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CASE REPORT

Severe thrombocytopenia and alveolar hemorrhage represent two types of bleeding tendency during tirofiban treatment: case report and literature review

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Abstract Tirofiban is a glycoprotein (GP) IIb/IIIa receptor antagonist used in the treatment of acute coronary syndrome (ACS). Thrombocytopenia is a well-known complication of GPIIb/IIIa inhibitors. Life-threatening complications such as alveolar and gastrointestinal system hemorrhages may occur in the course of thrombocytopenia. Platelet count should be monitored closely, including during the first few hours of the infusion. Adverse events may be prevented by prompt discontinuation of the therapy. Herein we present two cases of profound and sudden thrombocytopenia associated with tirofiban use in the treatment of ACS together with a review of the literature.

Keywords Tirofiban · Thrombocytopenia · Acute coronary syndrome · Alveolar hemorrhage

Introduction

Glycoprotein (GP) IIb/IIIa receptor antagonists such as abciximab, eptifibatide, and tirofiban inhibit platelet aggregation via preventing the binding of fibrinogen to platelets. These drugs decrease the rate of ischemic complications associated with non-ST-segment elevation acute coronary syndrome (ACS) and percutaneous coronary intervention [1]. However, GPIIb/IIIa receptor antagonists are reported to be associated with thrombocytopenia [2, 3]. Although the risk of thrombocytopenia is higher with treatment with abciximab, there are several reports about the incidence of severe and abrupt thrombocytopenia occurring within a few hours of tirofiban use [2, 4]. Herein we present two cases of profound and sudden thrombocytopenia associated with tirofiban use in the treatment of ACS together with the review of the literature.

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Case presentations

Patient 1

A 47-year-old male patient was admitted with severe chest pain and he was finally diagnosed as non-ST segment elevation myocardial infarction (NSTEMI). He had no chronic illness in his past medical history. Physical examination was normal. Treatment was started with acetyl-salicylic acid (ASA), clopidogrel, metoprolol, enalapril, nitroglycerin infusion and intravenous (IV) heparin. Tirofiban (10 μg/kg/min for 3 min followed by 0.15 μg/kg/min IV as continuous infusion) was started simultaneously with the coronary angiography which revealed 80 % stenosis of the circumflex artery. A total dose of 7,500 U of heparin was used during the procedure. The baseline platelet count was 280×10^9/L. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were within normal limits as other biochemical tests including kidney and liver function tests. Complete blood cell count (CBC) at 6 h revealed thrombocytopenia (platelet count, 29×10^9/L). A thorough examination of the blood film under a microscope confirmed the finding of marked thrombocytopenia without evidence of microangiopathic hemolytic anemia. Accordingly, heparin, tirofiban, clopidogrel, and ASA were immediately discontinued. The clinical picture seemed not to be related with heparin-

induced thrombocytopenia (HIT) because this patient had no prior exposure to heparin, or did the onset of thrombocytopenia fit which was sudden after heparin and antiplatelet therapy initiation. At follow-up, no thrombotic or bleeding complication occured. After 18 h of discontinuation of antiplatelet and anticoagulant therapy, the platelet count increased to 49×10^9/L. The course of platelet counts after the initiation of tirofiban was presented in Fig. 1. Unfractionated heparin (UFH), ASA and clopidogrel were resumed when platelet count reached to 100×10^9/L on the 4th day. At follow up, the platelet count reached normal level and the patient remained stable without evidence of restenosis.

Patient 2

A 73-year-old male patient was referred to the coronary intensive care unit with the diagnosis of ST segment elevation myocardial infarction (STEMI). The current episode of chest pain started 3 h before admission. He had ventricular fibrillation two times, and successfully defibrillated with 360 J. There was no major finding on physical examination. Left coronary artery was found to be totally occluded. Balloon angioplasty and stent implantation were successfully performed. ASA, clopidogrel and IV heparin were started. Tirofiban was also started simultaneously (tirofiban 10 μg/kg/min for 3 min followed by 0.15 μg/kg/min IV as continuous infusion). A total of 7,500 U of heparin was used during the procedure. The patient's baseline platelet count was 170×10^9/L. At 1 h of the intervention, bleeding from femoral sheath was observed. CBC at that time, revealed a very severe thrombocytopenia (platelet count 5×10^9/L). Review of the peripheral smear of an ethylenediaminetetraacetic-acid blood sample confirmed the profound lack of platelets with no clumping. ASA, heparin, clopidogrel and tirofiban were immediately stopped. Biochemical tests, PT and aPTT were found to be still normal. Platelet transfusion was started in an effort to maintain a count of $>100 \times 10^9$/L. Totally 12 random units of platelets were promptly administered. Blood pressure remained stable. His hemoglobin level fell from 13 to 11 g/dL. After 10 h of discontinuation of antiplatelet and anticoagulant therapy, the platelet count was 50×10^9/L. Course of platelet counts associated with tirofiban use was presented in Fig. 2. On the 30th hour of his admission, shortness of breath, and hemoptysis of bright red blood were observed when the platelet count reached to the normal level as being of 207×10^9/L. Physical examination revealed rhonchi in the base of both lungs and respiratory rate of 38 breaths/min. He had no fever (36.6 °C). Arterial blood pressure was stable and measured as 110/72 mmHg and tachycardia (120 beats/min) was present. His oxygen saturation fell from 95 % to 60 %. Intravenous furosemide (40 mg) was administered for presumed pulmonary edema, and supplemental oxygen was provided through a facemask. The patient hemoglobin level fell to 10 g/dL. He was monitored in intensive care unit. The echocardiographic examination showed that right heart chambers were in normal width, and there was no pericardial effusion. He underwent emergency fiberoptic bronchoscopy, which revealed diffuse oozing of blood from all lung segments. Alveolar hemorrhage was diagnosed. The treatment was continued as intensive supportive care. At follow-up his general condition improved, dyspnea disappeared and hemoptysis did not recur. The treatment of DAH consisted of only administration of oxygen, tranexamic acid and monitorization in the intensive care unit. Since DAH was not a component of vasculitis, no specific immunosuppressive treatment was administered. The patient completely recovered with supportive treatment at follow-up. Low-dose UFH and clopidogrel were prescribed again on the 7th day. The platelet count remained stable.

Discussion

The glycoprotein (GP) IIb/IIIa inhibitors are new class of antithrombotic agents acting via blockage of the binding of fibrinogen to activated GPIIb/IIIa, thereby inhibiting platelet–platelet interaction and thrombus formation. GPIIb/IIIa receptor inhibitors are currently successfully used in the treatment of ACS [1, 4–9].

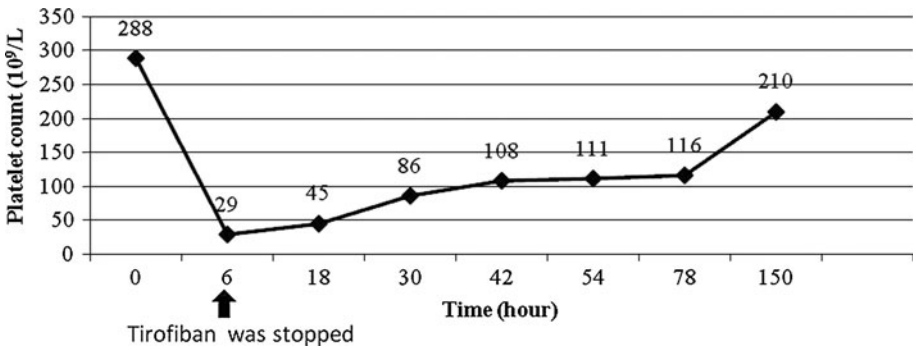

Fig. 1 Platelet counts ($\times 10^9$/L) after the initiation of tirofiban use (Patient 1)

Acute profound thrombocytopenia (APT) is a serious complication of GPIIb/IIIa inhibitor therapy characterized by a precipitous decline in platelet count to $<20 \times 10^9$/L within few hours of therapy initiation [2, 3, 10–17]. A second class of GPIIb/IIIa inhibitors, such as tirofiban an eptifibatide, the ligand-mimetic agents, act by binding specifically to the Arg–Gly–Asp (RGD) recognition site on GPIIb/IIIa, thereby rendering the integrin incapable of binding to fibrinogen. The potentially devastating event, APT is extremely uncommon in patients receiving the ligand-mimetic agents. Studies and case reports concerning the tirofiban-induced thrombocytopenia are shown in Tables 1 and 2, respectively. The findings indicate that APT after the administration of tirofiban or eptifibatide may be caused by drug-dependent antibodies.

Drug-induced immune thrombocytopenia (DITP) is an idiosyncratic immune-mediated reaction which develops in an unpredictable way and sometimes results in serious bleeding events. Drug-dependent anti-platelet antibodies typically occur after exposure to a new drug for 1–2 weeks or suddenly after a single dose if the drug has been previously taken. Recovery from a DITP usually begins within 1–2 days of cessation of the drug and usually thrombocytopenia disappears within a week [18]. The common pathogenetic feature among all drugs that cause immune-mediated thrombocytopenia is that thrombocytopenia only occurs in the presence of the drug. Patients may have a high titer of drug-dependent anti-platelet antibodies for many years with no problems, until drug exposure occurs again. 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. In tirofiban-associated thrombocytopenia, the drug-dependent antibodies are directed against the GPIIb/IIIa complex and can bind after drug-induced conformational changes to the receptor complex [19]. These drug-dependent antibodies are ''naturally occurring'' or are induced by prior exposure to drug and suggested to be the human analogs of mouse monoclonal antibodies that recognize ligand-induced binding sites (LIBS) induced in the GPIIb/IIIa heterodimer when it reacts with a ligand-mimetic drug [13, 20, 21]. In the study by Bougie et al. [13], 9 patients who developed severe thrombocytopenia within several hours of treatment with the tirofiban (4 patients) and eptifibatide (5 patients) were investigated and in each patient, serum contained a high titer IgG antibody that reacted with the glycoprotein IIb/IIIa complex only in the presence of the drug used in treatment. No tirofiban- or eptifibatide-dependent antibodies were found in any of 100 randomly selected healthy blood donors, and only 2 of 23 patients receiving tirofiban or eptifibatide who did not experience significant thrombocytopenia had extremely weak tirofiban-dependent antibodies. Evidence was obtained that the antibodies recognize multiple target epitopes on GPIIb/IIIa complexed with the inhibitor to which the patient was sensitive.

DITP is a diagnosis of exclusion. The diagnosis is established in general according to the clinical criteria; other etiologies of thrombocytopenia should be excluded; the drug should be administered before thrombocytopenia;

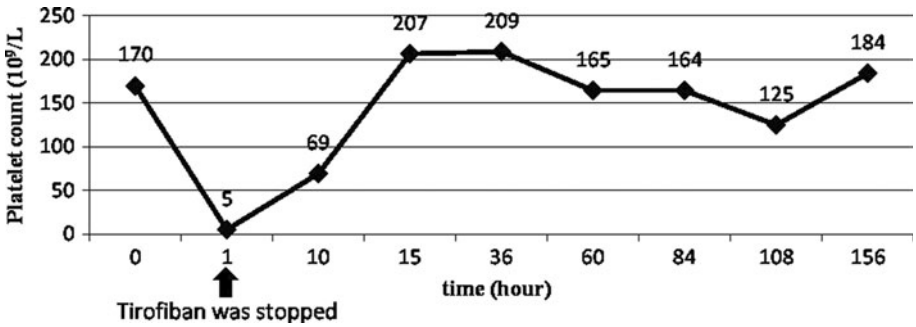

Fig. 2 Platelet counts ($\times 10^9$/L) after the initiation of tirofiban use (Patient 2)

Table 1 Thrombocytopenia in tirofiban studies

Study (*n*)	Drug	Platelet count ($\times 10^9$/L)	Placebo + Heparin (*n*)	Tirofiban + Heparin (*n*)	Statistical parameters
PRISM-PLUS (1,915) [36]	Tirofiban	<90	0.6 %	1.3 %	$P = 0.27$
		<50	0.3 % (797)	0.5 % (773)	
PRISM (3,232) [37]	Tirofiban	<100	0.4 %	1.1 %[a]	OR 3.02
					95 % CI 1.15–9.32
		<50	0.1 % (1,616)	0.4 % (1,616)[a]	OR 3.01
					95 % CI 0.54–30.5

[a] These patient groups received only tirofiban without heparin

Table 2 Reported cases of thrombocytopenia related with tirofiban

Authors	Age (years)/ sex	PLT count ($\times 10^9$/L)		Time	Time 2	PLT transfusion	Alveolar Hemorrhage	Other bleeding complication
		Before Tirofiban	Nadir					
Ali et al. [11]	70/F	Unknown	106	Unknown		No	Yes	No
Patel et al. [12]	80/M	180	3	4 h	Day 8	Yes	No	No
Bugie et al. [13]	78/M	212	1	1 h	Day 4	Yes	No	No
	65/M	200	19	6–24 h	Day 3	Yes	No	No
	64/M	192	5	6–24 h	Deceased	Yes	Yes	Yes
	78/F	200	2	6–24 h	>Day 5	Yes	No	No
Demirkan et al. [14]	58/M	165	17	2 h	36 h (reach 50 $\times$ 10^9)	No	No	No
Mulot et al. [15]	47/F	267	11	36 h	75 h	No	No	No
	67/M	215	79	27 h	7 h	No	No	No
	72/F	222	63	4 h	14 h	No	No	No
Eryonucu et al. [16]	68/M	240	4	12 h	Day 3	Yes	No	Yes
Dunkley et al. [17]	70/M	546	5	6 h	Day 7	Yes	No	No
	57/M	210	3	12 h	Day 5	Yes	No	Yes
Clofent-Sanchez et al. [27]	57/M	240	4	Day 10	Day 51	Yes	No	No
Bosco et al. [28]	80/M	240	1	Day 9	Day 13	Yes	No	No
	67/M	212	13	Day 7	Day 11	No	No	No
Sakellariou et al. [30]	58/M	403	7	4 h	48 h	No	No	No
Tuhta et al. [38]	57/M	260	11	48 h	96 h	No	No	No
Rahman et al. [39]	50/M	246	1	12 h	Day 4	Yes	No	No
Our cases	47/M	288	29	6 h	42 h	No	No	No
	73/M	170	5	1 h	15 h	Yes	Yes	Yes

F female, *M* male, *time 1* time elapsed between tirofiban bolus and observed nadir PLT count (h/day), *time 2* time to reach 100 $\times$ 10^9/L after tirofiban cessation (h/day)

recovery from thrombocytopenia should be complete and sustained after the discontinuation of the drug; re-exposure to the drug should result in recurrent thrombocytopenia [18, 22–25]. Demonstration of drug-dependent anti-platelet antibodies is important to confirm the etiology of DITP. Such testing is not widely available and requires substantial time. It is not feasible to wait for test results before deciding whether to discontinue a potential causative drug. Moreover, tests for drug-dependent antibodies can be negative in patients with probable DITP because assay methods may be insufficiently sensitive to detect some antibodies, some drugs are relatively insoluble in water and are difficult to incorporate into in vitro assays, and a metabolite formed in vivo, rather than the primary drug, may be responsible for the thrombocytopenia [18].

For the diagnosis of thrombocytopenia associated with tirofiban, initially pseudothrombocytopenia and HIT should be excluded. Pseudothrombocytopenia may easily be excluded by peripheral blood smear. Differential diagnosis between HIT and tirofiban-induced thrombocytopenia necessitates the evaluation of clinical history including heparin exposure and arterial thrombosis development. In HIT, the platelet count will fall 5–14 days after the initiation of the heparin treatment if the patient has received heparin previously, the fall in platelet count may occur sooner, sometimes within a day [26]. Demonstration of anti-platelet factor 4 antibodies can clarify the differential diagnosis. For our cases, timing of thrombocytopenia and absence of thromboembolic events make the diagnosis of HIT unlikely. In both patients, heparin was re-administered when the thrombocyte counts normalized and thrombocytopenia did not recur which was strongly against the diagnosis of HIT. Thus both HIT type I and type II might be excluded in these cases.

Two distinct presentations of thrombocytopenia were identified, one occurring acutely, and the second a delayed thrombocytopenia occurring after several days of tirofiban exposure [27, 28]. In both of our cases, thrombocytopenia occurred acutely. Discontinuation of the tirofiban is usually sufficient for treatment of thrombocytopenia because it is cleared from the circulation within the first hours of cessation of the drug [4]. Platelet transfusion is recommended if the platelet count decreases to the levels below 10 $\times$ 10^9/L or if there is life-threatening bleeding [29].

Intravenous immunoglobulin has been successfully applied in patients with prolonged thrombocytopenia [27, 28, 30]. In addition, as a precaution, the dose of tirofiban in ACS may be reduced without a decrease in therapeutic efficiency [31].

Diffuse alveolar hemorrhage (DAH) is defined as the bleeding from the bronchial vessels, the pulmonary vessels, or the microcirculation of the lung. All causes of DAH have the common denominator of an injury to the alveolar microcirculation. The clinical syndrome includes hemoptysis, anemia, diffuse radiographic pulmonary infiltrates, and hypoxemic respiratory failure, which can be severe. The most common underlying histology of DAH is of a small vessel vasculitis known as pulmonary capillaritis, usually seen with seropositive systemic vasculitides or connective tissue disorder. Bland pulmonary hemorrhage and diffuse alveolar damage may occur due to a number of injuries including drugs, coagulation disorders, and infections. Alveolar hemorrhage during the course of tirofiban treatment is very rare; however, it has been reported previously in the literature [11, 32, 33]. Physicians need to be aware of this potentially life-threatening complication of GPIIb/IIIa inhibitors because early treatment increases the chance that the patients will survive. From the literature, in the case of Bugie et al. [13], alveolar hemorrhage occurred with platelet counts of 5×10^9/L, however, in the report by Ali et al. [11], it occurred while the platelet count was 106×10^9/L. Interestingly in our case, alveolar hemorrhage occurred during the recovery phase with platelet counts of 207×10^9/L. Alveolar hemorrhage may develop during GPIIb/IIIa inhibitor therapy independent of the thrombocytopenia. Suggested facilitating conditions for alveolar hemorrhage may be the presence of underlying lung disorder, such as chronic obstructive pulmonary disease, pulmonary hypertension, high pulmonary-capillary wedge pressure, and elevated left ventricular end diastolic pressure. However, no such facilitating condition was present in our patient. In our patient, bronchoscopy revealed diffuse oozing of blood from all lung segments which confirmed the diagnosis of the alveolar hemorrhage. Secondary main causes of alveolar hemorrhage such as valvular heart disease and massive pulmonary thromboemboli were largely excluded with normal echocardiographic examination findings. There was no any evidence of systemic disease such as connective tissue disorder or vasculitis and he was cured without a specific treatment. So the diagnosis of tirofiban-induced DAH was established. Drug-induced lymphocyte stimulation test and leukocyte migration test which were reported to be performed for the diagnosis of drug-induced allergies such as pneumonia, skin eruption, hepatic injury and blood disorders [34, 35] might be also useful in the diagnosis of tirofiban-induced DAH.

In conclusion, acute severe thrombocytopenia and life-threatening bleeding complications especially alveolar hemorrhage may develop in the course of tirofiban treatment. Platelet count should be closely monitored during the first few hours of the infusion.

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