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Letters to the Editor

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Does 'more' mean maximal therapy

In their review about chronic refractory angina, Mannheimer *et al.*[1] take for granted that the combination of a calcium antagonist with a beta-blocker or a nitrate is effective in stable angina. However, are such combinations more effective than a single-drug therapy with appropriate doses of a beta-blocker? This is far from certain.

It sounds logical to consider that these compounds exhibit complementary effects: one family of compounds (beta-blockers) decreases oxygen needs, while the other two families (nitrates and calcium antagonists) increase oxygen supply to the myocardium. Yet things are not that simple; these compounds have multiple common effects: beta-blockers increase oxygen supply by extending diastole duration, thus increasing coronary blood flow and improving perfusion of submyocardial layers. On the other hand, calcium antagonists reduce oxygen consumption through a decrease in left ventricular wall pressure and both chronotropic and inotropic effects (for verapamil and diltiazem). Therefore, the value of such combinations should be questioned, and only an analysis of the published clinical studies can provide the answer.

An early review published in 1989[2] has addressed all studies in which beta-blockers were used in combination with nifedipine, diltiazem and verapamil. The conclusion was that it appears wiser to increase the dosage of the drug prescribed first, in order to achieve an effective dosage level or to substitute the second drug if the patient appears to be a non-responder to the first one, rather than adding a second drug.

The advent of newer dihydropyridines does not change this conclusion: the TIBET Study[3] carried out in 608 patients concluded that the efficacy of a beta-blocker+sustained-release nifedipine combination is not improved compared to single-drug therapy with a beta-blocker; furthermore, the effectiveness of amlodipine given in combination with beta-blockers is not clearly demonstrated[4].

Regarding nitrates, their administration in combination with beta-blockers and calcium antagonists was only assessed in early, small-sized trials, which seldom used those assessment criteria (e.g. ischaemic threshold) taken into account in more recent studies. Moreover, the findings of these older trials are controversial, and often negative[5]. One should also keep in mind that no studies primarily aimed at assessing the combination of a nitrate patch with a beta-blocker are currently available.

It is amazing to note that the combination of haemodynamic treatment and cardiac metabolic agents is not mentioned whereas this combination is actually effective (at least in the countries where these agents are available) and widely demonstrated in the CARISA study (unpublished) for ranolazine and in the TRIMPOL II study for trimetazidine. This effectiveness is comprehensible because their action is truly different from the action of the other antianginal agents.

In conclusion, contrary to generally accepted concepts, the evidence that combining the three families of compounds most widely used in stable angina may be more effective than using appropriate doses of a single-drug therapy is weak, whatever the assessment criteria used: life expectancy, ischaemic threshold during exercise, exercise duration, weekly frequency of angina episodes. Can we consider that 'maximal' therapy is truly maximal if we do not use a combination of metabolic and haemodynamic agents?

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A reply

The letter regarding our 'Report from ESC joint Study Group on the Treatment of Refractory Angina', raised several interesting and important questions.

From a scientific standpoint we agree that there is meagre evidence in the literature supporting the combination of antianginal drugs in stable angina. However, we think that in clinical practice there is general acceptance for the testing of combination therapy in patients with severe angina, especially if invasive treatment modalities are not suitable. This is especially true for patients with refractory angina. In the study report, the discussion concentrates on optimizing medical treatment in refractory angina which in not equivalent to 'maximal therapy'.

The author finds it 'amazing' that we did not discuss metabolic agents in the management of refractory angina. The concept of optimizing the metabolism in the ischaemic myocardium by shifting metabolism from fatty acids towards more glucose utilization was approached many years ago. Perhexiline[1], ranolazine and more recently trimetazidine[2] have been documented in angina. However, not until recently has more extensive experience been reported in stable angina over a limited time. Some use of perhexiline in severe angina has been described[1]. However, this treatment is associated with neurotoxicity, limiting its usefulness. Other available agents require longer use and in more advanced patients before extended recommendation can include patients with refractory angina. We think that unpublished data in patients with stable angina cannot be referred to in this context.

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