Proischemic Complications of Dihydropyridine Calcium Channel Blockers

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The concept of proarrhythmia, the realization that antiarrhythmic drugs can occasionally drastically aggravate the very problem for which they were prescribed, is now widely appreciated and has undoubtedly lead to an overall improvement in the use of these drugs. Proarrhythmia is a particularly dangerous type of side effect: It is unpredictable, may easily escape detection, and can turn a benign arrhythmia into a life-threatening predicament.

Proischemia, a term that I have just coined, can be defined as the potential of an antianginal drug to occasionally worsen ischemia in an unpredictable and dangerous manner. Proischemia is not as important a problem as proarrhythmia. Indeed, most antianginal drugs are unlikely to be proischemic; although circumstances can be envisaged in which a β-adrenergic blocker, for example, might worsen ischemia, such as in patients with coronary spasm,1 in clinical practice only the dihydropyridine calcium channel blockers carry a serious risk for proischemia.

The report by Thadani et al2 in this issue of Circulation provides disquieting information on the potential magnitude of this risk. During 2 weeks of therapy with nisoldipine, six of 137 stable coronary patients developed myocardial infarction or unstable angina. No such coronary events occurred in any of the 48 patients randomized to placebo. That the disproportionate distribution of coronary events in the active treatment group is merely a coincidence is belied by the results of previous studies with this class of drugs. In a trial to assess the utility of nifedipine in threatened infarction, Muller et al3 reported seven deaths in 89 nifedipine patients compared to none in 82 placebo patients after 2 weeks of therapy (p=0.018). One possible explanation for this difference was the unexpected absence of mortality in the placebo group.

However, an increased incidence of nifedipine-related events was also seen in the Holland Inter-university Nifedipine Metoprolol Trial.4 This trial was discontinued prematurely because the risk of developing myocardial infarction within 48 hours was two times higher (95% CI, 1.1 to 3.6) in unstable angina patients randomized to nifedipine monotherapy than to placebo. The Secondary Prevention Re-infarction Israeli Nifedipine Trial (SPRINT) II enrolled high-risk patients early after myocardial infarction and was also stopped early due to nifedipine-induced proischemic events.5 Among the entire population of 1,373 randomized patients, the mortality rate was 15.8% with nifedipine and 12.6% with placebo. The difference was due to an excess mortality within the first 6 days, mostly in patients with hypotension on admission.

Unanswered Questions

Is proischemia a clinically relevant feature of all dihydropyridines? The case against nifedipine is strongest, probably because it has been studied the most extensively. However, intravenous nicardipine6 and isradipine7 have provoked ischemia at rest in isolated cases. Among 46 stable angina patients in a double-blind, cross-over study with nicardipine,8 four experienced unstable angina and two others developed non-Q wave infarctions, all in relation to active treatment. Nicardipine was reported to have worsened angina in three of 63 patients in another trial.9

Is the risk of proischemia greater with nisoldipine than with other dihydropyridines? Nisoldipine is a more potent vasodilator than nifedipine.10 But proischemic complications with nisoldipine were not reported in the studies referenced by Thadani et al nor in a recent report by Tzivoni et al.11 This question is of more than theoretical interest because nisoldipine has already been approved for the treatment of angina in several European countries and Japan.

Mechanism of Proischemia

Do dihydropyridines cause proischemia by reducing coronary resistance or by reducing peripheral vascular resistance? Theoretically, these drugs could provoke or worsen ischemia by vasodilating coronary resistance vessels distal to a severe stenosis and redistributing blood flow away from needy suben-
This type of coronary steal can be readily demonstrated in the experimental animal with other vasodilators, but not with nifedipine. A more likely possibility is that dihydropyridine-induced peripheral vasodilation simultaneously reduces coronary perfusion pressure and reflexly increases heart rate. In a patient with severe multivessel coronary disease, this combination could produce unstable angina, myocardial infarction, or death. In theory, dihydropyridines with a gradual onset of action or slow release formulations might be less likely to trigger proischemia, and concomitant \( \beta \)-blocker administration might also decrease the risk.

What type of patient is most at risk for proischemia? Severe multivessel disease was present in the patients described in isolated case reports, and the risk for proischemic complications appears to increase in the acute phase of unstable angina or myocardial infarction. A disturbing aspect of the study by Thadani et al is that proischemia occurred in stable angina patients. More information is needed both about the mechanism of proischemia and the type of patient at risk.

**Antianginal Efficacy of Nisoldipine**

The improvements in exercise test end points in this study were meager and of borderline statistical significance; nisoldipine did not reduce angina frequency or nitroglycerin consumption. In a double-blind, placebo-controlled, parallel-design study of 82 patients, Tzivoni et al reported that nisoldipine significantly improved exercise test parameters but only marginally reduced ischemic episodes during daily activity. Previously reported results with nifedipine are similar: Most studies showed an improvement in exercise tolerance. Ischemic episodes detected by ambulatory electrocardiographic monitoring were reduced in some studies but not changed at all in others. Taken together, the available evidence indicates that the risk-to-benefit ratio of nisoldipine in the treatment of angina is tilted in the direction of risk.

**Future of Dihydropyridine Calcium Channel Blockers**

This class of drugs has proven to be effective and popular in the treatment of hypertension. Although nifedipine is not usually the best choice as monotherapy for stable angina, it is often very useful in combination with a \( \beta \)-blocker. Recent studies suggest that dihydropyridines may retard the progression of early coronary atherosclerosis. These drugs may also prevent myocardial infarction during coronary bypass surgery and even improve the neurologic outcome in some patients with acute ischemic stroke.

Dihydropyridine proischemia must be better understood so that we can limit its occurrence and fully exploit the potential benefits of this class of drugs.

**References**


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