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Ticlopidine in Unstable Angina

In response to the editorial comment by Dr. FitzGerald concerning our article, we have some observations. The purpose of our study was not to compare the clinical efficacy of ticlopidine with that of aspirin but rather to evaluate whether an antiplatelet drug with a mechanism of action different from that of aspirin could reduce cardiovascular complications in patients with unstable angina. Such a study could be useful to reaffirm the role of platelets in the evolution of unstable angina and to consequently define another therapeutic approach that, like aspirin, could improve the clinical course of such patients. Our study provides affirmative feedback to both points but does not indicate that ticlopidine is better than aspirin. We agree with Dr. FitzGerald that further study is necessary to assess the latter possibility. Nevertheless, from the clinical practice viewpoint, the data from our study should be carefully considered, especially as 10–20% of patients with unstable angina cannot be treated with aspirin.

Concerning the potential contamination of the trial results by the use of aspirin, as either prescribed or consumed independently by the patients, it can easily be argued that if there was contamination in the two groups, it would have been at the same or higher level in the control group. In that case, the comparison between the two treatments can be reasonably considered unbiased. Moreover, it should be pointed out that in Italy the use of aspirin in the prevention of occlusive ischemic events in patients with unstable angina is not a common practice, and that aspirin associated with ticlopidine markedly increases bleeding time. If there had been contamination, many bleeding disorders would have been observed in the ticlopidine group, but this did not occur.

With regard to the fact that our study was not controlled, we reply that the trial was a controlled, multicenter, and completely and centrally randomized trial; the routine therapy used in every center was compared with the same therapy plus ticlopidine. In this way, it was not necessary to modify the common therapeutic policy followed in the individual centers, and data were quickly obtained that could be transferred to clinical practice. Confirmation of this advantage is demonstrated by the 10 months of recruitment in our study compared with the 4 and 7 years of the studies of Lewis et al and Cairns et al, respectively, necessary to enroll a comparable number of patients. Our methodologic approach was consequently of a pragmatic type, like the model adopted by GISSI. For the same reason, the standard therapies adopted by the centers (calcium antagonists in 86% of the cases) were a spontaneous choice and not based on the meta-analysis of Held et al, which was published after our study concluded.

The decision to prematurely interrupt enrollment of patients was made not by the sponsor but by the study executive committee in accordance with the protocol (see “Sample Size”). Dr. FitzGerald also stresses that ticlopidine did not appear to have any preventive effect in our study during the first 20–30 days of treatment. This may be true, but it may not be correct to make such an extrapolation after the fact, keeping in mind that the scope of the study was to verify the efficacy of the drug in the prevention of fatal occlusive ischemic events within 6 months. In fact, many primary end points were observed in the control group after 16–180 days of treatment. This causes us to at least consider using antiplatelet treatment for a prolonged period of time, not just in the acute phase. Moreover, heparin may be preferable to aspirin in the early phase.

The “canard” of the possible different efficacy of aspirin with respect to sex could provide a basis for discussion, and we respect the opinion of Dr. FitzGerald. However, we would like to emphasize, as we stated, that Table 6 (concerning the frequency of events in relation to sex and to previous myocardial infarction) had only a descriptive purpose. In fact, we did not make any evaluation of such subgroups.

Finally, with regard to the increase in cholesterol levels induced by the chronic use of ticlopidine observed in a US study and a Swedish study, in our experience, such an effect has not been verified either in the unstable angina study or in our previous short- and long-term experiences.

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References

99mTc-MIBI and 201Tl as Perfusion Indicators

In his editorial comment,1 Dr. Willerson relates the results of our in vitro investigation of technetium-99m — hexakis 2-methoxy-2-isobutyl isonitrile (Tc-MIBI) and thallium-2012 to a recently published clinical study from his own institution demonstrating that Tc-MIBI provides superior-quality images and marginally improves coronary artery disease detection compared with 201Tl.3 Apparently feeling that there is a conflict between the results of his clinical study and our data showing that 201Tl is initially a better perfusion indicator than Tc-MIBI, Dr. Willerson indicates that results obtained in isolated hearts may not accurately reflect the relative advantages of myocardial perfusion agents such as Tc-MIBI and 201Tl and that in vivo evaluation of these tracers using contemporary imaging devices is necessary to determine their clinical usefulness. Although we do not disagree with either of these assertions, we feel there is no conflict between the results of these two studies and that these statements do not pertain to the comparison of our in vitro investigation with his in vivo study4,5; in addition, these statements tend to obscure the importance of in vitro evaluation of Tc-MIBI and 201Tl as perfusion indicators. The rationale of why we believe that these two studies are compatible is outlined below.

First, it is important to distinguish between the accuracy with which Tc-MIBI and 201Tl measure myocardial blood flow and their respective abilities to detect clinical coronary artery disease. Data acquired in vivo using standard single-photon imaging techniques are products of the individual imaging characteristics of the radionuclide used and the accuracy with which the radionuclide measures blood flow. Because 99mTc is clearly superior to 201Tl as an imaging nuclide, Tc-MIBI should be superior to 201Tl in detecting clinical coronary artery obstruction if these two tracers were equal in their accuracy of perfusion measurement. However, in reported studies,4,5 Tc-MIBI has been only marginally superior to 201Tl in the detection of coronary artery disease. One explanation for the current clinical results is that 201Tl might be superior to Tc-MIBI in the measurement of blood flow in some patients at the time of image acquisition. This explanation is also compatible with the data obtained in our in vitro investigation.

Second, in contrast to our single-pass evaluation of Tc-MIBI and 201Tl, data acquired in vivo after systemic administration reflect both first-pass and recirculating tracer extraction and retention. Previous studies have documented important differences in myocardial 201Tl kinetics when comparing results obtained in the presence with those obtained in the absence of 201Tl recirculation.5 In our “Discussion,” we clearly indicate that Tc-MIBI recirculation will alter in vivo Tc-MIBI kinetics and its stabilizes a perfusion indicator relative to that reported in our in vitro single-pass study. Similarly, our results also suggest that 201Tl might be superior to Tc-MIBI as a perfusion indicator for only a short time after tracer introduction and that it is impossible to predict the exact time at which 201Tl will lose its advantage over Tc-MIBI in individual patients. Therefore, our results are consistent with the possibility that Tc-MIBI might measure blood flow more accurately than 201Tl in some patients at the time of clinical image acquisition, a possibility that is also compatible with the study reported by Dr. Willerson's group.

The results of currently reported in vitro and in vivo investigations are compatible, as we support and encourage continued evaluation of Tc-MIBI as a perfusion indicator.

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References

Reply

I did not intend to imply that there is some conflict between the results of the study of Dr. Marshall and associates1 and our earlier in vivo evaluation.2 I apologize for any misunderstanding. However, I did state that in vivo assessments of the comparative value of thallium-201 and technetium-99m–MIBI have been made using single-photon emission computed tomography, and the results from those studies are consistent with the notion that 99mTc-MIBI will be valuable in the noninvasive analysis of myocardial perfusion using nuclear imaging methodology.2,3 I stress the need to obtain in vivo assessments of perfusion markers to make final determinations about the usefulness of such agents in the evaluation of myocardial perfusion in humans. Of course, it is important to also study pathophysiology and mechanisms of uptake and washout of myocardial perfusion agents in isolated hearts and experimental animal models. The data available, including Marshall et al’s1 and several other experimental and clinical evaluations,4–5 provide considerable optimism that 99mTc-MIBI will be a very good alternative to 201Tl for noninvasive myocardial perfusion evaluations in humans.

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