Thrombocytopenia and Glycoprotein IIb/IIIa Inhibitors: Causation or Association?

To the Editor:

Trials of glycoprotein IIb/IIIa inhibitors (GPI) in acute coronary syndromes (ACS) reveal that thrombocytopenia occurs with an incidence of up to 3.7%.1 McClure et al2 confirm the association of thrombocytopenia and ACS and correlate this with adverse bleeding and ischemic events. However, unlike previous studies, they found no association between GPI and thrombocytopenia.3 Understanding the mechanism of thrombocytopenia may aid in resolving this discrepancy.

The method of platelet count determination may help identify the mechanism of the thrombocytopenia. Platelet counts are determined by techniques that rely on their size. A gate is set, above which platelets are not included in the count, even when present. This forms the basis for detecting microaggregation.4 Many modern hematological analyzers provide a size histogram for platelets that extends beyond the counting gate. This enables “true” thrombocytopenia to be differentiated from “microaggregation thrombocytopenia.”

Microaggregation is important because unstable angina can cause platelet activation via P-selectin and other inflammatory mediators. Thus, the thrombocytopenia may represent an extensive inflammatory response causing secondary platelet activation.

Thrombocytopenia per se (eg, idiopathic thrombocytopenia) does not increase the incidence of acute coronary events, but it does increase bleeding complications. However, thrombocytopenia in the presence of microaggregation (eg, thrombotic thrombocytopenia purpura and antiphospholipid syndrome) is associated with both bleeding and thrombotic complications, including acute coronary events.

Possible mechanisms of GPI-induced thrombocytopenia include the following: (1) the inhibition of megakaryocytes expressing glycoprotein IIb/IIIa receptors5 (this is unlikely because platelet half-life is 10 days and ACS thrombocytopenia usually occurs within 48 hours); (2) increased destruction, as in Kasabach-Merritt syndrome, although the small size of the coronary thrombus makes this unlikely; and (3) increased microaggregation secondary to activation of the inflammatory system. The association between thrombocytopenia and GPI may be spurious due to selection bias, because those not on GPI therapy may have died before counts could be taken, whereas treatment may have allowed the high-risk patients to survive.

The mechanism of thrombocytopenia has important implications for treatment because a non-glycoprotein IIb/IIIa mechanism, such as in idiopathic thrombocytopenia (Fc-mediated) and thrombotic thrombocytopenia purpura (Von Willebrand multimeric protease deficiency), would predict a poor response to GPI. The different ligand affinities of the various GPIs further complicate the issue. Far from actually being associated with thrombocytopenia, GPIs, by reducing platelet fibrinogen interaction, may reduce the high risk associated with microaggregation thrombocytopenia, which can be easily detected clinically by using the size histogram function of the common laboratory Coulter counter.6

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