Heparin-Induced Thrombocytopenia Occurring After Discontinuation of Heparin

Minesh R. Shah, MD, and Jeanne P. Spencer, MD

Background: Heparin-induced thrombocytopenia is caused by antibody formation to heparin-platelet factor 4 complexes. It typically develops 5 to 14 days after the initiation of heparin, but it can occur up to 3 weeks after the patient stops taking it. Early recognition by monitoring platelet counts during heparin therapy can decrease associated mortality and morbidity.

Methods: A case is described of a patient with severe morbidity as a result of heparin-induced thrombocytopenia. The medical literature was searched using the key words “heparin/adverse effects” and “thrombocytopenia.”

Results and Conclusions: The severe morbidity and potential mortality associated with heparin-induced thrombocytopenia are caused mainly by thrombosis. If it is suspected, all heparin products should be immediately stopped. Platelet counts usually return to normal after the heparin is discontinued. Approximately 50% of patients with heparin-induced thrombocytopenia develop thrombotic events. Patients should receive anticoagulation with agents other than heparin or low molecular weight heparin. As early detection of heparin-induced thrombocytopenia seems to improve outcome, it is recommended that all patients on heparin should have frequent monitoring of platelet counts. (J Am Board Fam Pract 2003;16:148–50.)
9.4 g/dL (94 g/L) and 28% (0.28), respectively, and her platelet count was 39,000/μL (39 × 10⁹/L). Heparin-induced thrombocytopenia was diagnosed, and lepirudin (recombinant hirudin, Refludan) was started. Within a few days, the platelet count increased to 100,000/μL (100 × 10⁹/L). She underwent debridement of both lower leg saphenous vein harvest sites and was given antibiotics. While hospitalized, her stool was positive for occult blood, and she became anemic. Her gastrointestinal tract showed no active bleeding. An inferior vena cava filter was placed. She was transferred to a semiacute care facility, and after demarcation of the necrosis, amputation of both feet was planned.

**Discussion**

For many years heparin medications have been widely used in prophylaxis and therapy of thromboembolic disorders. Nevertheless, the serious side effects of heparin-induced thrombocytopenia have recently attracted increased attention. Heparin-induced thrombocytopenia is classified into types 1 and 2, the first being benign and the latter severe. Type 1 occurs early after heparin initiation, manifesting as a moderate decrease in the platelet count (counts generally remain greater than 100,000/μL (100 × 10⁹/L). Thromboembolic complications are rare. This condition requires close monitoring of platelet counts, but discontinuation of heparin is often not necessary.¹

Type 2 heparin-induced thrombocytopenia is caused by antibody formation to heparin-platelet factor 4 complexes.¹ It occurs in approximately 5% of patients given heparin and about 4% of those who receive prophylactic doses. Mortality can be reduced from more than 30% to less than 10% with early recognition of the syndrome.² It typically develops between 5 and 14 days after heparin therapy is started.³ As in our case, it can occur up to 3 weeks after heparin therapy is discontinued.⁴ The pathogenesis of heparin-induced thrombocytopenia and heparin-induced thrombosis involves the formation of IgG antibodies to the multimolecular complexes between heparin and platelet factor 4. Platelet factor 4 is a normal platelet α-granule moiety that is released by platelets when they are activated by agonists, including heparin. The immune complexes composed of heparin, platelet factor 4, and anti–heparin-platelet factor 4 antibodies interact with platelet FcγII receptors, leading to potent platelet activation, platelet aggregation, procoagulant platelet microparticle formation, and a marked increase in thrombin generation. These immune complexes can also activate the endothelium directly, again leading to excess thrombin formation.²,³

Thrombosis is the major complication of heparin-induced thrombocytopenia. Venous thrombosis is more common than arterial thrombosis, especially in patients who receive heparin for postoperative deep-vein thrombosis prophylaxis. The deep-vein thrombosis is most frequently encountered in the extremities, followed in frequency by pulmonary embolism and cerebral sinus thrombosis.³ Patients with cerebral sinus thrombosis can have headache, papilledema, focal neurologic deficits, or seizures. Magnetic resonance imaging with venography is the investigation tool of choice.⁵

**Diagnosis**

A baseline platelet count is advised for any patient starting heparin therapy. Heparin-induced thrombocytopenia and associated thrombosis should be strongly considered in any patient whose platelet count rapidly drops to less than 100,000/μL (100 × 10⁹/L) or 40% to 50% of the baseline value after day 5 of heparin treatment. A 30% decrease in baseline platelet count, combined with any form of thrombosis in a patient receiving heparin, should be considered heparin-induced thrombocytopenia and thrombosis until proved otherwise.

Heparin-induced thrombocytopenia type 2 is a clinicopathologic syndrome that should be confirmed by laboratory testing. The two major classes of assays to detect heparin-induced thrombocytopenia antibodies are activation and antigen assays. Activation assays infer the presence of antibodies based on the ability of the patient’s serum to cause heparin-dependent platelet activation. Antigen assays detect binding of heparin-induced thrombocytopenia antibodies to heparin-platelet factor 4 complexes.⁶ Because results of these tests might not be immediately available, management should begin at the earliest clinical suspicion of the syndrome.

**Management**

If type 2 heparin-induced thrombocytopenia is suspected, all heparin products (including heparin flushes) should be discontinued immediately.³,⁷ Despite heparin discontinuation and platelet count recovery, patients with serologically confirmed
heparin-induced thrombocytopenia have an approximately 50% risk of developing a thrombotic event during the 30-day period after discontinuing heparin.3 This potential, in addition to the original indication for anticoagulation, implies that most patients with heparin-induced thrombocytopenia need anticoagulation. Because of the high cross-reactivity with the heparin-dependent antibody, subsequent therapy with low-molecular-weight heparins is also contraindicated.8

There are various alternative anticoagulant options available. Lepirudin is a factor IIa inhibitor originally isolated from the salivary gland of the medicinal leech. It does not show any reactivity in in vitro systems positive for heparin and heparin-induced antibodies. Lepirudin inactivates not only free thrombin but also fibrin clot-bound thrombin. Its anticoagulation effect can be monitored by activated partial thromboplastin time.8


Argatroban (Acova) is a synthetic direct thrombin inhibitor derived from L-arginine. It binds directly to the catalytic site of thrombin and has a short elimination half-life, so the drug effect is reversed more quickly on discontinuation. Its excretion is unaffected by moderate renal failure, and it can be monitored by activated partial thromboplastin time.1,9 It seems to cost less than the alternative agents.10

Because early detection of heparin-induced thrombocytopenia seems to improve outcome, all patients on heparin should have a platelet count measured before the start of heparin treatment, on the first day thereafter, and then regularly on every second day from day 5 to day 20 of treatment.11

Conclusion
Heparin-induced thrombocytopenia is caused by antibody formation to heparin-platelet factor 4 complexes. It typically develops 5 to 14 days after the initiation of heparin, but it can occur up to 3 weeks after its discontinuation. If heparin-induced thrombocytopenia is suspected, all heparin products should be immediately discontinued. Platelet counts usually return to normal after the heparin is discontinued. To prevent thrombosis, patients with heparin-induced thrombocytopenia should receive anticoagulation with agents other than heparin or low-molecular-weight heparin. Because early detection seems to improve outcome, it is recommended that all patients on heparin should have frequent monitoring of platelet counts.

References