Commentary on Current Literature

Richard A. Johnson, MD

Effect of Calcium Antagonists on Plasma Norepinephrine Levels, Heart Rate, and Blood Pressure

Grossman E, Messerli FH. *Am J Cardiol.* 1997;80:1453–1458.

To evaluate the effects of calcium antagonists on sympathetic activity in hypertensive patients, a MEDLINE search for English language articles published between 1975 and May 1996 using the terms calcium antagonists, sympathetic nervous system, and catecholamines was conducted. Clinical studies only reporting the effects of calcium antagonists on blood pressure, heart rate, and plasma norepinephrine (NE) levels in patients with hypertension were included. Data were combined and analyzed according to class of calcium antagonist (dihydropyridine vs nondihydropyridine), their duration of action (short-acting [SA] vs long-acting [LA]), and treatment duration. We identified 63 studies involving 1,252 patients. Acutely after single dosing, SA calcium antagonists decreased mean arterial pressure by 13.7 ± 1.1% and increased heart rate by 13.7 ± 1.4% and NE levels by 28.6 ± 2.5%. Change in NE levels correlated with change in heart rate ($r = 0.59$, $p < 0.01$) and inversely with change in arterial pressure ($r = 0.46$, $p < 0.05$) in patients taking dihydropyridine calcium antagonists acutely. With sustained therapy, both classes of SA calcium antagonists increased NE levels. Whereas NE levels remained slightly elevated and heart rate unchanged with LA dihydropyridine calcium antagonists, both heart rate and NE levels decreased with LA nondihydropyridine calcium antagonists. SA calcium antagonists stimulate sympathetic activity when given acutely and over the long term, irrespective of their molecular structure. Sympathetic activation is less pronounced with LA dihydropyridine calcium antagonists and decreases with LA nondihydropyridine calcium antagonists. These data offer a possible pathophysiologic explanation for the increase in morbidity and mortality observed in some studies using SA calcium antagonists.

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The paper by Grossman and Messerli is a review of the medical literature on the effect of calcium channel blockers (CCBs) on the sympathetic nervous system. The analysis compares results by short- and long-acting CCBs, and by dihydropyridine (DHP) and non-dihydropyridine (non-DHP) subclasses of calcium channel antagonists. Short-acting CCBs of both classes, DHP and non-DHP, produced increased activation of the sympathetic nervous system as measured by increases in heart rate and plasma norepinephrine levels with short-term administration, and DHP produced the most significant changes. In contrast, long-acting (single daily dosing) formulations of non-DHP CCBs produced reductions in both heart rate and plasma norepinephrine levels, whereas long-acting DHP CCBs were more similar to short-acting CCBs. The authors speculate that this tendency for all short-acting CCBs to increase sympathetic activity may be associated with reports of higher cardiovascular morbidity and mortality with these agents. It is apparent that as we begin to dissect the effects of classes, subclasses, and even individual drugs on various biological end points, our job as physicians becomes harder and harder, but ultimately more rewarding. Clearly the physician should now be aware that the long-acting CCBs, which have been shown to have as good, if not better, blood pressure control properties when compared to other antihypertensive classes, really represent 2 classes of drugs, the DHPs and non-DHPs. The non-DHPs decrease intrinsic sympathetic activity and the DHPs increase intrinsic sympathetic activity.

Commentary on Current Literature

Richard A. Johnson, MD

Blood Pressure Morning Surge and Hostility

Pasic J, Shapiro D, Motivala S, Ka Kit Hui.
Am J Hypertens. 1998;11:245–250.

This study examined the effects of hostility on blood pressure (BP) during the early morning hours before awakening and several hours afterward. Our objective was to determine whether the pattern of BP change and the slope of the morning BP surge were related to hostility. The subjects were 32 patients with a history of Stage 1 hypertension. The morning surge in BP was derived from ambulatory BP monitoring of sleeping and waking hours, which were averaged per subject and centered around the wake-up hour. The periods used were 3 h before and 3 h after awakening. Only systolic blood pressure (SBP) is being reported on in this paper as this is the primary measure found relevant to the morning surge phenomenon. Hostility was assessed by the Buss-Durkee Hostility Inventory (total score). The results revealed significant differences between low and high hostility subjects for overall levels of sleep SBP: 120 ± 11.4 mm Hg for low hostility and 131.3 ± 14.9 mm Hg for high hostility subjects (P = .02). Low hostility subjects showed a steep rise in SBP from sleeping to waking while high hostility subjects had almost reached their post-sleep level of SBP in the hours immediately before waking up (P = .03). These data indicate that individual differences in hostility are related to different patterns of BP during sleep and the early morning hours, a period of the day that has been associated with an increased risk of cardiovascular incidents. The data also suggest the need for further study of the significance of hostility and other personality traits and the relationship of these traits to the mechanisms of the morning surge and the risk of cardiovascular events.

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This primary investigation by Pasic et al, acquired 24-hour ambulatory blood pressure data on individuals with Stage 1 hypertension. These data were then compared with psychological test scores for hostility and anxiety as measured by the Buss-Durkee Hostility Inventory and the Taylor Manifest Anxiety Scale, respectively. Interestingly, those patients with low hostility scores had the greater rate of rise of early morning blood pressure, because they had reached lower nocturnal baseline levels, when compared with those with higher hostility scores. There were no differences seen in the high- and low-anxiety groups. It has been felt that the larger the rate of change in blood pressures during this morning period, the greater the increase in relative risk for adverse cardiovascular events. On the other hand, the higher sustained nocturnal blood pressures, as seen in the high-hostility group, are associated with a greater relative risk for end-organ damage from hypertension, such as renal disease and left ventricular hypertrophy. Therefore, the take-home message from this small study of individuals might be that if you are of the mellow disposition, it is good in the long run for your heart, kidneys, and blood vessels, but you need to wake up and get going slower than your hostile counterparts.