Ischemic Cardiovascular Complications Concurrent with Administration of Captopril

A Clinical Note

KENNETH M. BAKER, M.D., DEARING W. JOHNS, M.D., CARLOS R. AYERS, M.D., AND ROBERT M. CAREY, M.D.

SUMMARY Administration of potent vasodepressor agents such as the angiotensin converting enzyme inhibitor, captopril, may precipitate myocardial ischemic events in patients with coronary artery disease, particularly if this treatment is preceded by a discontinuation of \( \beta \)-blocking drugs such as propranolol. In one case studied, a patient experienced three episodes of angina pectoris under these conditions; in another, acute anterior myocardial infarction was suspect. (Hypertension 2: 73-74, 1980)

KEY WORDS • vasodepressor agent • angiotensin converting enzyme inhibitor • captopril • \( \beta \)-blocking drug • propranolol

THE oral angiotensin converting enzyme inhibitor 1-(D-3-Mercapto-2-methyl-1-oxopropyl)-L-proline (captopril) has been associated with two reported side effects. Skin rash developed in 10% of the patients who received 800-1000 mg per day, and a decrease in renal function developed in one patient. We have treated 43 patients with captopril and in this report will describe two cases in which myocardial ischemic events occurred during captopril therapy.

Patient 1

A 46-year-old man with treatment-resistant essential hypertension was hospitalized for captopril therapy on August 22, 1978. In 1973 he had an inferior myocardial infarction and prior to this admission experienced angina pectoris on exertion and at rest. His supine outpatient blood pressure was 160/105 mm Hg, and his heart rate was 88/min. Medical therapy consisted of hydralazine (200 mg/day), propranolol (320 mg/day), and hydrochlorothiazide (100 mg/day) in divided doses. Propranolol was tapered over 6 days before admission, and discontinued at 10 a.m. on the day of admission. Hydralazine and hydrochlorothiazide were discontinued at 10 p.m. on the day of admission. Captopril was begun on the second hospital day. At 8 a.m., 1 hour after the initial dose of captopril, the patient experienced a 15-minute anginal episode which responded to the administration of nitroglycerin. During the episode of angina pectoris, the supine blood pressure was 138/78 mm Hg and the heart rate 108/min. For 24 hours, 25 mg of captopril was administered every 8 hours. During this time, the patient was asymptomatic; his blood pressure and heart rate were 130/78 mm Hg and 96/min respectively. The patient was discharged on August 24, receiving 75 mg/day of captopril in divided doses.

During the thirty-second hour of treatment, the patient was resting at home and developed angina pectoris one-half hour after the fifth dose of captopril. This episode of angina subsided without administration of nitroglycerin. One-half hour after the sixth dose of captopril, the patient experienced a 1-hour episode of substernal chest pain which was not relieved by nitroglycerin. He was hospitalized on August 25, and treatment was discontinued. Cardiac enzymes including lactate dehydrogenase, serum glutamic-oxyaloacetic transaminase, creatine phosphokinase, and creatine phosphokinase isoenzymes were normal.

Patient 2

The second patient was a 62-year-old woman who had a left renal endarterectomy with vein patch angioplasty in 1975 for atherosclerotic left renal artery stenosis. Her hypertension did not improve after surgery. Renal arteriography in 1976 revealed a 50% to 80% stenosis at the site of the endarterectomy.
The patient had no history of coronary artery disease. On admission (June 18, 1978), the patient's medications included hydralazine (200 mg/day), propranolol (160 mg/day), and hydrochlorothiazide (100 mg/day). These medications were replaced by a placebo. The supine blood pressure was 198/102 mm Hg and the heart rate 80/min. On June 22, the patient received 25 mg of captopril. The blood pressure decreased to 150/100 mm Hg and the heart rate increased to 88/min. One hour after the initial dose of captopril, the patient complained of substernal chest pain, which subsided without treatment. The patient received three additional 25 mg doses of captopril over 12 hours, during which she frequently complained of 5- to 10-minute episodes of substernal chest discomfort. At 6 a.m. the following day, 9 hours after the last dose of captopril, the patient had a prolonged episode of substernal chest pain during which her supine blood pressure and pulse rate increased to 290/180 mm Hg and 128/min respectively. Electrocardiograms revealed changes compatible with an acute anterior myocardial infarction. The creatine phosphokinase rose from 80 to 979 IU/liter with a positive muscle-brain fraction, thus confirming the impression of a myocardial infarction.

**Discussion**

The cardiovascular complications occurring in these two patients may have been related to propranolol withdrawal and/or captopril administration. The syndrome associated with abrupt propranolol withdrawal includes the following: angina, ventricular arrhythmias, myocardial infarction, and death. These withdrawal phenomena usually occur from 1 day to 2 weeks after the drug is discontinued. Hospitalized patients seem to be at less risk of developing complications from abrupt cessation of propranolol. In a retrospective analysis of 102 patients, Shiroff et al. reported only one hospitalized patient considered to have propranolol-withdrawal phenomena. The mechanism of rebound hyperactivity of the sympathetic nervous system after propranolol withdrawal could be explained by an increase in the number of receptors.

The mechanism of these cardiovascular ischemic complications occurring after angiotensin converting enzyme inhibition may be related to adrenergic stimulation. Angiotensin I and bradykinin, both of which increase with inhibition of angiotensin converting enzyme, may be agonists in the adrenal medulla, and thus contribute to changes mediated by the sympathetic nervous system. In the hypertensive patient receiving converting enzyme inhibitors, however, plasma norepinephrine concentration appears unchanged, therefore, this mechanism remains speculative.

A significant decrease in perfusion pressure coupled with a critical obstructive lesion in the coronary circulation also may lead to myocardial ischemia. Following administration of captopril, the mean arterial pressure decreased from 123 to 98 mm Hg in the first patient and from 160 to 117 mm Hg in the second. It is possible that this degree of vasodepressor response decreased coronary artery perfusion to such an extent that myocardial ischemia and necrosis occurred.

Since several mechanisms may have contributed to the myocardial complications in these patients, it is unwarranted to ascribe these side effects to the administration of captopril alone. Potent vasodepressor agents, however, such as angiotensin converting enzyme inhibitors, should be administered with caution to patients with known or presumed coronary artery disease, particularly following discontinuation of β-blocking drugs such as propranolol.

**References**

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