

Thrombocytopenia and Acute Respiratory Distress Associated with Intravenous Bolus Heparin Exposure

Robert M. Perkins, MD

Jessica D. Lee, MD

Samara Rutberg, MD

David E. McCune, MD

Ronald H. Cooper, MD

Two distinct forms of thrombocytopenia are known to develop in approximately 3% of patients exposed to heparin.¹ Type I heparin-induced thrombocytopenia (HIT-I) typically has a mild course and often resolves even with ongoing administration of heparin. However, the clinical course of type II heparin-induced thrombocytopenia (HIT-II) is generally more serious in nature and mandates immediate cessation of heparin therapy. Although signs and symptoms of HIT-II usually result from arterial and venous clot formation, pulmonary complications of less clearcut origin—including acute respiratory distress—have been documented.

This article reports the case of a 71-year-old man admitted to our hospital with urosepsis who developed a venous thrombosis of the superficial femoral vein, received intravenous heparin therapy, and then developed severe thrombocytopenia and respiratory distress that resolved after discontinuation of heparin therapy. The pathophysiology of HIT-II is discussed, as are the possible etiology of pulmonary involvement and the recommended management of the disorder.

CASE PRESENTATION

A 71-year-old man with urosepsis developed a right superficial femoral vein thrombosis 4 days into a previously uneventful hospitalization. Ten minutes after receiving a loading dose of heparin intravenously, the patient was found to be unresponsive. Respiratory rate was 32 breaths/min, and oxygen saturation measured by pulse oximetry was 73%. Blood pressure, heart rate, and axillary temperature were all within normal limits. Results of physical examination were remarkable for diaphoresis, rigors, and diffusely diminished breath

sounds. Results of electrocardiography were unchanged from prior studies and showed no evidence of cardiac ischemia or right-heart strain. A plain radiograph of the chest also was unremarkable. Arterial blood gas analysis while the patient was receiving supplemental oxygen (fraction of inspired oxygen of 70%) showed the following results: pH, 7.28; PCO₂, 43 mm Hg; PO₂, 230 mm Hg; bicarbonate, 19 mEq/L. A chemistry panel was remarkable only for an anion gap of 18. Complete blood count results revealed a platelet count of $30 \times 10^3/\text{mm}^3$; 10 hours earlier (and prior to heparin exposure), the patient's platelet count had been $240 \times 10^3/\text{mm}^3$. A blood smear showed no evidence of erythrocyte fragmentation or platelet clumping. Because of the acutely falling platelet count and its temporal relationship to heparin exposure, the heparin was discontinued.

Within 3 hours of heparin cessation, the patient was fully alert and at baseline mental status. By this point, his oxygen requirement had markedly decreased as well; 12 hours after discontinuation of heparin, he required no supplemental oxygen. Repeat chemistry panel and blood gas analysis performed on blood samples obtained 8 hours after initial onset of signs and symptoms showed resolution of the anion gap and the acidosis. His platelet count, which had increased to $85 \times 10^3/\text{mm}^3$ 4 hours after discontinuation of heparin, continued to trend upwards over the next 3 days to pre-heparin exposure

Dr. Perkins is a Resident, Department of Internal Medicine; Dr. Lee is a Resident, Department of Medicine, Neurology Services; Dr. Rutberg is a Resident, Department of Internal Medicine; Dr. McCune is Chief of Hematology and Oncology; and Dr. Cooper is a Staff Internist, Department of Internal Medicine, Madigan Army Medical Center, Fort Lewis, WA.

baseline levels of $220\text{--}250 \times 10^3/\text{mm}^3$. Results of heparin antibody assays were positive.

The patient had no known prior complications of heparin therapy and was wearing pneumatic compression devices prior to heparin exposure. It was subsequently learned that he had received subcutaneous heparin therapy for prophylaxis of deep vein thrombosis in the previous month during an unrelated admission. Anticoagulation therapy was continued with recombinant hirudin, and the remainder of the patient's hospitalization was uneventful.

DISCUSSION

Pathophysiology

HIT-I is a non-immune-mediated phenomenon that occurs secondary to heparin-induced platelet aggregation. In this common form of thrombocytopenia, the decrease in platelet count is typically mild (ie, $< 50\%$ from pre-exposure baseline levels), and serious complications are rare. As stated previously, HIT-I often resolves even while patients continue to receive heparin therapy. In contrast, the mechanism of HIT-II involves the development of antibodies directed against a heparin-platelet factor 4 complex and against platelet factor 4 bound to heparin-like proteins on endothelial cells, producing vascular microinjury. The net result is a profound decrease in platelet count and development of a prothrombotic state (Table 1).

Clinical Manifestations

The time course for the clinical presentation of HIT-II varies, but manifestations of the disorder typically occur at least 5 days after initial heparin exposure.³ However, the case presented, as well as others, suggests that there is a subset of patients who present more acutely. The key determinant in these acute presentations appears to be the timing of prior heparin exposure. Warkentin and Kelton recently published a review of 243 patients with HIT-II and found that heparin exposure within the preceding 100 days was a significant risk factor for rapid onset of HIT-II.⁴

The clinical manifestations of HIT-II are usually related to arterial and venous clot formation secondary to platelet activation and endothelial injury. Pulmonary embolus, deep venous thrombosis, myocardial infarction, disseminated intravascular coagulation, and cerebrovascular accident or transient ischemic attack have all been noted to occur.⁵ Our patient, in contrast, developed hypoxia and respiratory distress within minutes of exposure to heparin. Pulmonary embolus, although not definitively ruled out, was considered unlikely, given the rapid resolution of symptoms with

Table 1. Diagnostic Criteria for Type II Heparin-Induced Thrombocytopenia*

Thrombocytopenia involving a significant (ie, $> 50\%$) decline in platelet count from baseline levels
Absence of other causes of thrombocytopenia
Confirmation of diagnosis with a heparin-antibody assay
Normalization of platelet count with cessation of heparin

*Data from Bick and Frenkel.²

heparin discontinuation. A published report by Popov and colleagues uses the term "pseudopulmonary embolus" to describe a patient of theirs who developed acute hypoxia presenting minutes after heparin exposure.⁶ As with our patient, their patient also was profoundly thrombocytopenic immediately after exposure to heparin, and both the hypoxia and thrombocytopenia resolved soon after cessation of heparin. This patient underwent a ventilation-perfusion lung scan and cardiac catheterization, results of which were unremarkable. A heparin antibody assay, however, was positive after the onset of symptoms. Moreover, accidental re-exposure to heparin several days later again resulted in acute hypoxia and thrombocytopenia.⁶

A case series published by Warkentin describes 6 patients with HIT-II who developed acute (ie, within minutes) systemic reactions (eg, rigors, diaphoresis, chills, nausea) to intravenous bolus heparin therapy.⁷ In 3 of the 6, the diagnosis was not initially made, and heparin administration continued; all 3 developed serious thrombotic complications, and 1 had a fatal stroke.

Possible Etiology of Pulmonary Involvement

The exact etiology of these atypical presentations remains unclear. They may occur, as Ortel has hypothesized,¹ secondary to microembolization or vasospasm in the pulmonary vessels. The presence of heparin-like ligands on the endothelial surface, to which activated platelet factor 4 particles attach, may be an additional target for heparin antibodies and may be instrumental in causing the acute pulmonary and systemic reactions to intravenous heparin therapy experienced by some patients.

Management

Management of HIT-II consists of immediate discontinuation of all heparin products and elimination of exposure to the drug, because even minimal exposures (eg, heparin flushes, prophylactic doses given subcutaneously) can induce thrombocytopenia and a prothrombotic state.⁸ Additionally, alternative anticoagulants

Table 2. Pharmacologic Management of Type II Heparin-Induced Thrombocytopenia After Discontinuation of All Heparin

Agent	Dosing	Monitoring	Comments
Recombinant hirudin	Intravenous push: 0.4 mg/kg body weight over 15 s Maintenance: 0.15 mg/kg per hr	Goal: aPTT that is 1.5 to 2.5 × baseline level. If aPTT is less than 1.5 × baseline level, in- crease dose by 20%; if aPTT is more than 2.5 × baseline level, decrease dose by 50%.	Warfarin should be started simultaneously; recombinant hirudin can be stopped when INR is greater than 2.0.
Argatroban	2 µg/kg per min, initially	Goal: aPTT that is 1.5 to 3 × base- line level but does not exceed 100 s. Adjust dose (up to 10 µg/kg per min) to achieve the desired aPTT.	Because of combined effect on INR, stop argatroban once INR is greater than 4.

Data from Lacy CF. Recombinant hirudin. Lexi-Comp. In: UpToDate 10.3 [database online]. Wellesley (MA): UpToDate; 2002 and Lacy CF. Argatroban. Lexi-Comp. In: UpToDate 10.3 [database online]. Wellesley (MA): UpToDate; 2002.

aPTT = activated partial thromboplastin time; INR = international normalized ratio.

should be started immediately, given the risk of arterial and venous clot formation. Two direct thrombin inhibitors are currently approved by the US Food and Drug Administration for use in cases of HIT-II, namely recombinant hirudin (lepirudin) and argatroban. Dosing and monitoring recommendations for these drugs are provided in **Table 2**. Danaparoid, a heparin-like product consisting of a mixture of glycosaminoglycans derived from porcine intestinal mucosa, has also been used successfully, but its use is complicated by the risk of cross-reactivity with heparin antibodies. This limitation is not observed with direct thrombin inhibitors.⁹

Clear guidelines for an appropriate period of anticoagulation do not exist. If long-term anticoagulation was indicated prior to onset of HIT-II, warfarin dosing can be safely initiated during therapy with direct thrombin inhibitors. If no other indication for anticoagulation exists, therapy with a direct thrombin inhibitor should be continued at least until the platelet count normalizes.

CONCLUSION

Hospitalized patients can develop acute respiratory distress from a host of insults, with HIT-II being one of the more obscure etiologies. Our case highlights the importance of recognizing the possible role of heparin in any acute respiratory distress involving patients in the hospital, where heparin exposure is common. The time course of events in this case suggests that there may be a subset of patients with HIT-II who present with acute pulmonary and/or systemic manifestations of the condition. Continuing heparin for what appears to be a pulmonary embolus but actually is a manifesta-

tion of HIT-II could have devastating consequences. Those at greatest risk appear to be patients with recent heparin exposure, as is common in those with frequent or prolonged hospital admissions. **HP**

REFERENCES

- Ortel TL. Heparin-induced thrombocytopenia. *Semin Hematol* 1998;35(4 Suppl 5):1–2.
- Bick RL, Frenkel EP. Clinical aspects of heparin-induced thrombocytopenia and thrombosis and other side effects of heparin therapy. *Clin Appl Thromb Hemost* 1999; 5 Suppl 1:S7–15.
- Chong BH, Eisbacher M. Pathophysiology and laboratory testing of heparin-induced thrombocytopenia. *Semin Hematol* 1998;35(4 Suppl 5):3–8.
- Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med* 2001;344: 1286–92.
- Spencer FA. Heparin-induced thrombocytopenia: patient profiles and clinical manifestations. *J Thromb Thrombolysis* 2000;10 Suppl 1:21–5.
- Popov D, Zarrabi MH, Foda H, Graber M. Pseudopulmonary embolism: acute respiratory distress in the syndrome of heparin-induced thrombocytopenia. *Am J Kidney Dis* 1997;29:449–52.
- Warkentin TE. Acute systemic reactions to intravenous heparin bolus therapy. *Blood* 1992;80 Suppl 1:160a.
- Ananthasubramaniam K, Shurafa M, Prasad A. Heparin-induced thrombocytopenia and thrombosis. *Prog Cardiovasc Dis* 2000;42:247–60.
- Januzzi JL Jr, Jang IK. Heparin induced thrombocytopenia: diagnosis and contemporary antithrombin management. *J Thromb Thrombolysis* 1999;7:259–64.

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