Short- Versus Long-Term Effects of Different Dihydropyridines on Sympathetic and Baroreflex Function in Hypertension

Guido Grassi, Gino Seravalle, Carlo Turri, Gian Battista Bolla, Giuseppe Mancia

Abstract—Antihypertensive treatment with dihydropyridines may be accompanied by sympathetic activation. Data on whether this is common to all compounds and similar in the various phases of treatment are not univocal, however. In 28 untreated essential hypertensives (age, 56.4±1.8 years; mean±SEM) finger blood pressure (BP, Finapres), heart rate (HR, ECG), plasma norepinephrine (NE, high-performance liquid chromatography), and muscle sympathetic nerve traffic (MSNA, microneurography) were measured at rest and during baroreceptor manipulation (vasoactive drugs) in the placebo run-in period and after randomization to double-blind acute and chronic (8 weeks) felodipine (10 mg/d, n=14) or lercanidipine (10 mg/d, n=14). Acute administration of both drugs induced pronounced BP reductions and marked increases in HR, NE, and MSNA. After 8 weeks of treatment, BP reductions were similar to those observed after acute administration, whereas HR, NE, and MSNA responses were markedly attenuated (−7%, −32%, and −14%, respectively; P<0.05). There was a small residual increase in sympathetic activity in the felodipine group, whereas in the lercanidipine group, all adrenergic markers returned to baseline values. Baroreflex control of HR and MSNA was markedly impaired (−42% and −48%, respectively) after acute drug administration, with a recovery and complete resetting during chronic treatment. Thus, the sympathoexcitation induced by 2 different dihydropyridines is largely limited to the acute administration. The 2 drugs have, nevertheless, a different chronic sympathetic effect, indicating that dihydropyridines do not homogeneously affect this function. The acute sympathoexcitation, but not the small between-drugs differential chronic adrenergic effect, is accounted for by baroreflex impairment. (Hypertension. 2003; 41:558-562.)

Key Words: autonomic nervous system ■ sympathetic nervous system ■ baroreflex ■ calcium ■ hypertension, essential

Several studies have shown that the hyperadrenergic state characterizing essential hypertension (1) favors the development and progression of the hypertensive state,1-7 (2) promotes and accelerates the occurrence of the hypertension-related cardiac and vascular damage,5-9 and (3) adversely modulates metabolic cardiovascular risk factors, including insulin resistance.5-5,7,10 This implies that antihypertensive treatment should be based on drugs that are capable of not only effectively reducing the elevated blood pressure (BP) but also avoiding the neuroadrenergic activation that may be reflexly triggered by the BP-lowering response.6-8,10-12

The effect of calcium antagonists of the dihydropyridine class on sympathetic cardiovascular drive has been investigated in a number of studies that have produced, however, different results (ie, an increase, no change, or even a decrease in sympathetic activity).13-20 This could be due to the different pharmacokinetic and/or pharmacodynamic properties of the drugs examined.21 It could also be accounted for, however, by the different characteristics of the studies. For example, (1) data were collected during the acute BP decrease induced by a single dose of the drug, ie, when a sympathetic activation reflexly triggered by baroreceptor unloading can hardly be avoided, no matter which drug is employed;22-24 (2) recruitment was limited to conditions in which the BP decrease induced by dihydropyridine drugs can be small or negligible, eg, a normotensive or a congestive heart failure state;18,25,26 or (3) the change in sympathetic cardiovascular drive was quantified by fallible indices such as plasma norepinephrine (NE) and heart rate (HR),27-30 particularly in conditions such as congestive heart failure, in which changes in the tissue clearance of the adrenergic neurotransmitter and loss of vagal tone, respectively, may be heavily involved.31,32

In the present study, we examined the effects of 2 dihydropyridines on sympathetic cardiovascular drive in an ex-
perimental setting that avoided some of the previous limitations: (1) sympathetic cardiovascular drive was assessed not only via plasma NE but also via direct quantification of efferent postganglionic muscle sympathetic nerve traffic (MSNA); (2) patients were studied if they had a chronic BP elevation and the drugs employed induced a clearcut BP fall; and (3) the sympathetic responses were examined both after acute and chronic administration of the drugs. The study also assessed baroreflex-sympathetic modulation to examine whether any sympathoexcitatory effect could be due to a drug-induced impairment of this key modulator of neuroadrenergic drive.5–7,32

Methods

Study Population

The study population consisted of 44 men with never-treated or moderate essential hypertensive, characterized by (1) a diastolic BP between 95 and 105 mm Hg at repeated sphygmomanometric measurements, (2) no history and no physical or laboratory evidence of cardiovascular disease or major target organ damage, and (3) no major concomitant noncardiovascular diseases. However, because of the inability to obtain stable MSNA in all experimental sessions (see below), the study was successfully completed in 28 patients. All patients were in sinus rhythm, and none was a cigarette smoker or had a body mass index >25 kg/m². The protocol of the study was approved by the ethics committee of our institution. The patients agreed to participate in the study after explanation of its nature and purpose.

Measurements

The methodological details of the procedures we used to assess sphygmomanometric and beat-to-beat (Finapres 2300, Ohmeda), HR, respiration rate (pneumotachograph), MSNA (microneurography, and venous NE (high-performance liquid chromatography) have been described in previous reports.12–14,26–29,33 With the exception of sphygmomanometric BP and NE, all variables were displayed on a thermic paper on an ink polygraph (Gould 3800). Baroreceptor modulation of MSNA and HR was assessed by intravenous infusion of vasoactive drugs.34 Briefly, phenylephrine was incrementally infused through the cannula placed in an antecubital vein at 0.5 and 1.0 μg·kg⁻¹·min⁻¹ to progressively increase mean BP (diastolic BP plus one third of pulse pressure) and, thus, stimulate arterial baroreceptors. Nitroprusside was also incrementally infused at 0.5 and 1.1 μg·kg⁻¹·min⁻¹ to progressively reduce mean BP and, thus, deactivate arterial baroreceptors. Both infusions were maintained for 10 minutes, each step lasting 5 minutes. The drug initially infused was followed by the second one, after a recovery time of 45 minutes. Mean BP, MSNA, and HR were averaged for 10 baseline minutes before infusion and for 5 minutes of each step. Baroreceptor modulation of MSNA was estimated by calculating the absolute changes in sympathetic bursts per minute and the percentage of changes in integrated sympathetic activity (sympathetic bursts amplitude × number of bursts per minute, expressed in arbitrary units) associated with changes in mean finger BP induced by each dose of phenylephrine and nitroprusside.

Protocol and Data Analysis

After recruitment, patients entered a 1-week run-in placebo period. The study proper consisted of 3 identical experimental sessions within a randomized double-blind design. In the first session, patients were taken to the laboratory in the afternoon after a light morning breakfast. They were placed supine and fitted with the various measuring devices. After 30 minutes, the venous blood sample was obtained, and BP was measured 3 times by a mercury sphygmomanometer, the values being averaged. Finger BP, HR, MSNA, and respiration rate were then measured continuously over a 10-minute baseline period, the stepwise infusion of one vasoactive drug, a second 10-minute baseline period, and the stepwise infusion of the second vasoactive drug. In half of the patients, the first drug to be infused was phenylephrine, whereas in remaining patients, it was nitroprusside. The patients were then discharged from the laboratory and randomized to take an oral dose of felodipine (10 mg, 14 patients; age, 56.1±2.4 years) or lercanidipine (10 mg, 14 patients; age, 56.9±2.3 years) after acute (dotted bars) administration of either felodipine or lercanidipine. Data are mean±SEM, *P<0.05, **P<0.01, between values obtained in the 3 conditions.

Figure 1. Bar graphs showing sphygmomanometric (sphygmo) and finger systolic (S) and diastolic (D) BP, HR, plasma NE, and MSNA (expressed as number of bursts per minute and as number of bursts corrected for HR) values in the placebo run-in period (open bars) and after acute (dotted bars) and chronic (dashed bars) administration of either felodipine or lercanidipine. Data are mean±SEM. *P<0.05, **P<0.01, between values obtained in the 3 conditions.

Results

Baseline Values

As shown in Figure 1, at the end of the run-in placebo period systolic BP, diastolic BP, HR, plasma NE, and MSNA were superimposable in the felodipine and the lercanidipine groups. When acutely administered, both felodipine and
lercanidipine induced marked sphygmomanometric and finger systolic and diastolic BP reductions, which were accompanied by a marked increase in HR, plasma NE, and MSNA, the magnitude of all changes being superimposable in the 2 groups. After 8 weeks of treatment, the BP reductions were similar to those seen after acute administration, whereas the increase in HR, plasma NE, and MSNA was in both groups markedly and significantly attenuated. Although in the felodipine-treated group HR, NE, and MSNA values remained significantly higher, in the lercanidipine-treated group, they all returned to the placebo run-in values.

Baroreflex Responses
Figure 2 shows the results obtained by baroreceptor stimulation and deactivation through vasoactive drugs infusion. At the end of the run-in placebo period HR (bpm) and MSNA (percentage of integrated activity and bursts number per minute) were (1) progressively reduced when mean finger BP was progressively increased by phenylephrine and (2) progressively increased when mean finger BP was progressively reduced by nitroprusside. The HR and MSNA responses to baroreceptor stimulation and deactivation were attenuated to a similarly marked degree after the acute administration of felodipine or lercanidipine. However, after the 8 weeks of treatment, they recovered and in both groups became almost superimposable to those seen in the run-in placebo period condition.

Figure 3 shows the baroreflex curves as absolute HR and MSNA values in response to absolute mean BP values before and during maximal baroreceptor stimulation and deactivation. Compared with the run-in placebo period, the curves showed not only a flattening but also an upward shift after acute administration of either felodipine or lercanidipine. The shift disappeared after 8-week administration of the 2 drugs when the curves became parallel to those seen in the run-in placebo period.

Discussion
The present study shows that, when in hypertensive patients, BP is acutely reduced to the same degree by a single oral dose of felodipine or lercanidipine, sympathetic activity undergoes a marked increase. It also shows, however, that the increase is substantially attenuated when the BP reduction is maintained.
for 8 weeks by daily administration of the 2 drugs. It finally shows that the attenuation is less for felodipine than for lercanidipine, the prolonged administration of which is capable of completely abolishing the initial sympathetic activation and making the during-treatment sympathetic activity values superimposable to the pretreatment ones. This allows to conclude that (1) sympathetic activity may be differently modulated by drugs of the dihydropyridine class that have similar BP-lowering effects, (2) this different modulation may not be seen soon after but only during prolonged drug administration, and (3) under prolonged drug administration, some dihydropyridines may be entirely devoid of any sympathostimulating effect, thereby avoiding its potential adverse cardiovascular consequences.

The present study does not clarify the mechanisms responsible for the different effect on sympathetic activity of felodipine and lercanidipine. We can exclude, however, that a differential effect on the baroreflex was involved because the baroreflex ability to modulate MSNA and HR was similarly affected by the 2 drugs. We can, on the contrary, suggest that the baroreflex played a role in the temporal pattern of the sympathetic responses that were seen with both treatments. This is because the initial sympathetic activation was associated with, and probably dependent on, a marked impairment and an incomplete resetting of the baroreflex, whereas the subsequent return toward pretreatment sympathetic activity values coincided with a complete restoration of the initial baroreflex characteristics. As, at variance from lercanidipine, this restoration did not prevent felodipine from being accompanied by a residual increase in sympathetic activity, it seems obvious that mechanisms other than the baroreflex are involved. We can speculate that this is not due to differences in the pharmacokinetic properties because both drugs share a long duration of action that provides a 24-hour BP-lowering effect when given once daily.\textsuperscript{34–37} It may rather be due to the greater lipophilicity of lercanidipine,\textsuperscript{34,37} which may favor a direct depressor effect on vasomotor center through its crossing of the blood—brain barrier. This has been shown for slow-release nifedipine, which also does not appear to have a chronic sympathostimulating effect.\textsuperscript{19,20} It may not be, in contrast, a prominent effect of amlodipine, which has a limited lipophilicity and has been shown to be accompanied by a persistent sympathostimulation when given to hypertensive patients with or without renal failure.\textsuperscript{19,37–39}

Three other points deserve to be mentioned. One, in our hypertensive patients different measures of sympathetic activity such as HR, plasma NE, and MSNA changed in a remarkably similar fashion in response to the acute and chronic administration of felodipine or lercanidipine. This strengthens the conclusion of the primary study on the acute and chronic differential sympathetic effects of different calcium antagonists. It further suggests that the changes we observed probably involved the sympathetic nervous system at cardiac, as well as at various vascular, levels. Two, previous observations by our groups and others have shown that an acute BP reduction leads to sympathostimulation, even when central sympathoinhibitory drugs are used.\textsuperscript{22–24} This is confirmed by the present findings, which additionally show this to be probably due to an acute baroreflex impairment. Three, our results emphasize a methodological issue; ie, performing studies on the effect of antihypertensive drugs on sympathetic cardiovascular drive in an acute setting have a limited relevance, because the results may bear no relationship with what happens to sympathetic activity under prolonged drug administration (ie, the condition that is relevant for patient’s protection by BP-lowering interventions).

Perspectives

As mentioned in the Introduction, studies on the effects of dihydropyridines on sympathetic function have provided heterogeneous results. Based on present, as well as previous, findings it is possible to suggest that several factors may be
variably involved. These include the different pharmacokinetic (eg, shorter or longer duration of action) and basic properties (eg, lipophilicity) of the drugs, and, at least in some conditions, the direct (eg, microneurography) versus the indirect (eg, norepinephrine assay) techniques used to quantify sympathetic function. They may also include, however, the time course of the disease and the nature of the disease itself.

References

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