Published in final edited form as:

Platelets. 2009 February ; 20(1): 64–67. doi:10.1080/09537100802592676.

Acute profound thrombocytopenia with second exposure to eptifibatide associated with a strong antibody reaction

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Abstract

We present a case of eptifibatide-induced acute profound thrombocytopenia in a 64-year-old male receiving eptifibatide for the second time during percutaneous coronary intervention. Although rare, short and self-limited episodes of acute and profound thrombocytopenia have been associated with eptifibatide exposure. The thrombocytopenia is thought to be immune mediated, and assays are available to test for eptifibatide-induced platelet antibodies.

Keywords

Eptifibatide; immune thrombocytopenia; thrombocytopenia

Background

The class of drugs which target platelet receptor Glycoprotein IIb/IIIa (GPIIb/IIIa inhibitors) include abciximab, eptifibatide and tirofiban. These drugs have been used increasingly for their anti-platelet aggregatory properties in acute coronary syndromes as well as in percutaneous coronary interventions. Current American College of Cardiology recommendations on unstable angina and non ST elevation myocardial infarction (NSTEMI) feature the use of GPIIb/IIIa inhibitors as first line therapy [1]. While abciximab-induced thrombocytopenia is relatively common and well documented, eptifibatide-induced thrombocytopenia appears to occur much less frequently. Moreover, though some reports suggest that eptifibatide-induced thrombocytopenia occurs more frequently upon a second exposure, there are few well-documented reports of this phenomenon. Here, we present a case of acute, profound thrombocytopenia associated with a second exposure to eptifibatide.

Case report

A 64-year-old male with a history of peripheral vascular disease, diabetes mellitus and hypertension presented with an episode of acute dyspnea occurring after physical activity

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

lasting 15 minutes. An electrocardiogram showed T-wave changes and his serum troponin-I was elevated at 0.36 ng/ml. He was diagnosed with a NSTEMI and admitted to the coronary care unit. He was started on enoxaparin (1 mg/kg every 12 hours), eptifibatide (180 mcg/kg bolus followed by 2 mcg/kg/min), clopidogrel 75 mg daily and aspirin 325 mg daily. His admission platelet count was 262,000/ μ l.

On hospital day two he developed epistaxis and gingival bleeding so eptifibatide was held; his platelet count at the time was 207,000/ μ l. Coronary angiography was performed the following day and he was found to have diffuse coronary artery disease with an 80% left anterior descending (LAD) artery lesion. He had a successful percutaneous intervention with deployment of a drug eluting stent to the LAD artery.

The remainder of the patient's stay in the coronary care unit was uneventful, though his discharge from the hospital was delayed due to alcohol withdrawal. On day eight of his hospitalization, however, he developed acute dyspnea and hypoxia requiring mechanical ventilation. His electrocardiogram showed ischemic changes and his serum troponin was elevated to 2.93 ng/ml, later peaking at 164 ng/ml. An echocardiogram showed anterior and lateral wall hypokinesis and the patient developed cardiogenic shock and vasopressors were started.

In-stent thrombosis was suspected and the patient was started on bivalirudin and heparin; aspirin and clopidogrel were continued. Urgent coronary angiography revealed a patent but narrowed LAD stent. Thrombus was noted beyond the stent with acute thrombosis suggested by the scalloped thrombus border. The previously placed stent was treated with balloon angioplasty, and a new stent was placed distally. The patient was also switched from bivalirudin to an infusion of eptifibatide at 1/mcg/kg/min with the intent to continue for 18 hours. The reduced dose of eptifibatide was chosen due to an unexplained hemoglobin drop of 1 gram/dl.

Six hours after the initiation of eptifibatide a routine complete blood count revealed that the platelet count had fallen from 346 000/ μ l to 1000/ μ l. Similarly low platelet counts were observed when blood was drawn in either citrate or EDTA and were confirmed by direct examination of the peripheral blood film. Upon discovery of thrombocytopenia, eptifibatide was discontinued immediately. However, the patient subsequently developed mucosal bleeding from the mouth, nares and endotracheal tube, though the hemoglobin remained stable. Within 8 hours of discontinuation of eptifibatide the platelet count rose to 8000/ μ l, and by 24 hours to 62 000/ μ l. The patient remained hemodynamically stable, was weaned off vasopressor support and extubated. No further episodes of thrombocytopenia occurred, and the patient was discharged home.

Discussion

In the presented case, the sudden and severe thrombocytopenia suggested eptifibatide-induced thrombocytopenia, however, other causes were considered. An abbreviated differential diagnosis of thrombocytopenia in this patient included heparin induced thrombocytopenia (HIT), disseminated intravascular coagulation (DIC), thrombotic

thrombocytopenic purpura and eptifibatide-induced thrombocytopenia. Laboratory tests to evaluate for these possibilities were obtained. A test for heparin-platelet factor 4 antibodies (the screening test for HIT) was positive, but the confirmatory serotonin release assay was negative (0% serotonin release). This finding, together with the severity of the thrombocytopenia, made the diagnosis of HIT unlikely [2]. The fibrinogen was normal and fibrin split products were not elevated, essentially excluding severe DIC. Additionally, abciximab has been reported to cause pseudothrombocytopenia, or clumping of platelets when exposed to EDTA in test tubes [3]. While this has not been, to our knowledge, reported with eptifibatide [4], we excluded this as a potential cause of the apparent thrombocytopenia by measuring the platelet count in citrate and carefully examining the peripheral blood film.

This diagnosis of eptifibatide-induced thrombocytopenia was further supported by the rapid resolution of thrombocytopenia upon cessation of the drug. Finally, antibody tests were markedly positive for eptifibatide dependent antibodies against GPIIb/IIa receptors (Figure 1), supporting the clinical diagnosis [5]. IgG antibodies were detected by flow cytometry in both the presence and absence of eptifibatide, but IgM antibodies were detected only in the presence of eptifibatide.

The increasing use of GP IIb/IIIa inhibitors has led to the recognition of acute thrombocytopenia induced by these agents. Abciximab has a well-documented association with thrombocytopenia, with mild thrombocytopenia ($<100\,000$ platelets/mm³) occurring in approximately 5% [6] of treated patients and more severe thrombocytopenia occurring 0.4% to 1.6% of exposed patients [7, 8]. Abciximab induced thrombocytopenia may be particularly problematic due to the long half life of the antibody, with abciximab-induced antibodies to platelets detectable up to 14 days after treatment [9]. Since the thrombocytopenia associated with abciximab may be both profound and prolonged, it has become standard practice to check a complete blood count 2–4 hours after starting the infusion [10].

The incidence of thrombocytopenia associated with eptifibatide is lower than that associated with abciximab. The PURSUIT trial found an incidence of profound thrombocytopenia to be 0.2% as compared to 0.1% with placebo [11]. Prior case reports show an onset of thrombocytopenia that may occur anywhere between two hours after initial exposure to eptifibatide and seven days of continuous therapy [12, 13]. Platelet counts typically recover within several days after discontinuation of eptifibatide [14].

The mechanism of eptifibatide-induced thrombocytopenia has not been clearly elucidated but is thought to be immune mediated. Immune-mediated thrombocytopenia after exposure to a drug generally involves an initial exposure, followed by the development of thrombocytopenia upon re-exposure. Though thrombocytopenia associated with both abciximab and eptifibatide may occur upon first exposure, the mechanism is thought to be immune mediated based upon the rapid onset of thrombocytopenia as well as the presence of circulating drug-dependent antibodies against GP IIb/IIIa in patients who developed thrombocytopenia following drug exposure [5]. The presumed molecular mechanism involves binding of the drug to a specific site on GP IIb/IIa, causing a structural change and

the formation of a “neoepitope” that is then recognized by specific antibodies to it [2]. Currently, the method most favored for measuring such antibodies is the use of flow cytometry to assess for immunoglobulins in patient serum that bind platelets only in the presence of eptifibatide [4].

One study demonstrated high titers of IgG antibodies that reacted with GPIIb/IIIa in the presence of eptifibatide in the serum of 5/5 patients with eptifibatide-induced thrombocytopenia [5]. Interestingly, a similar antibody was detected in the pre-treatment serum of one patient with eptifibatide-induced thrombocytopenia, suggesting that some of the causative antibodies may be naturally occurring. The presence of these naturally occurring antibodies might explain why some patients develop thrombocytopenia with eptifibatide upon first exposure.

In addition to our case, other reports have shown that eptifibatide-induced thrombocytopenia occurred only upon readministration; Nagge et al. reported that of eight patients with acute profound thrombocytopenia associated with eptifibatide, three had a prior exposure to eptifibatide without thrombocytopenia [12]. The clinical scenario of minimal or no reaction upon first exposure to the drug and dramatic reaction upon readministration is suggestive of the classic form of immune sensitization. While additional nonimmune mechanisms have been suggested for abciximab-induced thrombocytopenia [15], no convincing nonimmune mechanism has been suggested for eptifibatide-induced thrombocytopenia [14].

Management

As severe thrombocytopenia and bleeding may be particularly dangerous in patients with acute coronary syndromes undergoing interventional procedures, we recommend checking platelet counts 2–4 hours after administration of eptifibatide, in agreement with the manufacturer’s current recommendations for abciximab [3]. If thrombocytopenia is noted, the platelet count should be repeated in citrate and the peripheral blood film closely inspected in order to exclude pseudothrombocytopenia. Upon confirming thrombocytopenia, the eptifibatide infusion should be stopped immediately. In most cases, the quick recovery of the platelet count typically does not necessitate platelet transfusion; however the patient’s bleeding status, hemodynamics and overall clinical picture should be factored into the decision of whether to transfuse.

We also recommend checking for eptifibatide-dependent anti-platelet antibodies to confirm the diagnosis. Though this is often a send-out test, and thus, like HIT, the diagnosis of eptifibatide-induced thrombocytopenia must be made clinically, documentation of the presence of such antibodies may direct future management decisions. Finally, accumulating data concerning the incidence, kinetics and clinical associations of these antibodies is likely to yield a more complete understanding of the pathogenesis of this intriguing disorder.

Acknowledgments

The authors wish to acknowledge funding provided by Grant P50HL081011 (R. Silverstein, PI; K. McCrae, Program 5).

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Figure 1.

Demonstration of an eptifibatide-dependent, platelet-reactive antibody. The patient's serum contained an IgG antibody that reacted with normal platelets in the presence (solid curve) but not in the absence (dashed curve) of eptifibatide. Mean fluorescence intensity values are shown adjacent to each peak. No eptifibatide-dependent reaction was obtained with normal serum treated similarly (not shown). 124 × 124 mm (96 × 96 DPI).