Journal of Thrombosis and Haemostasis, **4**: 678–679

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Thrombocytopenia associated with the use of GPIIb/IIIa inhibitors: position paper of the ISTH working group on thrombocytopenia and GPIIb/IIIa inhibitors

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To cite this article: Aster RH, Curtis BR, Bougie DW, Dunkley S, Greinacher A, Warkentin TE, Chong BH on behalf of The Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Thrombocytopenia associated with the use of GPIIb/IIIa inhibitors: position paper of the ISTH working group on thrombocytopenia and GPIIb/IIIa inhibitors. *J Thromb Haemost* 2006; **4**: 678–9.

GPIIb/IIIa inhibitors are known to reduce the incidence of adverse complications after coronary angioplasty by inhibiting the reaction of fibrinogen with the activated platelets, and are now widely used. Acute thrombocytopenia is a recognized side effect of the three clinically approved inhibitors – tirofiban and eptifibatide, synthetic compounds that mimic or contain the Ang-Gly-Asp (RGD) peptide and bind tightly to the RGD recognition site in GPIIb/IIIa, and abciximab, a chimeric Fab fragment specific for an epitope on GPIIIa [1,2]. Although most patients experiencing thrombocytopenia after treatment with these drugs recover uneventfully, severe bleeding and fatalities have been described. Here, we review the clinical presentation, pathogenesis, and diagnosis of this disorder, and highlight the unresolved issues that deserve further study.

Clinical presentation

Recognized presentations associated with the use of GPIIb/IIIa inhibitors are summarized in Table 1 with selected references [3–13]. Most reported cases occurred after first exposure to one of these drugs, but the incidence of thrombocytopenia appears to be greater in patients treated a second time, especially with abciximab [6]. Occasional patients have acute hypersensitivity reactions that can be fatal [7]. In most reported cases, thrombocytopenia was severe (platelets $< 10\ 000\ \mu L^{-1}$) but bleeding symptoms were variable, ranging from none to a few petechiae to fatal intracranial hemorrhage. Upon discontinuation of treatment, platelet levels returned to normal in 2–5 days [1,2].

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Pathogenesis

Acute platelet destruction occurring after exposure to a GPIIb/IIIa inhibitor suggested that non-immune factors might be operating. However, studies failed to support this possibility [1,2] and recent reports indicate that, in most instances, platelet destruction is caused by drug-dependent antibodies [3,4,8,10]. Thrombocytopenia occurring after first exposure to a GPIIb/IIIa inhibitor appears to be explained by the fact that antibodies are naturally present in some normal individuals [4]. Delayed onset of thrombocytopenia is explained by persistence of platelet-bound drug for several weeks after treatment, rendering platelets susceptible to destruction by newly formed antibody [10].

Antibody detection

Various assays have been used to show that most patients developing thrombocytopenia after treatment with a GPIIb/IIIa inhibitor have antibodies that recognize GPIIb/IIIa occupied by the provocative drug (Table 2). The favored method involves flow cytometric detection of immunoglobulins in patient's serum that bind to normal platelets in the presence, but not in the absence, of the implicated drug. Antibodies are not detectable in all patients, even those with a history strongly suggestive of drug sensitivity, possibly because optimal conditions for antibody detection have not yet been defined. A single method may not suffice for all patients, as antibodies specific for ligand-mimetic drugs vary in their requirement for ionized calcium [4]; and special procedures are needed to distinguish pathogenic antibodies capable of causing thrombocytopenia in patients given abciximab from apparently 'benign' ones that also recognize abciximab-coated platelets [8,10].

Table 1 Characteristics of thrombocytopenia in patients treated with GPIIb/IIIa inhibitors and selected references

Presentation	Tirofiban, eptifibatide, and roxifiban	Abciximab
Acute, severe (platelets often < 10 K) thrombocytopenia within 12 h of first exposure	[3,4]	[5,6]
Acute thrombocytopenia within 12 h of second exposure	[7]	[8]
Delayed thrombocytopenia 5–7 days after treatment	[9]	[10]
Anaphylaxis after first or second exposure	[7,11]	[8,12]
Pseudothrombocytopenia (asymptomatic)	Not reported	[13]

Table 2 Detection of antibodies in patients with thrombocytopenia induced by GPIIb/IIIa inhibitors

Method	Ligand-mimetics [References]	Abciximab [References]
Flow cytometry	[3,4]	[8,10]
Solid phase ELISA	[3,4]	[8]
Serotonin release	[14]	Not reported
Immunoblotting	[3]	Not reported

Table 3 Unresolved issues concerning thrombocytopenia in patients treated with GPIIb/IIIa inhibitors

Clinical issues

1. What is the physiologic significance of naturally occurring antibodies that recognize GPIIb/IIIa occupied by an inhibitor?
2. Do antibodies induced by ligand-mimetic inhibitors predispose patients to platelet activation and thrombosis?
3. Can the incidence of thrombocytopenia be reduced by prescreening for antibody before administering a GPIIb/IIIa inhibitor? If so, is this practical?
4. Do non-immune mechanisms cause thrombocytopenia in some patients?

Technical issues

5. What conditions are optimal for detection of antibodies capable of causing thrombocytopenia in patients given a GPIIb/IIIa inhibitor?
6. What is the best way to distinguish between antibodies that cause thrombocytopenia in patients given abciximab and those that recognize abciximab complexed with GPIIb/IIIa but do not affect platelet survival?
7. How common is abciximab-induced pseudothrombocytopenia and what is the best way to distinguish it from 'true' thrombocytopenia?
8. What target epitopes on ligand-occupied GPIIb/IIIa are recognized by antibodies that cause thrombocytopenia?

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Unresolved issues

Further studies to understand thrombocytopenia induced by GPIIb/IIIa inhibitors and improve antibody detection are needed. Some unresolved questions deserving the attention of investigators are listed in Table 3.

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