Increased Mortality With Long-Term Platelet Glycoprotein IIb/IIIa Antagonists: An Explanation?

To the Editor:

The increased mortality during long-term administration of oral glycoprotein IIb/IIIa antagonists as secondary prevention reported by Chew et al is indeed unexpected and perplexing. A possible hint may be given by the recent in vitro observations of Li et al. When platelets are activated with collagen in hirudinized whole blood in the presence of a glycoprotein IIb/IIIa antagonist, more platelet-leukocyte conjugates are formed. Conjugate formation is a consequence of P-selectin expression on the activated platelets and interaction of P-selectin with P-selectin glycoprotein ligand-1 and CD15 on leukocytes. Presumably because of the inhibition of platelet-platelet aggregation by glycoprotein IIb/IIIa antagonists, more activated platelets are available for heterotypic conjugation. Such platelet-leukocyte conjugates not only express tissue factor activity; they also facilitate the adhesion of leukocytes to the vessel wall in areas of high shear stress. They therefore may enhance inflammation in atherosclerotic plaques and thereby promote plaque destabilization. In vivo confirmation of the in vitro observations of Li et al may help solve the glycoprotein IIb/IIIa antagonist paradox.

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6. Theilmeier G, Witting S, Ziemer L, et al. Increased platelet count is predominantly observed as a greater rate of increased adverse event rate associated with an elevated white cell count is predominantly observed as a greater rate of mortality (D. Bhatt, MD, personal communication, 2001).

Response

The increased mortality observed with the prolonged administration of the oral glycoprotein IIb/IIIa antagonists currently defies adequate explanation. To date, few clinical data shedding further light on the mechanisms of this fatality risk are available. Several putative explanations have been raised, including suboptimal plasma levels associated with oral dosing, yet it is difficult to account for the obvious “disconnect” between the suppression of platelet aggregation and the excess mortality. This point is underscored by the improved long-term outcome associated with clopidogrel in addition to aspirin observed in the recently completed Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial. We agree with Dr Vermeylen and colleagues, finding the link between the long-term use of glycoprotein IIb/IIIa receptor antagonists and proinflammatory effects particularly intriguing. The observation that moderate levels of inhibition with these agents is associated with increased expression of CD40 ligand (D. Phillips, PhD, personal communication, 2000) also deserves further investigation. These data are consistent with the evidence implicating inflammatory processes in the short- and long-term outcomes after coronary instability. Of note, the increased adverse event rate associated with an elevated white cell count is predominantly observed as a greater rate of mortality (D. Bhatt, MD, personal communication, 2001).

However, the precise mechanism by which inflammation contributes to excess risk requires further elucidation. Although inflammation and thrombosis are undoubtedly one and the same process, the clinical data thus far accumulated do not necessarily indicate an increased rate of epicardial plaque instability and thrombosis. In the meta-analysis of the 4 initial glycoprotein IIb/IIIa trials, we found an excess in mortality only, with a neutral effect on myocardial infarction and a reduction in revascularization. These findings were subsequently corroborated by the Blockade of the IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO) trial, which brings the total phase III trial experience to 42,523 patients. Again, in this trial, mortality was increased without an increase in myocardial infarction. Thus, although mechanisms that promote the proinflammatory role of platelets may well underlie this fatality risk, the current data are more in keeping with effects on the distal microcirculation or directly on the myocardium. Whether these effects are inflammatory or toxic remains speculative.

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_Circulation_. 2001;104:e109

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/104/20/e109

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