Letters to the Editor

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Efficacy of Nisoldipine

Thadani et al reported in a recent issue of Circulation that nisoldipine, given in different dosages twice daily, was not superior to placebo therapy in patients with stable angina pectoris. They also showed that the 10 mg b.i.d. therapy resulted in a clinically important, although statistically insignificant, increase in the incidence of serious adverse events. The conclusions drawn by the authors regarding the lack of efficacy of nisoldipine seem to me unjustified by the data presented because key information is missing in the report. Calcium antagonists in general and dihydropyridines in particular are very frequently used in patients with stable angina pectoris. Which were the treatments that enrolled patients were taking before entering in the single-blind phase? How many of them were chronically treated with calcium antagonists? This information is very relevant for interpretation of the results of the study, especially if calcium antagonists were the previous antianginal medications used by the majority of the patients who entered the double-blind phase.

Selection of patients is known to be the most critical step in pharmacological studies. Withdrawing a drug and then enrolling patients who remain stable after withdrawal in a trial that evaluates a drug that has a mechanism of action similar to the one of the withdrawn drug carries the risk of selecting nonresponders to that drug. As a direct consequence of that selection, it is of little surprise that the study drug shows little, if any, effect. This could be the case of the study of Thadani et al. Conversely, if only patients who deteriorated in their clinical condition after withdrawal of the drug are enrolled, the trial will be biased toward selecting responders to that drug.

From a methodological point of view, patients who are taking drugs that have a mechanism of action that is similar or closely related to that of the study drug should not be included in this kind of trial.

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Reference


Reply

Dr. Fresco states that patient selection bias could have accounted for the lack of efficacy of twice-daily therapy with nisoldipine in patients with angina pectoris in our recently published multicenter study. We feel that Fresco is misinterpreting the results of our study. We found that compared with baseline values during single-blind placebo therapy, nisoldipine increased total exercise duration and reduced angina frequency during daily activities. However, these beneficial effects were not statistically different from the results obtained in a group of patients who received double-blind placebo therapy. This highlights the importance of rigorous placebo-controlled studies to evaluate antianginal drugs.

We did not provide detailed data regarding therapy with previous antianginal drugs including the dihydropyridine group of calcium channel blockers. Fresco has presumed that patients who were entered in our study were nonresponders to calcium channel blockers, especially dihydropyridine agents, as these patients did not deteriorate after withdrawal of antianginal therapy before entry in the study. We stated that 98% of patients were on previous antianginal drug therapy. The therapy included nitrates, β-blockers, calcium channel blockers, or a combination. The breakdown of previous antianginal therapy with regard to calcium channel blockers was Procacid, 22%; diltiazem, 25%; and verapamil, 5%. β-Blockers as monotherapy or in combination with nitrates or calcium channel blockers were used by 53.5% of the patients. It is true that previous therapy with antianginal drugs was discontinued before patient entry into the study. However, no formal testing of efficacy was performed to determine whether patients were responders or nonresponders to such therapy.

The fact that patients were weaned off therapy without problems does not in any way imply that these patients were nonresponders. In the absence of serial exercise tests or assessment of frequency of anginal attacks during daily activities before study entry and during withdrawal of therapy under blinded conditions, it would be impossible to assess the response to previous therapy. Of the 231 patients who entered the study and received single-blind placebo therapy, the reasons for disqualification from the double-blind segment of the study in the 46 patients (20%) was as follows: lack of reproducible exercise tests as defined in the protocol, 21 patients (9%); less than an average of three attacks of angina per week, eight patients (4%); concomitant disease, four patients (1%); patient refusal, six patients, (3%); protocol violation, three patients (1%); and worsening of anginal symptoms, five patients (2%). Thus, worsening of symptoms was the reason for exclusion from the double-blind portion of the study in only 2% of the 231 patients who entered the study.

All patients who entered the double-blind phase of the study stopped exercise due to angina of moderate severity and had an average of at least three attacks of angina per week during single-blind placebo therapy. This does not imply that these patients were either responders or nonresponders to previous antianginal therapy.

In a similar study design in a similar cohort of patients with stable angina pectoris who were receiving antianginal therapy, similar to the one used in our study, isradipine (another dihydropyridine calcium channel blocker) increased exercise duration compared with double-blind placebo but did not reduce angina frequency.1 In another similar study, diltiazem SR2 not only increased exercise duration but also decreased angina frequency compared with double-blind placebo therapy. Therefore, we do not agree with Fresco’s conclusion regarding his suggested reasons for the negative results of our study. The approach suggested by Fresco for designing studies to evaluate antianginal drugs is impractical and not based on any published scientific data.

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Efficacy of nisoldipine.
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