Rebound of vasospastic angina after cessation of long-term treatment with nifedipine

JEAN LETTE, MD
ROGER-MARIE GAGNON, MD
JEAN G. LEMIRE, MD
MARTIN MORISSETTE, MD

The beneficial effect of calcium antagonists in the treatment of vasospastic angina is now well recognized. Although withdrawal symptoms have been reported following abrupt cessation of therapy with some cardiovascular drugs, there is no detailed report on similar complications of the cessation of therapy with calcium antagonists. In a 4-month period eight patients with well documented and well controlled vasospastic angina experienced a marked increase in the frequency and duration of anginal episodes at rest following the involuntary cessation of treatment with nifedipine, 10 to 20 mg four times a day. The increase began within 2 to 5 days after the cessation of treatment. Substitute therapy with isosorbide dinitrate, 30 mg, and verapamil, 80 to 120 mg, each four times a day, was effective in all cases. Although the mechanism responsible for this rebound phenomenon is not known, awareness of its existence is essential considering the widespread use of calcium antagonists.

L'effet bénéfique des antagonistes des ions calcium dans le traitement de l'angine angiospastique est maintenant bien reconnu. Alors que des symptômes de sevrage ont été signalés après l'interruption brusque de traitements à certains médicaments cardiovasculaires, on ne retrouve aucun rapport détaillé de complications similaires étant survenues après l'interruption de traitements aux antagonistes des ions calcium. Sur une période de 4 mois huit patients souffrant d'une angine angiospastique bien documentée et bien stabilisée ont subi une nette augmentation de la fréquence et de la durée des crises d'angine au repos après l'interruption involontaire d'un traitement à la nifédipine, 10 à 20 mg quatre fois par jour. Cette augmentation est survenue de 2 à 5 jours après l'interruption du traitement. Une thérapie de remplacement au dinitrate d'isosorbide, 30 mg quatre fois par jour, et au vérapamil, 80 à 120 mg quatre fois par jour, a été efficace dans tous les cas. Même si le mécanisme responsable de ce phénomène de rebondissement n'est pas connu, son existence doit être gardée à l'esprit, compte tenu de l'usage répandu des antagonistes des ions calcium.

From the cardiology division, department of medicine, Notre-Dame Hospital, Montreal

Reprint requests to: Dr. Roger-Marie Gagnon, Cardiology division, Notre-Dame Hospital, 1560 Sherbrooke St. E, Montreal, PQ H2L 4K8

Nifedipine, a calcium antagonist, has been shown to be effective in the treatment of coronary artery spasm.[1,2] A marked reduction in the frequency of anginal attacks, often with complete control of symptoms of myocardial ischemia, was observed in patients with vasospastic angina receiving long-term oral therapy with nifedipine.[3] In such patients the results of the ergonovine provocation test will frequently become negative or will be positive only with a higher dose of ergonovine.[4]

Although withdrawal syndromes have been reported to occur when treatment with cardiovascular drugs such as propranolol[5] and clonidine[6] has been stopped abruptly, there are few reports in the literature of complications following cessation of treatment with coronary vasodilators. We report a withdrawal syndrome following involuntary cessation of nifedipine therapy in eight patients with vasospastic angina.

Observations

Between June and September 1981, because of a shortage of the drug, nifedipine therapy was stopped in 8 of 30 patients being treated at our clinic for patients with vasospastic angina. All eight patients were known to have angina at rest; seven of them had undergone coronary angiography (Table I). Total or nearly total coronary artery spasm was provoked by ergonovine testing in five patients; in two of them the spasm occurred spontaneously and was not catheter-induced, and in one patient the spasm was induced by simultaneous hyperventilation and intravenous injection of 44 mmol of bicarbonate. One patient had not undergone coronary angiography; the diagnosis had been based on a history of nocturnal and rest pain associated with transient inversion of T waves in the anterior electrocardiogram leads. A summary of the clinical and angiographic findings appears in Table I.

When the diagnosis of vasospastic angina was made four of the patients were being treated with β-blockers, two with sublingual nitroglycerin and two with long-acting nitrates. In every case, therapy with nifedipine was substituted immediately. All the patients noted a marked decrease in the frequency of anginal episodes while taking nifedipine.

After nifedipine therapy was stopped the patients experienced an increased frequency and duration of chest pain at rest; the increase began 2 to 5 days after the discontinuation of nifedipine and lasted until substitute therapy was begun. The mean number of chest pains experienced weekly per patient before, during and after nifedipine therapy was 10.1, 1.0 and 30.6 respectively. After nifedipine therapy was stopped there were no episodes of myocardial infarction or malignant ventricular arrhythmias, but five patients were admitted to our coronary care unit. All eight patients improved after therapy with isosorbide dinitrate, 30 mg every 6 hours, and verapamil, 80 to 120 mg every 6 hours, had been instituted. The symptoms of three patients were subsequently well controlled by

verapamil alone, and these patients continued to use this drug. In the others, however, treatment with nifedipine was again begun, at similar doses.

During a short-term follow-up period, 2 to 5 months, the condition of each patient was stable, with the same pattern of angina as before the cessation of nifedipine therapy. Fig. 1 shows the patterns of angina before, during and after nifedipine therapy.

Discussion

The role of coronary artery spasm in the pathogenesis of myocardial ischemia has been increasingly recognized recently.[7] Once considered a rare disorder, coronary artery spasm is now thought to play a role in unstable angina,[8] myocardial infarction,[9] ventricular arrhythmias and sudden death.[3,10,11] With nifedipine, a powerful coronary vasodilator, most patients will experience a marked reduction in the frequency of anginal episodes or even a complete disappearance of angina.[3]

In spite of the small number of patients in our study, the cyclic nature of vasospastic angina[12,13] and the possible placebo effect of any antianginal drug, our observations suggest the existence of a nifedipine withdrawal syndrome. While our patients were taking this drug their symptoms were well controlled; after its withdrawal we could find no other explanation for the sudden increase in the frequency and duration of the patients' angina, such as emotional stress, change of lifestyle or ingestion of other drugs.

Withdrawal syndromes following cessation of therapy with other cardiovascular drugs have been well described. Abrupt cessation of clonidine therapy may lead to a hypertensive crisis, possibly resulting from excessive rebound sympathetic stimulation.[6] Accelerated angina, myocardial infarction, ventricular arrhythmias and sudden death have been reported, classically in patients with severe obstructive coronary artery disease, following the abrupt cessation of propranolol therapy.[5]

There are few reports in the literature of complications following withdrawal of treatment with coronary vasodilators. In 1972 Lange and colleagues[14] described in nine workers chronically exposed to nitroglycerin a rebound peripheral and nonatheromatous type of coronary vasospasm — the "dynamite heart syndrome". Since then 2 cases of myocardial infarction[4] and 10 of unstable angina[15,16] following the tapering or cessation of therapy with calcium antagonists have been reported in patients with vasospastic angina.

Although the true frequency of withdrawal phenomena is unknown,

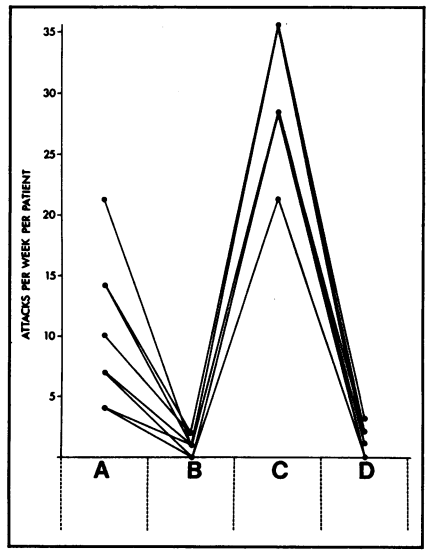

Fig. 1—Patterns of vasospastic angina in eight patients before (A), during (B) and after (C) nifedipine therapy, as well as during substitute therapy (D). Periods A and B lasted 10 to 120 (mean 38.7) months and 3 to 24 (mean 12.9) months respectively; frequency of angina increased in period C after delay of 2 to 5 days.

Table I—Summary of clinical and angiographic findings in eight patients with vasospastic angina treated with nifedipine

Patient no.	Age (yr), sex	Duration of symptoms (yr)	Nifedipine therapy: Duration (mo)	Nifedipine therapy: Daily dose (mg)	Occlusion (%) observed by angiography*: During spasm	Occlusion (%) observed by angiography*: Not during spasm	Changes in ECG during pain†	No. of chest pains per week: Before nifedipine therapy	No. of chest pains per week: During nifedipine therapy	No. of chest pains per week: After nifedipine therapy	No. of chest pains per week: During substitute therapy
1	55, F	4	3	80			↓ T wave (V_1 to V_4)	7	0	28	0
2	51, M	2	24	80	R, 100	None	↑ ST segment (V_1 to V_4)	4	1	28	0
3	53, M	4	18	80	R, 100	C, 70 R, 40	↓ ST segment (II, III, aVF, V_5, V_6)	7	1	35	1
4	47, F	10	6	80	LAD, 90 C, 50	None	↓ T wave (V_1 to V_4)	4	0	21	0
5	43, F	5	24	80	R, 100	LAD, 50 R, 20	↑ ST segment (III, aVF)‡	14	2	35	2
6	57, F	7	12	40	R, 50	C, 50 R, 50 LAD, 90	↓ ST segment (V_5, V_6)	14	1	35	2
7	41, F	3	6	80	R, 100 C, 90	None	None	10	2	35	3
8	55, F	10	10	80	R, 90 LAD, 90	None	Transient LBBB	21	1	28	2

*Angiography was not done in patient 1. R = right; LAD = left anterior descending and C = circumflex coronary arteries.
†ECG = electrocardiogram; LBBB = left bundle branch block.
‡Spasm induced by respiratory and metabolic alkalosis.

Subramanian and associates[17] observed, during routine ambulatory monitoring of 143 patients taking calcium antagonists, 5 instances of deterioration of angina control after cessation of treatment with these drugs. Freedman and colleagues,[18] in a study of the long-term effects of verapamil and isosorbide dinitrate, found that after a mean of 15 months of therapy angina developed in less than 48 hours in 10 of 26 patients after supervised withdrawal from treatment in hospital; in contrast, angina recurred in all six instances of unsupervised, patient-initiated withdrawal. Failure to stop smoking was positively associated with a recurrence of angina when treatment was stopped.[18] These data and the findings in other studies are shown in Table II.

It is difficult to postulate a mechanism for this rebound vasospasm since the pathophysiologic aspects of coronary artery spasm have not been clarified. Rebound spasm following the cessation of treatment with powerful coronary vasodilators may be nonspecific and may occur in healthy individuals, as Lange and colleagues[14] observed in the workers exposed to nitroglycerin.

The potential hazards of calcium antagonist withdrawal after prolonged use in patients with healthy hearts should be further studied since these drugs are considered to be of potential value in a variety of clinical situations, such as chronic stable angina,[19] heart failure,[20] systemic hypertension,[21] peripheral vasospasm[22] and pulmonary hypertension.[23]

The natural history of vasospastic angina is not known, and spontaneous remissions have been described.[12,13] A withdrawal syndrome in our eight patients, whose symptoms had been well controlled by nifedipine therapy, might have been predicted by repeat ergonovine testing, as described by Waters and associates,[12] 24 to 48 hours after cessation of the therapy. It could thus have helped to differentiate the patients with true spontaneous remission from those who were asymptomatic but drug-dependent.

Awareness of the existence of such a withdrawal syndrome is essential considering the potential widespread use of this powerful calcium antagonist.

Table II—Withdrawal phenomena following cessation of therapy with calcium antagonists observed during studies of the efficacy of these drugs

Study	Phenomenon	No. of patients affected
Waters et al[4]	Myocardial infarction	2
Johnson et al[15]	Unstable angina	4
Heupler et al[16]	Unstable angina	6
Subramanian et al[17]	Worsening of angina	5
Freedman et al[18]	Recurrence of angina	16
Present study	Unstable angina	8

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the familial forms of the disease are characterized by irritability, fever, pallor, swelling of the affected bones and tenderness, which suggest an acute inflammatory response.

Laboratory investigations usually reveal mild anemia, leukocytosis and an elevated erythrocyte sedimentation rate. Pathologically the periosteum is thickened and edematous with the production of new osteoid and bony trabeculae. An acute inflammatory response is provoked in the overlying fascia and muscle.[9]

In most affected infants the disease is benign and self-limited, with clinical and roentgenographic evidence of complete recovery usually by the time the infant is 30 months old. Treatment is primarily directed at relieving pain and discomfort. Late recurrence of the disorder, with persistent pain and deformity, is relatively uncommon. When the pain is persistent, late radiographic signs include loss of modulation, bowing, enlarged marrow cavities and streaks of incompletely absorbed cortical remnants.[10-12] The only late complication we have encountered in this pedigree is persistent bowing of the tibiae, associated with intermittent pain and discomfort, in two patients (V-37 and V-38) (Fig. 3) and their mother (IV-7).

Our experience, and that of others,[13] indicates that the sporadic form of the disease is disappearing. At University Hospital in Saskatoon only three such cases were seen between 1956 and 1960, two cases between 1961 and 1965, one case between 1966 and 1970, one case between 1971 and 1975 and none since 1976. However, we still see familial cases.

In sporadic cases the bones most often affected are the mandible, ulna and clavicle; there is also fairly frequent involvement of the ribs and scapulae.[14] However, in our series radiographic studies of 14 children showed no evidence of involvement of the ribs or scapulae and revealed clavicular involvement in only 3. Of the 24 bones found to show overt hyperostosis, only 6 were ulnae and only 4 radii. New bone formation was detected in 26 different bones, 23 of which were tibiae.

Despite nearly four decades of experience with infantile cortical hyperostosis, the cause of the disease remains obscure. Whether there are two forms, one genetic and inherited in an autosomal dominant fashion with incomplete penetrance and variable expressivity, and the other an environmentally induced phenocopy, is entirely speculative. Evidence for an environmentally induced form was found in Ueda and associates' study,[15] in which cortical hyperostosis was reported to develop following long-term administration of prostaglandin E_1 in low doses to infants with ductus-dependent congenital heart disease. The bone lesions resolved when the treatment was stopped.

The results of our studies of 34 members of one family confirm the vertical mode of inheritance, including male-to-male transmission, consistent with a single autosomal dominant gene. Because the trait shows incomplete penetrance and variable expressivity some carriers of the gene become only subclinically affected or are unaffected.

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