Safety of Placebo-Controlled Trials in Vasospastic Angina

Chahine et al. (1) recently reported the results of a randomized placebo-controlled trial investigating the effects of the long-acting dihydropyridine calcium antagonist amiodipine in 52 patients with vasospastic angina. All patients were in an acute phase of variant angina, with angiographically documented spasm of a major coronary artery and a mean number of 12 anginal attacks/week. Nevertheless, they were randomized to take amiodipine (10 mg once daily) or placebo for 4 weeks in double-blind conditions without any background prophylactic treatment. During the 4 weeks of the study, placebo-treated patients continued to suffer from a mean of 15 to 6 attacks/week, whereas the rate was reduced to 5 to 6 attacks/week in amiodipine-treated patients.

We (2,3) have previously argued that placebo-controlled trials should be avoided in variant angina because, during the active phase of this syndrome, acute myocardial infarction and sudden death may occur in up to 20% and 10% of patients, respectively, and calcium antagonists have clearly been shown to prevent these major cardiovascular events (4,5). Probably for this reason, placebo-controlled trials are not even requested by the Food and Drug Administration to support approval for vasospastic angina (particularly when a drug has already been approved for stable effort angina). The high number of anginal attacks reported for 4 weeks by the placebo-treated patients in the study of Chahine et al. (1) reinforces our arguments. In addition, 7 (26%) of their 27 placebo-treated patients were withdrawn from the study because of "therapeutic failure." What actually happened to these patients was not specified by the authors, although this information is of the greatest importance, because such "therapeutic failures" may mean intolerable angina, myocardial infarction or sudden death; in fact, two patients (8%) in the amiodipine group were "... withdrawn from the study because of therapeutic failure (one patient because of admission to the hospital to rule out myocardial infarction and one as a result of persistent intolerable angina)."

With regard to the efficacy of amiodipine, the authors conclude that "amiodipine given once daily is efficacious... in the treatment of vasospastic angina." Although several studies in hypertension and stable angina have shown the long duration of action of amiodipine, the conclusion that once-daily amiodipine is an effective treatment for vasospastic angina is only partially supported by the data of the Amiodipine Study 160 (1). Although amiodipine-treated patients experienced a reduction in the anginal attack rate from 12 to 5 attacks/week, the circadian distribution of these residual anginal episodes is not described by the authors. In vasospastic angina, anginal attacks are preferentially grouped in the early morning hours, and it is extremely important that any antianginal medication be effective during this time (6). This is particularly true for once-daily medications, which might lose efficacy toward the end of the dosing interval.

Reply

Ardissino and Savonitto primarily express their concern about performing placebo-controlled trials in vasospastic angina, and once more they recommend instead "active-controlled trials." Although it is understandable that one would be concerned about using placebo in any patient with cardiac symptoms, there is a consensus that this is still the best way to demonstrate efficacy and safety of newer therapy. The CAST study (1) and its results represent the best response to questions about the ethics of performing placebo-controlled trials in cardiac patients.

In our opinion, the concerns of Ardissino and Savonitto about the ethics of using placebo controls in our study are totally unjustified. We strongly feel that the benefits of our choice of protocol clearly outweigh the small and acceptable risks. The duration of the placebo phase in our study was short and patients were closely monitored. If there was any significant exacerbation of symptoms or adverse effects, the drug was stopped and patients were placed on open therapy. Our patients represented a rather low risk group: 75% had angiographically normal or near normal coronary arteries. No catastrophic events occurred during the placebo phase of our study or in the half-dozen or more placebo-controlled trials referenced in our study and the letter of Ardissino and Savonitto. Patients were properly informed of the potential risks, and our protocol was approved independently by the 15 different institutional review boards of the centers contributing to the trial. Further, the relative protective effects of the calcium antagonists were observed in long-term open studies but were never proved by controlled trials. To our knowledge, the Food and Drug Administration considers approval of newer therapies for vasospastic angina on the basis of at least one controlled trial (2). This singular requirement may be related more to the difficulty of finding enough patients to enroll than to ethical concerns.

References


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Although seven therapeutic failures were observed during the placebo phase of our study, nine patients had a partial or complete spontaneous remission, thus further emphasizing the importance of placebo controls. With respect to our coverage of the diurnal distribution of attacks of vasospastic angina, we believe that Savonitto and Ardissino have answered the question themselves, acknowledging that studies in hypertension and stable angina have demonstrated the long duration of action of amlodipine. They have also used a similar dosing schedule in their active-controlled trial of felodipine (3).

Finally, we are surprised that the letter of Morikami and Yasue (4) did not lay to rest the concerns of Savonitto and Ardissino about placebo-controlled trials in variant angina. All things considered, we wonder whether it would not be more justified to request long-term, randomized, placebo-controlled trials to effectively test the hypothesis that calcium antagonists are truly protective from myocardial infarction and sudden death in patients with variant angina than to continue to raise questions about short-term controlled trials.

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