Editorial Comment

Ticlopidine in Unstable Angina
A More Expensive Aspirin?

Garret A. FitzGerald, MD

Unstable angina is a syndrome in which the occlusion of coronary arteries by platelet-dependent thrombus formation may result in myocardial infarction and death.\textsuperscript{1} Angiographic\textsuperscript{2} and angioscopic\textsuperscript{3} evidence of thrombus formation is complemented by the measurement of increased concentrations of thromboxane (TX) metabolites in plasma and urine during ischemic episodes in patients with this disease.\textsuperscript{4} TXA\textsubscript{2} is the major cyclooxygenase product of arachidonic acid metabolism in human platelets and is a potent platelet activator and vasoconstrictor. Aspirin, which irreversibly inhibits this enzyme by acetylation of a serine residue close to the active site,\textsuperscript{5} has been shown to reduce significantly myocardial infarction and death in four placebo-controlled, double-blind trials.\textsuperscript{6-9} Although it is possible that other pharmacological properties of aspirin are relevant, its efficacy has been explicable in terms of its action as an inhibitor of platelet cyclooxygenase.

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It is recognized that cyclooxygenase blockade is not the optimal means of platelet inhibition. For example, endogenous compounds other than TXA\textsubscript{2}, including thrombin, collagen, epinephrine, and adenosine diphosphate, are recognized to aggregate platelets. Although it seems odd that inhibition of just one pathway of activation should have effects sufficiently profound as to be detected by so crude an instrument as a clinical trial, this may reflect the role of TXA\textsubscript{2} as an amplifying signal for other platelet agonists. Furthermore, coincident inhibition of the vascular synthesis of platelet inhibitory prostaglandins, such as prostacyclin, may limit the efficacy of even low doses of aspirin. These observations have prompted the evaluation of alternative strategies, including inhibition of phosphodiesterase and thromboxane synthase enzymes, blockade of thromboxane and serotonin receptors, and the infusion of platelet inhibitory prostaglandins and combinations of these drugs.

Despite the logic that underlies the quest for a “better aspirin,” the clinical development of promising candidates has been tempered by concern that the result of this effort may be merely a “more expensive aspirin.” Both the risks and benefits that may be derived from developing a successor to aspirin are exemplified by ticlopidine. The mechanism of action of ticlopidine is unclear. The most careful study suggests that it induces a defect in the mobilization of the glycoprotein IIb/IIIa complex in activated platelets, so that its ability to serve as a receptor for adhesive macromolecules, such as fibrinogen, is compromised.\textsuperscript{10} Such adhesive interactions are thought to represent a final step in the stabilization of platelet aggregates,\textsuperscript{11} and studies of antibodies,\textsuperscript{12,13} venoms,\textsuperscript{14} and synthetic peptides\textsuperscript{15} directed against this complex suggest that prevention of these interactions is a potent approach to platelet inhibition. Small studies have demonstrated the effects of ticlopidine on indices of platelet function, such as inhibition of platelet aggregation ex vivo\textsuperscript{16} and prolongation of platelet turnover time\textsuperscript{17} in patients with atherosclerotic disease. More impressively, in two large multicenter double-blind placebo-controlled clinical trials,\textsuperscript{18,19} ticlopidine has been shown to reduce the incidence of stroke in patients with transient ischemic attacks.\textsuperscript{18,19} In one of these, the efficacy of ticlopidine (250 mg twice per day) was marginally superior to aspirin (650 mg twice per day), with which it was compared. The 3-year event rate for nonfatal stroke or death was 17% for ticlopidine and 19% for aspirin. The 95% confidence interval for the percentage risk reduction with ticlopidine varied from −2% to 26%, but this difference from aspirin was significant at \( p=0.048.\textsuperscript{18} \) Ticlopidine has now been approved for sale in several European countries but not, as yet, in the United States or Canada. It is more commonly prescribed as a platelet inhibitor than is aspirin in Japan, where its sales exceeded $240 million in 1988–1989.

Such observations would appear to provide ample justification for the decision to invest further in the clinical development of a theoretically more effective challenger to aspirin. However, ticlopidine also illustrates the risk; an unanticipated side effect of the drug was a small (<0.9%) but definite incidence of…
neutropenia, which in some cases was profound (<450 cells/cmm). An additional finding that was unexpected was an increase in serum cholesterol of roughly 10% on ticlopidine. The implications of this latter observation remain to be explored.

In this issue of Circulation, Balsano et al report on their experience with ticlopidine in 652 of 2,438 patients screened for entry into a study of unstable angina. The principle finding of this randomized trial is that patients who received ticlopidine (250 mg twice per day) had a significant (p < 0.009) reduction in the incidence of the combined primary end point (vascular death and nonfatal myocardial infarction) — from 13.6% to 7.3% — compared with patients who did not receive ticlopidine. From these observations, it is suggested that ticlopidine now constitutes an alternative to aspirin in the treatment of this condition. However, there are several reasons that this conclusion may be viewed as premature.

Despite the title of the article by Balsano et al, the trial was not controlled. Thus, the patients who were randomized not to receive ticlopidine did not receive a ticlopidine placebo; they received “conventional treatment” alone. This included nitrates and antagonists of both calcium channels and β-adrenergic receptors, which meant that the study was not blinded. Although the Validation Committee was blinded, both the patient and the physician were potentially aware of who was or was not receiving ticlopidine. This issue is of relevance to the potential contamination of the trial results by aspirin, either as prescribed or consumed independently by the patients. Two double-blind, placebo-controlled studies had been published demonstrating that aspirin reduced the incidence of myocardial infarction and death by 50% in patients with unstable angina by 1985. The study by Balsano et al, designed in 1986, excluded aspirin. This seems odd, given the lack of comparable data at the time for calcium channel blockers, which were administered to 86% of the patients. Indeed, a recent meta-analysis of trials with these agents supports the contention that calcium antagonists have no effect on myocardial infarction or death in patients with unstable angina.

While the ethics of the decision to exclude aspirin seem at least questionable, it must be recognized that it is a point of view which may not have been adhered to by either the participating patients or their doctors (including those outside the study). Given the absence of a biochemical measurement to screen for compliance with the request to abstain from aspirin and the unblinded trial design, the extent of aspirin consumption by both groups must remain an open question.

A second concern relates to the nature of the data analysis. This was performed by the sponsoring drug company, Midi-Sanofi. Detection of the projected 10% reduction in the primary end point would have required 474 patients in each group. It is unclear whether the decision to terminate the study prematurely when data were available on roughly two thirds of that number was made entirely independently of Midi-Sanofi. Such concerns confounded the interpretation of an earlier trial of the platelet inhibitor sulfipyrazone in the secondary prevention of acute myocardial infarction. They are pronounced when it is decided to terminate a trial prematurely, a decision that tends to amplify the magnitude of a positive result. Clearly, such concerns can be addressed by designating data manipulation and analysis to an independent academic center, as has become the convention with large-scale clinical trials in cardiovascular disease.

Finally, this study highlights two properties of drug action that apply to both ticlopidine and aspirin. Aspirin inhibits the cyclooxygenase irreversibly; thus, in the platelet, which cannot synthesize new enzyme, repeated exposure to incompletely effective doses will result in cumulative inhibition of TXA2 formation. In practice, it takes several days to inhibit platelets completely with 30 mg/day aspirin, whereas maximal inhibition occurs after a single dose of 100 mg aspirin or above. Similarly, 500 mg/day ticlopidine has been shown to take up to 5 days to achieve 90% inhibition of ADP-induced platelet aggregation and of the binding to fibrinogen to platelet membranes. This may relate to the possibility that ticlopidine, like sulfipyrazone, functions as a pro-drug. The delayed onset and offset of its action and the more striking platelet inhibitory effects of ticlopidine ex vivo than in vitro are consistent with this possibility. However, conclusive evidence in support of this assumption remains to be published, and a candidate metabolite has not been identified in man. A delayed onset of action may represent a limitation in patients presenting with unstable angina. Interestingly, the divergence in the cumulative event rates in the two groups described by Balsano et al was not observed until 20–30 days after entry into the trial. Like aspirin, the offset of action of ticlopidine corresponds to platelet turnover time.

The second point relates to the sex dependence of the antiplatelet effects of both drugs. This canard derives from the apparent failure to detect an impact on the small number of women in a clinical trial of aspirin for the prevention of stroke. However, there is no basis for such a difference in studies of the pharmacokinetics or pharmacodynamics of aspirin. Neither the study of aspirin in stroke nor the present study of ticlopidine contains sufficient numbers to address the possibility of sex-related differences in drug effect. In addition, neither addressed this possibility a priori; the pitfalls of post hoc analysis were nicely illustrated by the convergence of the response to thrombolysis with signs of the zodiac in ISIS-2. Based on our knowledge of the pharmacology of both drugs, there is no reason to suspect that either will be less effective in women than in men; however, this hypothesis remains to be addressed definitively.

Is ticlopidine merely a “more expensive aspirin” for use in unstable angina? To answer this question we need to assess price, side effects, and efficacy. Ticlopidine, like any foreseeable new drug in this
area, is likely to be more expensive than aspirin. In Italy, where both drugs are on the market and where the study of Balsano et al was conducted, the yearly cost per patient is $750 for ticlopidine (500 mg/day) and $20–24 for different brands of aspirin (500 mg/day). Adverse effects are relatively uncommon with both drugs. However, neutropenia is a worry with ticlopidine, and we need more information to reassure us of the frequency and reversibility of this risk. Given its low incidence in a larger study,18 the failure to detect “abnormalities of clinical importance” in the work of Balsano et al20 does not exclude this concern. Less serious but more frequent adverse effects of ticlopidine include gastrointestinal upsets and skin rashes. The most common side effects with aspirin are skin rashes. However, these are dose related. Given the unique response of the platelet to aspirin, it is possible to reduce significantly myocardial infarction and death in patients with unstable angina with daily doses (75 mg) at which the incidence of gastric complaints does not exceed that on placebo.9 Clinically significant bleeding complications have not been evident with either drug. Even if we can be reassured about neutropenia, does the greater effectiveness of ticlopidine justify the difference in price? Although ticlopidine may be superior to aspirin in the prevention of stroke, insight into their comparative efficacy in unstable angina will derive only from a randomized, double-blind comparison of the two drugs. A failure to undertake this “aspirin challenge” will paralyze the development of ticlopidine and other potentially more efficacious antithrombotic drugs.

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G A FitzGerald

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