Immune Thrombocytopenia Caused by Glycoprotein IIb/IIIa Inhibitors*

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Agents that react with the platelet glycoprotein (GP) IIb/IIIa complex (αIIb/β3 integrin) to block fibrinogen binding and platelet-platelet aggregation have been proved to be effective in reducing the incidence of complications following coronary angioplasty and are now widely used for this purpose. Acute thrombocytopenia, which is sometimes severe and life-threatening, is a recognized side effect of this class of drugs. In contrast to other types of drug-induced thrombocytopenia, this complication can occur within a few hours of a patient's first exposure to the medication. Accumulating evidence has indicated that drug-dependent antibodies, which can be naturally occurring, are the cause of platelet destruction in such individuals. In this review, we will consider the clinical aspects of thrombocytopenia resulting from sensitivity to GPIIb/IIIa inhibitors and will review evidence that the platelet destruction is antibody-mediated.

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Key words: abciximab; eptifibatide; glycoprotein IIb/IIIa inhibitors; thrombocytopenia; tirofiban

Abbreviations: DITP = drug-induced immune thrombocytopenia; EDTA = ethylendiaminetetraacetic acid; GP = glycoprotein; RGD = Arg-Gly-Asp

The glycoprotein (GP) IIb/IIIa inhibitors are a new class of antithrombotic agents that are effective because they block the binding of fibrinogen to activated GPIIb/IIIa, thereby inhibiting platelet-platelet interaction and thrombus formation.[1–3] GPIIb/IIIa inhibitors have been shown to reduce secondary complications following coronary angioplasty and are now being evaluated for their ability to prevent thrombosis in patients with other conditions. Three GPIIb/IIIa inhibitors, abciximab, tirofiban, and eptifibatide, have been approved for clinical use in the United States and other countries. All are given by IV administration, usually for 12 to 18 h after the patient undergoes angioplasty. Agents designed for oral administration are in various stages of development.[4]

Drug-induced immune thrombocytopenia (DITP) is an unpredictable and sometimes serious side effect of many medications, including heparin, quinine, sulfonamides, and other antibiotics, especially vancomycin, rifampicin, cephalosporins, other sulfonamide compounds, and nonsteroidal antiinflammatory drugs.[5,6] It has been recognized[7,8] that DITP is a relatively common side effect of GPIIb/IIIa inhibitors. The mechanisms by which GPIIb/IIIa inhibitors induce thrombocytopenia differ from those thought to be responsible for thrombocytopenia induced by drugs such as quinine and certain antibiotics. This review will consider the clinical features and pathogenetic mechanisms of thrombocytopenia induced by the GPIIb/IIIa inhibitors.

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Immune Thrombocytopenia in Patients Treated With Abciximab

Clinical Presentation

Acute Thrombocytopenia After First or Second Exposure to Abciximab: Abciximab (ReoPro; Eli Lilly; Indianapolis, IN) is a chimeric (human/mouse) Fab fragment that is derived from a murine monoclonal antibody, 7E3, that binds to an epitope on the GPIIb/IIIa complex close to a critical binding site for fibrinogen, thereby inhibiting its reaction with the activated integrin.[1] To create abciximab, N-terminal sequences in 7E3 that control its specificity were incorporated into a human IgG1 framework. The intact chimeric IgG molecule then was cleaved by papain to produce the Fab fragment abciximab.[1] In clinical trials[8,9] of abciximab and in subsequent experience, it was found that about 1% of patients

given this drug experienced acute, often severe thrombocytopenia. After a second exposure to the drug, the rate for this complication rises to about 4%.[10] In some instances, the onset of thrombocytopenia was accompanied by fever, dyspnea, hypotension, and even frank anaphylaxis, occurring soon after starting the drug.[11–13] Although most patients with abciximab-associated thrombocytopenia recover uneventfully, life-threatening bleeding has been described,[13] and several patients have experienced intracranial hemorrhage.[14,15]

Delayed Thrombocytopenia After Abciximab: Although abciximab-induced thrombocytopenia usually occurs within a few hours of starting therapy with the drug, a subgroup of patients has been described in whom the drop in platelet levels occurred 5 to 8 days after the drug was administered.[16,17] Recent studies have provide an explanation for this type of presentation (see below).

Abciximab-Associated Pseudothrombocytopenia: A subset of patients with abciximab-induced "thrombocytopenia" actually will have a circulating platelet count in the normal range. In such cases, low platelet counts obtained with automated counting instruments were found to be a consequence of the *in vitro* clumping of platelets in blood samples anticoagulated with ethylenediaminetetraacetic acid (EDTA).[18,19] Pseudothrombocytopenia in patients who have received abciximab can usually be distinguished from true thrombocytopenia by repeating a platelet count in blood that has been anticoagulated with citrate and/or by estimating the platelet levels in a peripheral blood smear prepared from a fingerstick. The mechanism by which abciximab promotes the *in vitro* clumping of platelets in blood anticoagulated with EDTA is not known.

Pathogenesis

The development of severe thrombocytopenia within hours of a patient's first exposure to abciximab is in distinct contrast to most types of DITP, which occurs in patients who have previously been exposed to the sensitizing drug or have received it for a number of days. Accordingly, nonimmune mechanisms were initially considered as a possible explanation for the acute platelet destruction that is typical of this condition. Some reports[20–23] were consistent with this possibility, but others[24,25] argued against it, leaving this question unresolved.

Thrombocytopenia After Second Exposure to Abciximab: Direct evidence for the immune destruction of platelets in patients who have received abciximab was provided by studies[13] showing that a group of patients who developed severe thrombocytopenia after a second exposure to the drug all had strong IgG and/or IgM antibodies that reacted with abciximab-coated platelets in a flow cytometric assay (Fig 1). The specificity of this finding was called into question by the observation that some healthy individuals (both those who were exposed to the drug and those unexposed) have similar types of antibodies, although they are generally weaker than those found in patients with abciximab-induced thrombocytopenia.[13] However, it was found that most antibodies from patients with abciximab-induced thrombocytopenia can be distinguished from the antibodies commonly found in healthy individuals in two ways. First, the antibodies found in healthy subjects recognize the papain cleavage site at the C-terminus of the abciximab molecule[13,26] and can thus be inhibited by Fab fragments, whereas patient antibodies are resistant to this treatment. Second, the antibodies from patients react preferentially with platelets coated with the intact monoclonal antibody 7E3, from which the specificity-determining sequences incorporated into abciximab were derived, whereas antibodies from nonthrombocytopenic individuals do not[13] (Fig 2). It has been known for many years that healthy individuals can have naturally occurring antibodies that recognize enzymatic cleavage sites in human Igs.[27,28] It appears that antibodies found in healthy individuals that react with abciximab-coated

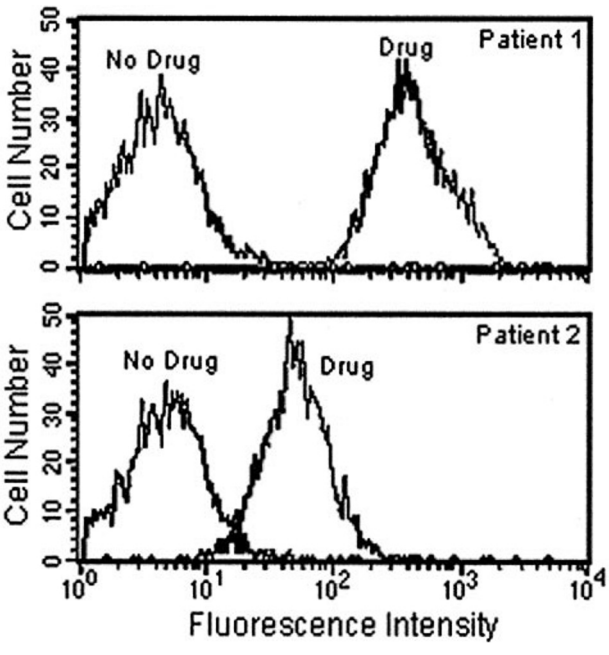

FIGURE 1. Reactions of strong IgG antibodies (*top*) and weak IgG antibodies (*bottom*) from patients with abciximab-induced thrombocytopenia with abciximab (Drug)-coated platelets. No reaction was obtained with uncoated (No Drug) platelets. From Curtis et al,[13] with permission.