Nifedipine Therapy for Prinzmetal’s Angina

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SUMMARY A case is described in which nifedipine, a new coronary vasodilator, was effective in relieving attacks of Prinzmetal’s angina unresponsive to conventional therapy. The extreme frequency of the anginal attacks provided evidence that lower doses of nifedipine lost their effectiveness approximately 4 hours after administration. A month after initiation of nifedipine, nitrates were withdrawn since they had been ineffective in controlling the attacks. A myocardial infarction occurred immediately, presumably due to coronary spasm.

SINCE its description in 1959,1 Prinzmetal’s angina has fascinated clinicians with its dramatic pathophysiologic events. The unprovoked attacks of chest pain and ST-segment elevation have been clearly shown to result from spasm of a major coronary artery.2 But despite this understanding of the mechanism of the disorder, therapy of Prinzmetal’s angina with conventional agents is often unsuccessful. Evidence from Germany3 and Japan4 indicates that nifedipine [4-(2’-nitrophenyl)-2,6-dimethyl-3,5-di-carbomethoxy-1,4-dihydropyridine], a potent coronary vasodilator, may be remarkably effective in the treatment of this disorder. We have recently had the opportunity to administer nifedipine to a patient with extremely frequent attacks of coronary spasm unresponsive to nitrates, beta or alpha adrenergic blockade. The elimination of these attacks by the combination of nifedipine and nitroglycerin, and the occurrence of a myocardial infarction (presumably due to coronary spasm) during withdrawal of nitroglycerin therapy, form the basis for this report.

Case Report

A 43-year-old white male was transferred to the Peter Bent Brigham Hospital for control of frequent attacks of Prinzmetal’s angina. He had been in relatively good health until two months prior to transfer when he noted the onset of episodes of substernal chest tightness, lasting one to three minutes, occurring usually at rest and only rarely with exercise. These episodes were occasionally accompanied by lightheadedness. On one occasion he experienced a brief loss of consciousness and presented to a nearby emergency room. An ECG recorded during an attack of chest tightness and dizziness revealed marked ST-segment elevation in leads I, aVL, V2–V6 followed by a run of ventricular tachycardia at a rate of 280 beats/min. The ECG returned to normal within minutes and enzymatic studies for myocardial necrosis were later found to be negative. He was hospitalized and treated with sublingual isosorbide dinitrate 5 mg q 3h, oral propranolol 80 mg t.i.d. and oral quinidine 300 mg q 6h. However, the frequent attacks persisted and he was transferred for further management.

On admission to the Peter Bent Brigham Hospital, he was noted to be a well-developed male in no acute distress. The vital signs were within normal limits as was the examination of the cardiovascular system. The admission ECG showed only minor nonspecific T wave changes. Cardiac catheterization revealed a normally-contracting left ventricle and angiographically normal coronary arteries. During the ensuing week he was noted to have more than 18 distinct episodes which were attributed to coronary artery spasm. A typical episode began with the appearance of ST-segment elevation in the monitor leads, followed within minutes by ventricular ectopic activity followed within several minutes by chest tightness (figs. 1, 2). All episodes terminated spontaneously or within 5 minutes of the administration of 0.3 to 0.6 mg nitroglycerin sublingually. Since propranolol had been ineffective in preventing the attacks and theoretically may have potentiated the coronary spasm by allowing unopposed alpha adrenergic-mediated vasoconstriction, it was discontinued. He was begun on a regimen of oral isosorbide dinitrate 5 mg q 2h and nitroglycerin ointment 1 in q 4h. Alpha blockade was initiated with phenoxybenzamine in a dosage of 10 mg q.d. which was increased over six days to 40 mg q.d. Despite this intensive therapy the attacks continued. On the tenth hospital day phenoxybenzamine was discontinued and nifedipine5 in a sublingual dosage of 10 mg q 6h was begun. Prior to the administration of nifedipine, the potential risks, benefits and experimental nature of the agent were fully explained to the patient, who indicated his consent in writing. There was an immediate decrease in the frequency of the attacks. Furthermore, the attacks always occurred when the pharmacologic action of nifedipine was expected to be at its nadir, i.e., 4–6 hours after the preceding dose. Gradual increases in the nifedipine dosage to 20 mg q 4h resulted in a complete elimination of the attacks for the last four days of his hospitalization (fig. 3). He was discharged on a regimen of isosorbide dinitrate 5 mg q 2h, nitroglycerin ointment 1 in q 4h, nitroglycerin 0.3 mg p.r.n. and nifedipine 20 mg q 4h. During the month following discharge he remained totally free of his typical episodes of chest tightness or syncope. He noted four episodes of slight chest discomfort occurring immediately before a nifedipine dose. A 24 hour Holter monitor recording showed several episodes of possible ST elevation but no ventricular ectopic activity. He remained disabled by the frequency and number of his medications.

One month following discharge he was readmitted for evaluation of his recurrent chest discomfort and possible simplification of his medical regimen. Observation in the hospital for 48 hours failed to reveal evidence of coronary artery spasm. Since long-acting nitrates had been ineffective in preventing his attacks, it was decided to discontinue them while maintaining nifedipine. For 24 hours after withdrawal of isosorbide dinitrate he remained free of symptoms and nitroglycerin ointment was then discontinued. Twelve hours after the last administration of nitroglycerin he began to ex-

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pericardium prolonged substernal pressure unrelieved by five (0.3 mg) sublingual tablets of nitroglycerin. An anteroseptal myocardial infarction occurred, complicated by ventricular fibrillation, from which he was successfully resuscitated. The electrocardiographic changes that characterized the infarction occurred in the same leads which showed ischemia during the attacks of Prinzmetal's angina. He tolerated his infarction well with no persistent ventricular ectopic activity or congestive heart failure. At the time of discharge he was free of angina pectoris, congestive heart failure or ventricular arrhythmias, off nifedipine, nitroglycerin and all other cardiac medication.

Discussion

This case of a patient with extremely frequent and severe attacks of Prinzmetal's angina provides information about the use of a promising new therapy. The agent, nifedipine, was synthesized by the West German firm, Bayer, in 1971. It is a dihydropyridine derivative (fig. 4) which produces marked coronary vasodilatation by blocking the slow calcium currents that are responsible for the action potential and contraction of smooth muscle cells. There have been extensive studies of the pharmacokinetics and safety of nifedipine in humans. In the doses used in this patient it has been shown to produce a slight fall in blood pressure leading to a slight reflex increase in heart rate, and variable but small (<12%) changes in contractility as measured by dp/dtmax. The use of nifedipine for Prinzmetal's angina was first reported by Hosada et al. The same group later reported the effectiveness of nifedipine in 19 patients with Prinzmetal's angina and normal coronaries.

The unusual frequency of the attacks in this patient allows an extension of these observations by indicating the apparent duration of nifedipine effect. In this patient the lower doses of nifedipine prevented attacks for four hours only, at which time "breakthrough" occurred. This interval coincides with observations in dogs that a single dose of nifedipine produces coronary vasodilatation for a four to five hour period.

The occurrence of an infarction during nitroglycerin withdrawal in a patient with angiographically normal coronary arteries adds support to the argument that in certain instances myocardial infarction can result from coronary spasm. Although postinfarction angiograms were not obtained, it is likely that in this patient the infarction resulted from intense and prolonged coronary vasoconstriction.

In addition, this case demonstrates an important relationship between nifedipine and nitroglycerin, an agent with which nifedipine will frequently be used. The reason for...
the occurrence of an infarction during withdrawal of nitroglycerin ointment is uncertain. It seems unlikely that nitrate withdrawal caused a rebound phenomenon since the duration of exposure was far shorter than that of individuals in whom infarction has been reported secondary to withdrawal from industrial exposure to nitroglycerin. More likely that the stimulus for spasm was sufficiently strong that both nitrates and nifedipine were necessary to prevent it. It might be expected that the vasodilatory actions of these two agents would be additive, because the nitrates can produce relaxation of smooth muscle in calcium-poor preparations, while nifedipine causes relaxation by blocking slow calcium currents. Further observations are needed but it is possible that nitrates plus nifedipine may be the therapy of choice for this disorder.

Finally, this experience with nifedipine adds to the evidence indicating the need for the randomized, double-blind study to assess its role in the therapy of Prinzmetal’s angina which is now in the planning stages. With such a trial the current optimism regarding the use of nifedipine for the treatment of Prinzmetal’s angina can be critically tested.

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**Figure 3**. The effect of nifedipine on episodes of coronary artery spasm. An episode was defined as the appearance of ST-segment elevation, and/or significant ventricular ectopy (i.e., couplets, bigeminy or ventricular tachycardia) and/or typical chest pain. The total number of episodes and their distribution during consecutive six hour periods pre-nifedipine (six days) are shown in the top row. In the middle and bottom rows the total number of episodes and time of their occurrence relative to the administration of lower dose (10 mg q 6h or q 4h, 20 mg q 6h) and higher dose (20 mg q 4h) nifedipine are shown. Pre-nifedipine the episodes occurred randomized throughout the 24 hour period. With lower dose nifedipine there was a marked decrease in the frequency of attacks (19 to 7) and most occurred four to six hours after nifedipine. The single at-
tack during the first hour occurred 10 minutes after the administra-
tion of nifedipine — before the expected onset of action of the new dose.

**Figure 4**. The chemical structure of nifedipine [4-(2'-nitro-
phenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine].

**Nifedipine** (Adalat, BAY a 1040)
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