REFRACTORY VARIANT ANGINA RELIEVED BY DENOPAMINE

— A Case Report —

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A 48-year-old man with severe variant angina refractory to conventional treatment with calcium antagonists and nitrates, or prazosin, or trihexyphenidyl hydrochloride, became symptom free rapidly when treated with denopamine, a adrenergic beta-1 agonist. Denopamine may prove to be an additional therapeutic agent in the management of severe variant angina. Therefore the response to denopamine and the lack of response to prazosin in this patient suggests that not only the adrenergic alpha receptor but also the adrenergic beta-1 receptor plays an important role in the production of coronary spasm, at least in some patients.

IT is now widely accepted that coronary spasm plays a dominant role in variant angina. Most patients with variant angina respond well to treatment with nitrates and calcium antagonists. However, some patients are refractory to these drugs. It has been reported that the use of prazosin,¹ trihexyphenidyl hydrochloride² or guanethidine and clonidine³ was occasionally effective in those patients. We report a case of a patient with variant angina refractory to conventional treatment who rapidly became symptom free when treated with denopamine, a selective adrenergic beta-1 agonist.⁴

CASE REPORT

A 48-year-old man was admitted to our hospital in March 1990 for evaluation and treatment of oppressive anterior chest pain. The pain occurred at rest in the middle of the night, lasting 10 to 20 min. He had a 30-year

history of smoking 20 cigarettes per day. Physical examination and chest X-ray on admission showed no abnormalities. The ECG was normal except during spontaneous chest pain, when ST elevation appeared in leads II, III, aV_F and ST depression in leads I, aV_L, V₂ to V₆. A treadmill exercise test had negative results even at high workloads. Routine hematological and biochemical assessment showed no abnormality. During hospitalization, the frequency of angina at rest increased to daily occurrences. Coronary angiography, performed at 2:00 p.m. of a day, demonstrated almost normal coronary arteries (Fig. 1A). During repeat coronary angiography, total occlusion in the midportion of the right coronary artery (segment 2) developed, accompanied by severe chest pain and ST elevation in inferior leads (Fig. 1B). The spasm and ST elevation did not disappear after the intracoronary administration of 200 mcg of nitroglycerin, but disappeared promptly after the intracoronary administration of 10 µg of norepinephrine (Fig. 1C). He became refractory to each

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Fig.1. Arteriograms of the right coronary artery in the left anterior oblique projection
 A: The control coronary arteriogram showed a normal coronary artery.
 B: During repeat coronary angiography, total occlusion in the mid-portion of the right coronary artery (segment 2) developed, accompanied by chest pain and ST elevation in inferior leads.
 C: After the intracoronary administration of 10 μ g of norepinephrine, spasm disappeared promptly.

Fig.2. The effects of various drugs on the anginal attacks. Various drugs did not suppress either anginal attacks or consumption of nitroglycerin (NTG). Anginal attacks were consistently abolished after denopamine was added to nitrate, but reappeared when denopamine was replaced with placebo.

combination of high doses of nitrates (isosorbide dinitrate up to 185 mg daily) and calcium antagonists (nifedipine up to 80 mg, diltiazem up to 240 mg daily). Prazosin (3 mg daily) or trihexyphenidyl hydrochloride (6 mg daily), which had been reported to be effective occasionally in patients who were refractory to treatment with calcium antagonists and nitrates^{1,2} were unsuccessful in

preventing the attacks (Fig. 2). Because of a decrease in blood pressure, we could not increase the dosage of prazosin. We decided to treat with denopamine, a adrenergic beta-1 agonist, since the refractory spasm which developed during cardiac catheterization disappeared promptly after the intracoronary administration of norepinephrine. Ischemic episodes subsided dramatically after denopa-

mine (40 mg daily) was added to isosorbide dinitrate (40 mg), but reappeared when denopamine was replaced with placebo.

COMMENT

This is the first report demonstrating the efficiency of denopamine in preventing anginal attacks due to coronary spasm.

Denopamine is an orally active, positively inotropic drug. Denopamine has been characterized as a selective adrenergic beta-1 agonist by pharmacodynamic and receptor-binding studies⁴. The drug was recently introduced for the treatment of patients with congestive heart failure. Some investigators^{5,6} have reported on the effectiveness of the drug in improving the cardiac performance of patients with congestive heart failure.

It is generally accepted that stimulation of adrenergic alpha receptors, or enhanced activity of the parasympathetic nervous system, play an important role in coronary spasm^{7,8}. However, the precise mechanism(s) by which coronary spasm occurs still remains unknown. It has been reported that beta blockers aggravate coronary spasm because the blockade of coronary beta receptors unmasks alpha adrenergic activity in the large coronary artery^{9,10}. However, Ozaki et al¹¹ reported that denopamine caused markedly significant concentration-related relaxations mediated by beta-1 adrenoreceptors in isolated canine coronary arterial strips contracted with prostaglandin F_{2α}. Therefore it is possible that the blockade of coronary vasodilating action through beta-1 receptors would trigger or facilitate spasm in highly sensitized coronary segments. The response to denopamine and the lack of response to prazosin in this patient suggests that not only the adrenergic alpha receptor but also the adrenergic beta-1 receptor plays an important role in the production of coronary spasm, at least in some patients.

It appears that this is a typical case sug-

gesting a correlation between coronary spasm and the sympathetic nervous system. Further studies are required to examine the exact role of the sympathetic nervous system in the development of coronary artery spasm.

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