Case Report

Severe Thrombocytopenia After Heparin Therapy in a Patient with Unstable Angina and Recent Stent Implantation

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Heparin-induced thrombocytopenia represents a serious side effect of heparin therapy. Immune-mediated platelet activation results in thrombocytopenia, endothelial thrombin release and development of thrombosis, mainly venous. We report the case of a man with a history of coronary artery disease and recent stent implantation. This patient developed severe heparin-induced thrombocytopenia type II after low molecular weight heparin administration because of unstable angina which occurred two months after stent implantation. The patient was treated with a new anticoagulant regimen, fondaparinux sodium. There were no complications and platelet counts were restored to normal levels.

Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening condition. Platelet activation via an immunological mechanism, the triggering of thrombocytopenia and the release of thrombin by the endothelium result in an unusually high susceptibility to thrombosis. The diagnosis, however, is often complicated because in many patients heparin causes a benign thrombocytopenia of non-immunological type.[1] Here we describe the case of a patient with unstable angina who exhibited severe HIT after the administration of low molecular weight heparin (LMWH) and we provide a brief review of the relevant literature.

Case description

A patient aged 54 years with a one-year history of coronary artery disease, under medication with clopidogrel (75 mg/day), aspirin (100 mg/day), atorvastatin (80 mg/day) and metoprolol (100 mg/day) came to the emergency department complaining of retrosternal pain with reflection to the neck and left arm. His history showed that he had four intracoronary stents that had been implanted two months before. Two of these were in the right coronary artery, one was in the anterior descending branch and the other in the second diagonal. The ECG showed ST-segment depression in the left precordial leads (Figure 1A). Laboratory tests showed normal levels of troponin and myoglobin. Unstable angina was diagnosed and the patient was admitted to the coronary care unit. Intravenous nitroglycerine and LMWH (enoxaparin 80 mg x 2) were added to the patient's medication. His blood examination on admission was normal (Table 1) but a repeat test 12 hours after admission showed platelets 15,000 /μL and HIT was diagnosed.

The patient himself was unaware that a blood examination eight days after the coronary stenting had shown a reduced platelet count. We learned this from a relative after the thrombocytopenia had already been diagnosed. The patient had been given LMWH in preparation for the angioplasty and stent-
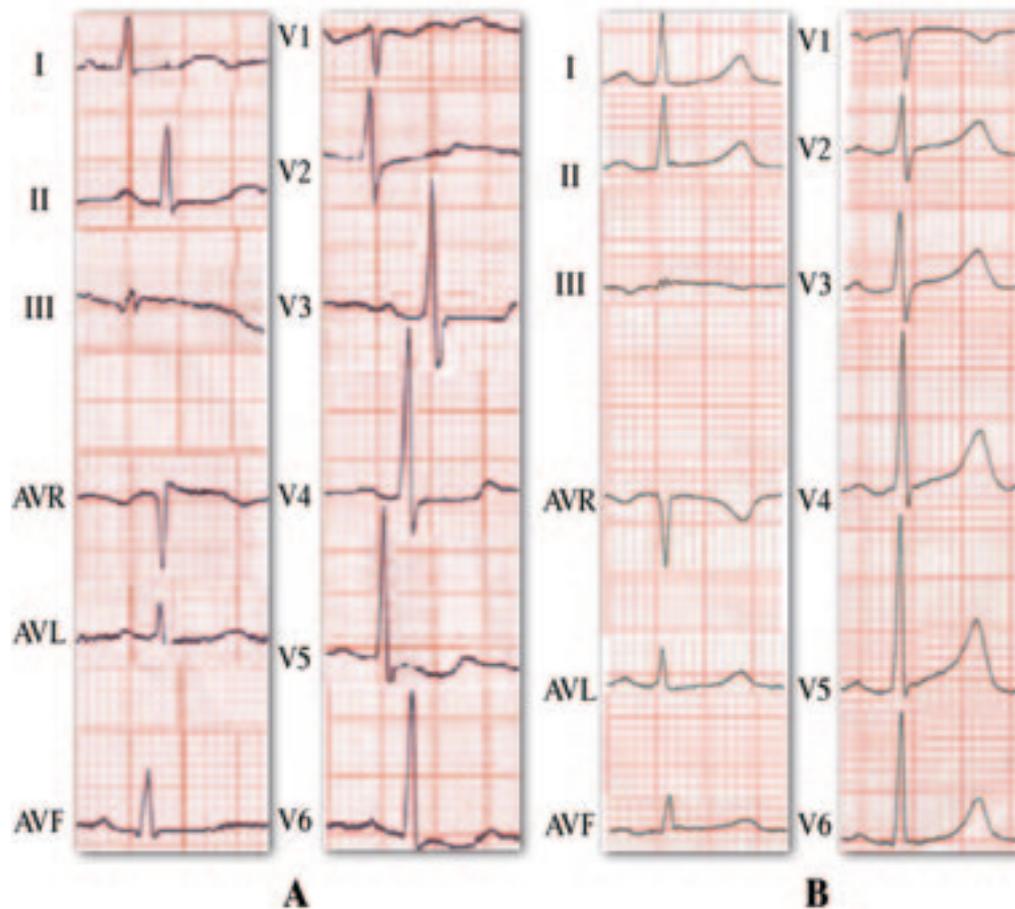
Figure 1. Repolarisation disturbances in the precordial leads on the patient's admission ECG (A), which disappeared two hours after medication was started (B).

ing procedure, but a haematological examination during his hospitalisation had shown no effect on his platelet count at that time. It should be noted that platelet glycoprotein IIb/IIIa inhibitors, which could have influenced the patient's platelet count, had not been administered either during stenting or in our own department. The thrombocytopenia that followed the stent implantation did not start to occur until after the patient's discharge. It was noticed on the eighth day after the LMWH administration and peaked on the twelfth day, when the platelet count reached 20,000 /μL. The patient's platelet count was restored to initial levels fifteen days after the diagnosis of thrombocytopenia.

In our department the heparin, aspirin and clopidogrel were all discontinued as soon as thrombocytopenia was diagnosed. Fondaparinux sodium was given subcutaneously in a dosage of 2.5 mg daily and treatment was continued for ten days in accordance with the manufacturer's instructions. The platelet count began to increase, touching 20,000 /μL after two days. No thromboembolic episodes or haemorrhagic complications were observed during the patient's hospitalisation. His ischaemia receded two hours after his admission and the ischaemic ECG changes disappeared without reappearing (Figure 1B). Haematological and biochemical examinations during the patient's ten days in hospital showed no changes in haematocrit, fibrinogen ($\approx$ 300 mg/dl) or fibrinogen breakdown products (<10 μg/dl).

Blood examination on discharge showed platelets 170,000 /μL, reaching 220,000 /μL two weeks later (Figure 2). Aspirin and clopidogrel medication was resumed after eight days.

Discussion

The term HIT covers a wide spectrum of clinical and haematological manifestations. Two types of HIT have

Table 1. Haematological and biochemical examinations on the patient's admission to hospital.

Haematological			Biochemical					
WBC	4.5	K/μL	Glucose	88	mg/dl	CPK	63	U/l
RBC	5.36	M/μL	Urea	30	mg/dl	LDH	328	U/l
Hb	13.0	mg/dl	Cholesterol	119	mg/dl	SGOT	25	U/l
Hct	42	%	Uric acid	5.4	mg/dl	SGPT	14	U/l
PLT	272	K/μL	Creatinine	0.9	mg/dl	K	4.1 mmol/l	
			Triglycerides	113	mg/dl	Na	142 mmol/l	
ESR	5	mm	HDL	35	mg/dl	Ca	8.6 mg/dl	
1st. hour			LDL	95	mg/dl			

been reported (Table 2). HIT type I (HIT I) refers to a non-immunological type of reaction to heparin that results in the activation and aggregation of platelets and leads ultimately to thrombocytopenia. The degree of thrombocytopenia is mild, with the platelet count not falling below 100,000 /μL; it appears during the first hours following heparin administration and thrombosis is not seen, in contrast to HIT type II (HIT II).[2] In the case of HIT II, however, the thrombocytopenia is based upon an immunological mechanism.[3,4] Specifically, in HIT II we see the formation of antibodies, usually IgG and more rarely IgM and IgA, which attack the heparin/platelet factor 4 (PF4) complex. PF4 is a protein that is normally released by the platelets after their activation by the heparin. The IgG-antibody/PF4/heparin immune complexes thus formed bond with the platelet FcγIIa receptors, causing activation of the platelets, their aggregation and the increased production of thrombin. The immune complex may also cause thrombin production via the direct activation of the endothelium, the release of tissue factor and activation of the coagulation cascade.[5]

Clinically, in HIT II the platelet count varies below 50% of its initial value or below 100,000 /μL.[6] Prompt diagnosis contributes to a reduction in mortality from 30% to 10%.[7] Thrombocytopenia usually appears five to ten days after the start of heparin administration, while the platelets return to normal levels 7-15 days after the heparin treatment is interrupted.[8] However, when a patient who is predisposed to HIT is exposed to heparin again within a hundred days of the previous heparin administration the fall in platelet count takes place over a few hours, because of the already circulating antibodies.[9] This was the case in our patient, who had been exposed to heparin during stent implantation two months previously.

The increased susceptibility to thrombosis that characterises HIT II leads to arterial or venous thrombosis in around 75% of cases.[10] Venous thromboses predominate, with lower limb deep vein thromboses and pulmonary emboli being the most common. In about half the patients with HIT II the diagnosis is made because of thrombus development.[11] In a smaller number of patients, 10-20%, skin lesions develop at the site of heparin delivery (dermal necroses and erythematosus plaques). Acute allergic reactions immediately after intravenous heparin administration may be seen, while development of hypo-fibrogenaemia may occur as a secondary consequence of uncompensated diffuse intravascular coagulation.[12]

Table 2. Types of heparin-induced thrombocytopenia.

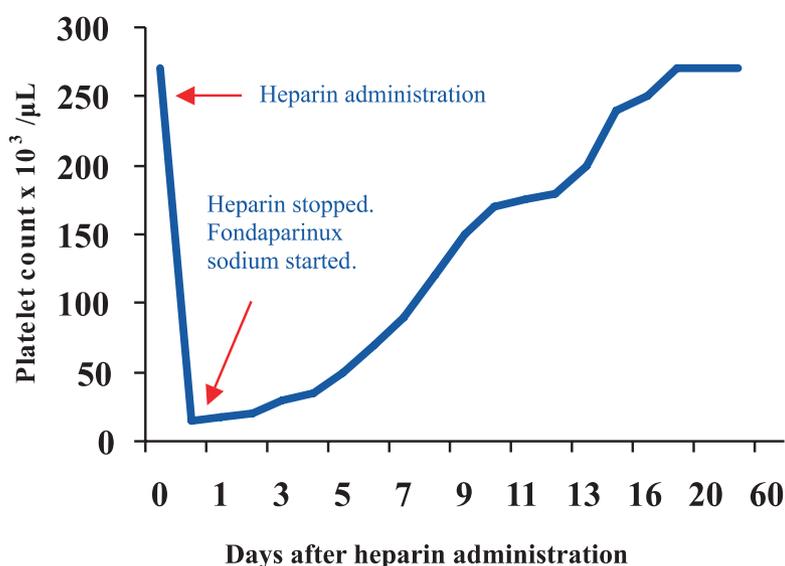|	HIT I	HIT II
Incidence	10% - 30%	1% - 4%
Time after heparin administration	1-3 days	Within hours if heparin has been given within the previous 100 days. Otherwise after 5-10 days.
Minimum platelet count	100,000 /μL	30,000 - 55,000 /μL
Antibody production	No	Yes
Thromboembolic episodes	No	In 60% of cases

Figure 2. Variation in the patient's platelet count after administration of low molecular weight heparin and fondaparinux sodium.

HIT II associated with the use of unfractionated heparin (UFH), administered in large doses for more than four days, is more common than in the case of LMWH.[13,14]

The diagnosis of HIT II is based on clinical data, their temporal relation to the heparin administration, and on laboratory confirmation. A fall in platelet count of more than 50% of the initial value, with or without thromboses, 5-15 days after heparin administration (or within hours if heparin has been administered on another occasion within the previous three months), which cannot be attributed to another cause, suggests a high probability of HIT II according to the clinical symptom grading system.[15] A laboratory finding of antibodies against heparin contributes to the confirmation of the diagnosis in those cases where it is necessary to differentiate it from other conditions that might cause a similar clinical and haematological picture. The laboratory methods available today fall into two categories: the immunological (ELISA techniques for detecting antibodies against the heparin/ PF4 complex[16,17]) and the functional (serotonin release test, platelet aggregation test and platelet activation with the cytometric flow method[18-20]). Given that no laboratory examination offers 100% sensitivity and specificity, if there is a high degree of clinical suspicion treatment should commence forthwith, without waiting for the results of the laboratory tests, which may be time-consuming or in many cases even unavailable. Furthermore, a negative laboratory examination does not rule out the diagnosis.

The clinical suspicion of HIT II means the immediate cessation of heparin administration. Platelet transfusion is rather contraindicated. In cases where HIT II is caused by UFH, LMWH is contraindicated because of the high incidence of cross-reactions.[21] The diagnosis of HIT II necessitates the administration of an alternative anticoagulant even in the absence of thrombi, in order to reduce the risk of their formation.[22] Possible alternatives include danaparoid sodium and the two direct thrombin inhibitors lepirudin and argatroban. Warfarin may be administered in the presence of thrombi only if the platelet count is as high as 100,000 /μL. Otherwise it will further increase the risk of thrombosis because of the reduction it causes in the anticoagulant action of C protein.

Another alternative anticoagulant factor is fondaparinux sodium, which has shown encouraging results so far in HIT II cases.[23,24] In the case reported here there was a high probability of HIT II syndrome according to the clinical symptom grading system (our patient scored 6). In view of this, together with the high risk of in-stent restenosis and the danger of haemorrhagic events, after consultation with haematologists in our hospital we decided to administer fondaparinux sodium. Although we were aware that there are only a few studies to support the use of this medication in HIT II, the results vindicated the decision. Two months later the patient is free of symptoms and has a normal haematological examination.

The main reason we used fondaparinux sodium, in spite of the limited support from the international literature concerning HIT II, was that lepirudin was not available in our hospital, while argatroban is not yet available on the Greek market. The action of fondaparinux sodium is based on the selective inhibition of

the activated Xa coagulation factor. It thus has a powerful antithrombotic effect, while the absence of any cross-reaction with antibodies against the heparin/PF4 complex means that it cannot be implicated in immune-mediated thrombocytopenia. No cross-reactions with heparins have been observed during its use, while it has no effect on prothrombin time or partial thromboplastin time.[25] The risk of clinically significant haemorrhage from the use of fondaparinux sodium is no different from that of LMWH.[26] Further studies are needed to determine its precise role in the HIT II reaction.[27]

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