Effect of Amlodipine on Hemodynamic and Endocrine Responses to Mental Stress

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Little is known about the effects of antihypertensive drugs on hemodynamic responses to mental stress. We studied 24 patients with mild-to-moderate hypertension in a double-blind random-sequence crossover study comparing placebo with amlodipine titrated up from 5 to 10 mg daily. After 1 month of treatment, the subjects performed 20 min of a frustrating cognitive task. At baseline before task, amlodipine significantly reduced systolic pressure (128.9 ± 8.2 mm Hg v 140.3 ± 10.7 mm Hg, P < .001), diastolic pressure (81.7 ± 7.7 mm Hg v 90 ± 7.5 mm Hg, P < .001), and total peripheral resistance (37.5 ± 15 v 45.6 ± 23.7 mm Hg/L/min, P < .05), while elevating baseline norepinephrine levels (2286 ± 6731 pmol/L v 1788 ± 546 pmol/L, P < .001).

Blood pressure during the stress task was significantly less with amlodipine than with placebo (systolic 142.3 ± 12.3 mm Hg v 150.9 ± 14.6 mm Hg, P < .001; diastolic 87.9 ± 8.4 mm Hg v 97.7 ± 9.3 mm Hg, P < .001), whereas norepinephrine was significantly higher (2754 ± 1007 pmol/L v 1970 ± 740 pmol/L, P < .001).

There were no significant differences in cardiac output, plasma lipids or lipoproteins, or markers of platelet activation. Heart rate increased significantly during stress, but there was no significant difference between amlodipine and placebo either at baseline or during stress. Our conclusion is that amlodipine reduces blood pressure at baseline and during mental stress, but raises basal and stress-related plasma catecholamines. This finding may have implications for the recent controversy over the safety of calcium channel antagonists, and suggests the potential relevance of combining amlodipine with adrenergic blockers. Am J Hypertens 2000;13:518–522 © 2000 American Journal of Hypertension, Ltd.

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The association between psychosocial stress and atherosclerotic events, such as myocardial infarction, has received considerable attention over the past two decades. Manuck and Krantz hypothesized that repeated physiologic arousal involving acute changes in hemodynamic and cardiac functioning in response to psychologic challenge could trigger atherogenic processes. Hemodynamic forces, such as turbulence and shear stress that increase with increased reactivity, may cause or exacerbate existing endothelial damage and promote the development of atherosclerotic lesions.

Manuck et al found that coronary atherosclerosis was twice as severe in dominant animals who were repeatedly exposed to a stressor, compared with stressed submissive monkeys, and compared with both dominant and submissive monkeys who were
not stressed. Furthermore, monkeys that exhibited high versus low reactivity to stress (threat with a capture glove) had more extensive coronary atherosclerosis.

We have shown in human subjects that the rise in blood pressure during mental stress with a frustrating cognitive task was a stronger predictor of carotid atherosclerosis progression over 2 years than any of the Framingham risk factors. There has been some indication that calcium channel antagonists may have antiatherosclerotic effects, and some evidence that nisoldipine, a dihydropyridine calcium channel antagonist, reduced responses to stress. Because it seemed likely that a long-acting calcium channel antagonist may provoke less sympathetic activation than short-acting calcium channel antagonists, we designed this study to test the effect of amlodipine, a long-acting dihydropyridine calcium channel antagonist, on hemodynamic and endocrine responses to mental stress.

MATERIALS AND METHODS

The study was a random-sequence double-blind crossover comparison of placebo versus amlodipine in patients with mild-to-moderate hypertension. Baseline screening included a history and physical examination, electrocardiogram, chest radiograph, urinalysis, and laboratory testing including hematology (CBC and differential) and biochemistry: glucose, urea, creatinine, electrolytes, creatine kinase, lactate dehydrogenase, uric acid, calcium and phosphorus, albumen, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase; women also had a β-HCG test to rule out pregnancy.

After a 4-week placebo run-in, the patients were treated with 4 weeks each of placebo and amlodipine, titrating up from 5 mg daily to 10 mg daily; there was a 2-week washout period between the placebo and active treatment period. Randomization of sequence by a table of random numbers, and dispensing of study medication, were done by the hospital research pharmacist.

At the end of each 4-week treatment period, the patients took their study medication 2 h before coming to the research unit.

Patients underwent a baseline examination including blood pressure measurement, and baseline blood work including platelet studies and plasma catecholamines. They then performed a frustrating cognitive task using a computerized version of the Stroop Color-Word Interference Task (Stroop), using an AT-compatible PC. This standardized procedure has been described elsewhere. Blood pressure and heart rate were recorded using a Critikon Dinamapp Vital Signs Monitor 8100 (Tampa, FL), whereas stroke volume and preejection period were measured by a Minnesota impedance cardiograph Model 304B (Instrumentation for Medicine, Greenwich, CT). Subjects were instructed to relax in the lab for 20 min before performing the task. Two baseline values and seven values each of the blood pressures, heart rate, and stroke volume during the color-word task were recorded automatically over 18 min at 3-min intervals. These values were summed and averaged to obtain baseline and task data points, respectively.

Lipid and Apolipoprotein Determinations Plasma lipids and lipoproteins were measured in the laboratory of Dr. Murray Huff at the Robarts Research Institute. They included total cholesterol, triglycerides, HDL, LDL, VLDL, ApoA1, and ApoB. Plasma catecholamines were measured by high-pressure liquid chromatography.

Inclusion Criteria Patients with mild-to-moderate hypertension were recruited from the Atherosclerosis Prevention Clinic at Victoria Hospital. Patients were eligible if they were aged 18 to 65 years, with a previous history of hypertension, and a sitting diastolic blood pressure of 90 to 110 mm Hg after 2 weeks of placebo washout.

Exclusion Criteria Excluded were women of child-bearing potential, and any patients who were taking treatment with any antihypertensive drug or any other experimental drug; planned to donate blood during the study or for 2 weeks afterward; taking nonsteroidal antiinflammatory drugs or high-dose aminosalicylic acid (ASA; >650 mg/day); taking anticoagulants or hormones; had insulin-treated diabetes mellitus or any significant hematologic, renal, hepatic, gastrointestinal, autoimmune, or cardiac disease; had Grade III or IV retinopathy; had 2nd- or 3rd-degree heart block, aberrant atrioventricular conduction pathways, or sinus bradycardia (<55 beats per minute off medication); had known adverse effects from or lack of response to calcium channel antagonists; had a history of alcohol or drug abuse, or psychologic or other emotional problems likely to invalidate informed consent or limit the ability of the patient to comply with protocol requirements; had orthostatic hypotension or dehydration; and had diastolic pressure persistently >110 mm Hg or >120 mm Hg on any occasion during the placebo run-in.

Subjects gave written informed consent to a protocol approved by the University of Western Ontario Review Board for Health Sciences Research Involving Human Subjects (review number 2774).

RESULTS

Thirty-one patients were screened for the study. One dropped out because he did not wish to continue, one
failed to return, two had blood pressures above the exclusion limit during placebo run-in, one had pressures too low during placebo run-in, and 24 completed the study (although one completed the study 2 weeks early because of moderate ankle edema). Results are presented as mean ± standard deviation (SD) for the 24 patients who completed the study; these were 17 men and 7 women, mean age of 46.8 ± 7.5 years.

Blood pressures were significantly lower both at baseline and at the 20-min mark of the stress task with amlodipine (Fig 1); peripheral resistance was significantly lower at baseline with amlodipine (Table 1). Heart rate increased significantly during stress on both placebo and amlodipine, but there was no significant difference between amlodipine and placebo either at baseline or during stress. Plasma norepinephrine levels were significantly higher both at baseline and during stress with amlodipine. There were no significant differences between baseline and 20 min after task, or between treatments, for plasma lipids or lipoproteins or for markers of platelet activation.

Adverse Effects  One patient complained of significant ankle swelling that led to his completing the study 2 weeks early; otherwise, there were no adverse effects reported during the 18 weeks of the study.

DISCUSSION

In our study of carotid atherosclerosis progression in relation to hemodynamic responses to mental stress, the mean blood pressure response was only approximately 10 mm Hg systolic and 6 mm Hg diastolic. However, the range of responses was up to 54 mm Hg systolic and 28 mm Hg diastolic, and it was the patients with the greatest rises in blood pressure during task who had the greatest progression of carotid plaque area during 2 years of follow-up. Indeed, in multiple regression analysis, the rise in blood pressure during task was a stronger predictor of carotid plaque progression than were any of the Framingham risk factors.

Similarly, in our prospective study of patients with untreated borderline hypertension followed untreated for 2 years with annual echocardiography and ambulatory blood pressure every 6 months,13 we found that the systolic pressure during mental arithmetic was a stronger predictor of an increase in left ventricular mass over 2 years than either the clinic pressure or ambulatory blood pressures.

As discussed in our recent review, it is likely that different drugs may have different effects on atherosclerosis and its complications.

The finding that amlodipine significantly reduces blood pressure during stress suggests that it may be antiatherosclerotic. It is possible, however, that the rise in plasma norepinephrine with amlodipine may be of concern not only with respect to atherosclerosis,
but in terms of issues such as myocardial infarction and sudden death related to increases in plasma catecholamines, which have been raised by the controversy over calcium channel antagonists. Although it has been widely assumed that longer-acting calcium channel antagonists such as amlopidine are safer than short-acting dihydropyridines such as liquid nifedipine pulvules, our findings suggest the need for further evaluation of that issue.

In conclusion, amlopidine significantly reduced baseline blood pressure before a mental stress task, and significantly reduced blood pressure during task. Plasma norepinephrine was significantly higher at baseline and after task during amlopidine treatment. There was no effect on plasma lipids or lipoproteins. The possible implications of these findings with respect to atherosclerosis, myocardial infarction, and sudden death will require further study. It appears likely that to maximize antiatherosclerotic effects, it may be important to combine amlopidine with adrenergic blockers.

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REFERENCES


