4 bpm in the amlodipine group, −0.7±1.4 bpm in the nifedipine group, and −1.7±1.4 bpm in the verapamil group; P=NS among groups. Reductions were greater before CPT compared with during CPT, independent of treatment (P=0.02 versus pre-CPT).

**Muscle Sympathetic Nerve Activity**

Resting MSA averaged 48.8±3.1 bursts/min in the amlodipine group (3.2 bursts/min after treatment), 48±2.8 bursts/min in the nifedipine group (2.0 bursts/min after treatment), and 49.3±2.2 bursts/min in the verapamil group (−0.9 bursts/min after treatment) (Figure 3, top). The overall change of MSA (bursts per minute, mean of rest and CPT) averaged 2.7±2.9 bursts/min with amlodipine, 3.4±2.8 bursts/min with nifedipine, and 0.1±2.9 bursts/min with verapamil group (P=NS versus baseline and among groups) and tended to be less in the verapamil group. Chronic treatment with amlodipine, nifedipine, and verapamil had no effect on resting MSA (verapamil−amlodipine=3.4 bursts/min; 97.5% CI, −6.4 to 13.7; P=NS. Verapamil−nifedipine=1.8 bursts/min; 97.5% CI, −8.1 to 11.7; P=NS) (Figure 3, bottom). The differences in bursts per minute were greater before CPT compared with during CPT (P<0.001 versus pre-CPT). The CPT increased MSA, independent of treatment (P<0.001), but there were no statistically significant differences between treatment groups before or during CPT, or for the change from pre-CPT to during CPT. The results were consistent for the analysis, including diastolic blood pressure as a covariate, because of slight baseline differences between the treatment groups.

For MSA (bursts/100 heart beats), there were no statistically significant treatment, time, or treatment-by-time inter-

**Figure 2. Effects of amlodipine, nifedipine, and verapamil SR on diastolic blood pressure (top). Treatment (verapamil) minus comparators (nifedipine/amlodipine) at rest and during CPT are shown as mean with 97.5% CI (bottom). Diastolic blood pressure was more markedly reduced at rest than during CPT (SP=0.008). The increase during CPT was less attenuated with verapamil than with the comparators (P=0.001 and P=0.006 vs verapamil, respectively).**
action effects. For MSA total activity, there was a statistically
significant time effect, with a greater increase during the cold
pressor test than at rest (ratio of visit 4 to visit 2: at rest, 0.99;
during cold pressor test, 1.45; corresponding to a 1% decrease
at baseline and a 45% increase during CPT). There were no
differences between the treatment groups.

Catecholamines
Resting norepinephrine plasma level decreased in the verap-
amil group from visit 2 (23.4±2.1 ng/dL) to visit 4 (21.6±2.4
ng/dL) compared with increases in the amlodipine (17.2±2.1
ng/dL to 25.3±3.2 ng/dL) and nifedipine (20.3±2.2 ng/dL to
27.1±2.7 ng/dL) groups (Figure 4). There was some evidence
of an overall treatment effect (averaged over rest and CPT) in
the analysis of norepinephrine with the verapamil group, with
the verapamil group decreasing from visit 2 to visit 4
(P=0.09 for treatment). There were no statistically signifi-
cant treatment, time, or treatment-by-time interaction effects
in the analysis of epinephrine.

Discussion
The present study demonstrates that in hypertensive patients,
the currently used slow release forms of verapamil, nifedi-
pine, and amlodipine do not change MSA and have compa-
rable antihypertensive effects. Although there was a trend
toward a decreased sympathetic activity as measured directly
by microneurography and by determination of plasma nor-
epinephrine during therapy with verapamil, this did not reach
statistical significance.

Previous studies in normotensive subjects have shown that
a single dose of short- and long-acting nifedipine leads to
increased sympathetic activity.9 Indeed, when given acutely,
both formulations of nifedipine markedly stimulated MSA,
whereas only short-acting nifedipine increased heart rate.
This observation obtained under acute conditions in subjects
with normal blood pressure could not be confirmed in this
chronic study in hypertensive patients. However, it cannot be
excluded that there might be an effect on sympathetic activity
during peak drug plasma levels, because all measurements in
the present study were made at trough. Kleinbloesem et al15
have demonstrated that it is the rate of administration of
nifedipine that determines the reflex tachycardia rather than
the duration of action.

As these acute effects of nifedipine are probably mediated
by the baroreflex, it appears that during prolonged antihyper-
tensive therapy baroreflex sensitivity and in turn the activity
of the sympathetic nervous system is reset in spite of
continued vasodilation induced by the calcium antagonists.
Amlodipine was thought to cause less stimulation of the
sympathetic nervous system than did nifedipine because of its
very long half-life; however, we could not observe any
difference to nifedipine, although—because of blinding is-
issues—we used the older slow-release tablet rather than the
new large gastrointestinal therapeutic system. In concordance
with our study, amlodipine did not increase MSA in another
study in patients with mild heart failure, but the drug also did
not reduce blood pressure under these conditions.16 In con-
trast, in patients with chronic renal failure of different causes,
amlodipine when given chronically decreased blood pressure but increased MSA.\textsuperscript{17} However, this was an open study enrolling patients with a different disease.

There is indirect evidence that the phenylalkylamine calcium antagonist verapamil may not stimulate sympathetic activity or even decrease it.\textsuperscript{18} Indeed, in a study involving 15 patients with essential hypertension, plasma levels of norepinephrine and chromogranin A (an indicator of catecholamine release-rate from prejunctional granules\textsuperscript{19}) were reduced during therapy with verapamil SR after 4 weeks; however, MSA was not measured in this study.\textsuperscript{12} In our study, MSA did not decrease during verapamil therapy, although there was a trend in favor of this calcium antagonist, particularly when compared with amlodipine and nifedipine. As in the previous study, there was some treatment effect on norepinephrine in the verapamil group only, with a small decrease of norepinephrine levels from visit 2 to visit 4, whereas the levels did not decrease during verapamil therapy, although there was a small decrease of norepinephrine levels from visit 2 to visit 4, whereas the levels increased in the amlodipine and nifedipine groups. These results are in line with those of a previous study\textsuperscript{20} using amlodipine and nifedipine slow release in hypertensives, in which the investigators found significantly higher levels of plasma norepinephrine after 6 weeks of treatment. However, our study is the first to compare verapamil with 2 dihydropyridines in a prospective double-blind fashion using both nerve traffic and the circulating levels of the adrenergic neurotransmitter as an endpoint.

Thus, in hypertension, slow release forms of verapamil, nifedipine, and amlodipine do not change MSA and have comparable antihypertensive effects. It is therefore unlikely that calcium antagonists exert harm through activation of the sympathetic nervous system. Indeed, the initially suspected negative effects of the drugs on prognosis suggested by a case-control study\textsuperscript{21} and a meta-analysis\textsuperscript{11} has not been confirmed in more recent trials.\textsuperscript{22–24}

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