Platelet Inhibition After Glycoprotein IIb/IIIa Inhibitor Therapy

To the Editor:

In their clinically sound GOLD (AU-Assessing Ultegra) study, Steinhubl et al\(^1\) reported striking results concerning the widely variable level of platelet function inhibition achieved with glycoprotein IIb/IIIa (GP IIb/IIIa) antagonists among patients undergoing percutaneous coronary intervention. They also documented the important clinical implications related to this variability, because low levels of platelet inhibition were linked to more periprocedural thrombotic events.

In the GOLD study, significant variability in the level of platelet inhibition was found in the Ultegra (Accumetrics, Inc) rapid platelet function assay with 3 different GP IIb/IIIa inhibitors 10 minutes after bolus (96\pm10\% after abciximab, 97\pm7\% with tirofiban, and 90\pm9\% after eptifibatide single bolus, \(P<0.001\) versus abciximab and tirofiban) and 1 hour later (96\pm7\% after abciximab, 95\pm6\% with tirofiban, and 89\pm9\% after eptifibatide, \(P<0.001\) versus abciximab and tirofiban).

A factor that should be emphasized is the small number of patients treated with eptifibatide in GOLD study (7\% versus 84\% who received abciximab). It should also be noted that blood samples from patients receiving eptifibatide were obtained in blood tubes containing Phe-Pro-Arg chloromethyl ketone (PPACK) anticoagulant, whereas samples from patients receiving abciximab or tirofiban were obtained in blood tubes containing a sodium citrate anticoagulant. In the Prairie ReoPro Versus Integrilin Cost Evaluation (PRICE) trial, the degree of platelet inhibition was assessed in 74 patients receiving abciximab and in 81 treated with eptifibatide.\(^2\) All blood samples contained the PPACK anticoagulant, and platelet aggregometry was evaluated by a platelet function assay similar to that used in the GOLD study. Platelet inhibition 10 minutes after GP IIb/IIIa inhibitor bolus was similar among abciximab- and eptifibatide-treated patients (95\% versus 96\% median values, respectively, not significant by ANOVA).\(^2\)

The use of citrate for anticoagulation in platelet aggregation assays leads to a decrease in ionized calcium concentration and, therefore, to an overestimation of the in vivo antiplatelet effects of GP IIb/IIIa blockers.\(^3\) In patients enrolled in the Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-II (IMPACT II) trial, the dosing regimens of eptifibatide (a bolus of 135 \(\mu\)g/kg followed by infusions of 0.5 to 0.75 \(\mu\)g \cdot kg\(^{-1}\) \cdot min\(^{-1}\)) yielded steady-state plasma concentrations expected to inhibit ADP-stimulated platelet aggregation by 70\% to 80\% in citrate-anticoagulated plasma samples.\(^4\) On the contrary, the degree of inhibition of ADP-induced platelet aggregation in PPACK-anticoagulated blood by similar eptifibatide infusion doses was found to be significantly lower (35\% to 50\%) and of limited clinical usefulness.\(^4\)

In their article, Steinhubl and coworkers\(^1\) report the strange finding of a decreasing risk of thrombotic events if platelet function is inhibited <85\% at 10 minutes. They interpret this result as a likely sampling aberrancy. I wonder whether the puzzling result of “down-and-up” risk for thrombotic events as the degree of inhibition approaches 95\% could be related to the different anticoagulants used. Among abciximab-treated patients, is the platelet inhibition–thrombotic events relationship also “down-and-up”?

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