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 A month after initiation of nifedipine, nitrates were withdrawn since they had been ineffective in controlling the attacks.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, 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. But despite this understanding of the mechanism of the disorder, therapy of Prinzmetal's angina with conventional agents is often unsuccessful. Evidence from Germany and Japan 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 therapy, 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 exertion. 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, V2-4, 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 catheteriza-
pericardium prolonged substernal pressure unrelated by five (0.3 mg) sublingual tablets of nitroglycerin. An anterosseal 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 1971.3 It is a dihydropyridine derivative (fig. 4) which produces marked coronary vasodilatation4 by blocking the slow calcium currents that are responsible for the action potential and contraction of smooth muscle cells.3 There have been extensive studies of the pharmacokinetics and safety of nifedipine in humans.6 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,7,8 The use of nifedipine for Prinzmetal’s angina was first reported by Hosada et al.4 The same group later reported the effectiveness of nifedipine in 19 patients with Prinzmetal’s angina and normal coronaries.9

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.9

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.10 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

**Figure 1.** The patient’s ECG prior to an episode of coronary spasm. Only nonspecific T wave changes are present.

**Figure 2.** The patient’s ECG during an episode of coronary spasm. A bigeminal rhythm has appeared. The ST segments are now markedly elevated in I, aV5, V3 – V6 and reciprocally depressed in III and aV5. Five minutes after the nitroglycerin was administered the ECG returned to its baseline appearance (fig. 1).
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,\textsuperscript{15} while nifedipine causes relaxation by blocking slow calcium currents.\textsuperscript{4} 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.

Acknowledgment

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References


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\caption{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 randomly 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 attack during the first hour occurred 10 minutes after the administration of nifedipine — before the expected onset of action of the new dose.}
\end{figure}

\begin{figure}
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\includegraphics[width=\textwidth]{figure4.png}
\caption{The chemical structure of nifedipine [4-(2'-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine].}
\end{figure}
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