Avoiding the "white clot" syndrome: Heparin-Induced Thrombocytopenia in a hospitalized patient

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INTRODUCTION

Heparin is among the most widely used medications in hospitalized patients, particularly for prophylaxis of deep vein thrombosis and pulmonary embolism. Unfortunately, in approximately 1 to 3% of patients receiving heparin therapy, an IgG-mediated immune response—known as Heparin-induced Thrombocytopenia (HIT)—has been reported.[1] Furthermore, a small percentage of patients with HIT go on to develop thrombotic complications including stroke, limb amputation or death. The thrombi associated with HIT involve aggregation of large numbers of platelets called a "white clot."

Early recognition and rapid treatment of HIT can reduce catastrophic thromboses resulting from irreversible aggregation of platelets known as the "white clot syndrome."

CASE REPORT

A 33-year-old African-American female with a history of uncontrolled hypertension, hepatitis C, HIV and end-stage renal disease presented to the emergency department with hypertensive urgency, headache and decreased vision in her right eye for one day. The patient was admitted and successfully treated for hypertension with IV labetalol and clonidine by mouth with resolution of symptoms.

As part of the hospital's deep vein thrombosis and pulmonary embolism prophylaxis, the patient was initially started on heparin 5,000 units every eight hours subcutaneously. Her platelet count at admission was 198 x 10^3/mm^3. However, on the first day of admission, the patients platelet count had dropped 44% to 110 x 10^3/mm^3. By the fourth day of admission, the platelet count had dropped a total of 65% to 70 x 10^3/mm^3 (see point A on graph) and the heparin was discontinued after a total of 13 doses.

Heparin-induced antibodies were then found to be present, though no platelet clumping was noted in her peripheral smear to indicate thrombotic thrombocytopenic purpura. A constant infusion of argatroban was started at the recommended rate (see table). The calculated therapeutic range for aPTT in this patient was 50-80 seconds. The patient's platelet count oscillated early in treatment and remained low (see interval B on graph) as she was found to be intermittently turning off the IV infusion pump several times per day. After counseling the patient and ensuring steady compliance with the infusion (see point C on graph), her platelet count then climbed to 133 x 10^3/mm^3 eleven days after beginning the infusion, the Argatroban was discontinued and she was discharged with a platelet count that was well within normal limits.

PATHOPHYSIOLOGY

Heparin forms a complex with Antithrombin III that inhibits thrombin's ability to convert fibrinogen to fibrin (see diagram). In HIT, the heparin molecules combine with an exogenous tetrameric protein, platelet factor 4 (PF4) which is seen as immunogenic. IgG is then produced by B-lymphocytes that respond to the "antigen" and also bind to the FcγRII receptor on platelets; this binding induces platelet activation and aggregation through a positive-feedback mechanism triggering coagulation. These events can play out in either the venous or arterial circulation, often leading to fatal complications.

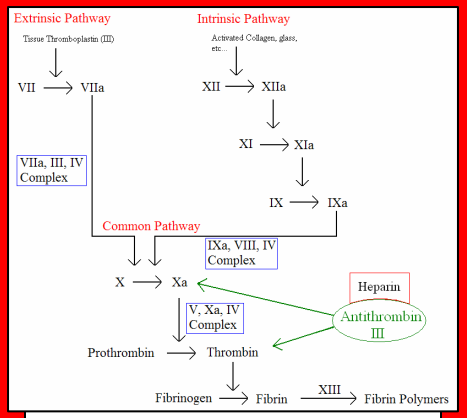
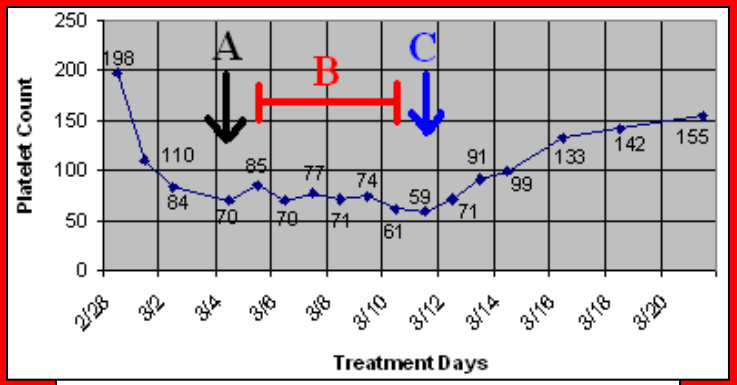


Diagram: Cascade showing action of Antithrombin III on clotting factors



Graph: Point A indicates the discontinuation of Heparin and the initiation of Argatroban. Interval B indicates the period of patient non-compliance. Point C is resumption of continuous therapy.

	Mechanism	Monitored by	Therapeutic Range	Dosing	Elimination and Half-life
Argatroban	Direct & selective thrombin inhibitor	aPTT	aPTT 1.5 – 3.0 times control	2 ìg/kg/min max 10 ìg/kg/min	Hepatic t ½ = 40 min
Lepirudin (Refludan®)	Direct inhibitor of free and clot-bound thrombin	aPTT	1.5 – 2.5 times the aPTT ratio	0.4 mg/kg bolus, then 0.15 mg/kg/hr infusion	Renal t ½ = 90 min
Bivalirudin (Angiomax®)	Direct thrombin inhibitor	Activated clotting time	200 – 400 seconds	1 mg/kg bolus, then 2.5 mg/kg/hr for 4 hours, then 0.2 mg/kg/hr for 14-20 hours	Enzymic 80%, Renal 20% t ½ = 25 min
Hirudin	Direct thrombin inhibitor	aPTT	aPTT 1.5 – 3.0 times control	0.4 mg/kg bolus, then 0.4mg/kg infusion	Renal t ½ = 60 - 90 min

Table: Antithrombin agents available for use in HIT.

DISCUSSION

Current research indicates that "HIT should be suspected clinically in a patient who has received heparin as recently as 5 days previously (or longer) and who has a platelet count that has decreased to less than 150,000/µL…or has decreased by 50% or more below baseline values."[3]

Three clinical syndromes in the HIT spectrum exist. First, HIT-antibody seroconversion alone exists in the absence of thrombocytopenia or clinical symptoms. Second, isolated HIT is defined as thrombocytopenia in patients with absence of clinical signs of thrombosis. Third, HIT with clinical thrombosis is the worst case scenario in the spectrum.

Patients who test seropositive for HIT antibodies but do not exhibit clinical findings must have heparin sources discontinued. Duplex ultrasonography to screen for sub-clinical deep vein thromboses may also be useful. Treatment with anticoagulant agents at this stage is not recommended, however. For patients in whom isolated thrombocytopenia is recognized, all sources of heparin exposure must be immediately discontinued. In these patients, appropriate anti-coagulant therapy should be administered. Choice of anticoagulant should be tailored to the individual patient. Patients are often treated with lepirudin, argatroban or bivalirudin (see table). In patients with clinical evidence of thrombi, immediate cessation of exposure to heparin and heparinized products along with rapid administration of appropriate anticoagulation and possibly thrombolytic therapy is essential. Prophylactic platelet transfusions are contraindicated as they can cause additional formation of thrombi. When considering alternate anticoagulation, low-molecular-weight heparins (LMWH) are also contraindicated in patients who have anti-heparin antibodies. Additionally, most sources agree that heparin should not be replaced with warfarin alone, as this can lead to venous limb gangrene[5].

CONCLUSION

Since HIT is a relatively unpredictable syndrome in individual patients, prevention strategies are targeted instead to populations. The broad use of LMWH when appropriate has been shown to significantly reduce the incidence of HIT. In one prospective study, 7.4% of patients who received unfractionated heparin developed anti-heparin antibodies compared with 2.4% of patients treated with LMWH[6]. Also, since bovine unfractionated heparins are more immunogenic than porcine, the use of the latter should be considered. Lastly, judicious use of heparin protocols will reduce the incidence of HIT.

Fortunately, the patient presented in the case report did not experience clinical thromboses or bleeding. This case illustrates that catastrophic thromboses and hemorrhage can be avoided when heparin-induced thrombocytopenia is recognized early and treated appropriately. It is therefore essential for clinicians to recognize HIT by pro-actively monitoring platelet levels in order to avoid the "white clot syndrome" of HIT in hospitalized patients.

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