

Excessive Anticoagulation and Anaphylactic Reaction After Rechallenge with Lepirudin in a Patient with Heparin-Induced Thrombocytopenia

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Approximately 40% of patients who receive lepirudin for 5–10 days develop antihirudin antibodies. These antibodies lead to decreased renal elimination of lepirudin, ultimately resulting in elevated activated partial thromboplastin times (aPTTs). A small percentage of patients with antihirudin antibodies develop hypersensitivity reactions to lepirudin with reexposure. Thus, patients who are reexposed to lepirudin must be monitored closely for hypersensitivity. A 45-year-old African-American woman received lepirudin for anticoagulation after being diagnosed with heparin-induced thrombocytopenia type II. She developed supratherapeutic aPTTs after 10 days of lepirudin therapy. Lepirudin was then withheld for 6 days, during which her aPTT remained supratherapeutic. After lepirudin infusion was restarted, the patient developed an anaphylactic reaction. She was treated appropriately with an antihistamine, a corticosteroid, and an anxiolytic agent. After the reaction resolved, the patient was rechallenged with lepirudin, and the anaphylactic reaction recurred.

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Heparin-induced thrombocytopenia (HIT) is defined as a decrease in platelet count to less than $150 \times 10^3/\text{mm}^3$ or a 50% decrease in total number of platelets after exposure to heparin.¹ There are two types of HIT: type I (HIT-I) and type II (HIT-II). The more frequently occurring form is HIT-I, a nonimmune-mediated thrombocytopenia resulting from the direct effect of heparin on platelet count. In contrast, HIT-II is an immune-mediated condition with a more drastic decrease in platelets and a high risk of thrombosis.²

The pathogenesis of HIT-II includes development of immunoglobulin G (IgG) antibodies after exposure to heparin.^{2,3} These antibodies bind to platelet factor 4 (PF4), present on the surface of endothelial cells, to form a heparin-

PF4 complex. This complex binds to the Fc receptors of circulating platelets, causing platelet activation and release of more PF4, thus perpetuating the cycle.²⁻⁴ This cycle eventually leads to thrombocytopenia and injury of the endothelial cell wall, increasing the risk for thrombosis and disseminated intravascular coagulation.⁵

Complications associated with HIT-II include thrombosis (> 50% of patients), amputation (~10–20%), and death (~10–30%).⁶⁻⁸ Thrombosis can be either arterial or venous, with venous thrombosis accounting for about 80% of all cases. Arterial thrombosis associated with HIT-II can lead to myocardial infarction, stroke, or acute limb ischemia with or without limb amputation. Venous complications include deep vein thrombosis, pulmonary embolism, and warfarin-associated limb gangrene.^{1,4,6,8,9}

An estimated 3% of patients who receive unfractionated heparin for 5–14 days develop HIT-II.² Heparin-induced thrombocytopenia

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(both types) can also occur with low-molecular-weight heparins, although the frequency is much lower than that with unfractionated heparin. The onset of HIT-II may be more rapid (within 30 min) if the patient has been exposed to heparin within the past 100 days.¹⁰ A diagnosis of HIT-II is done mainly by clinical and laboratory assessments. Significant findings include a decrease in platelet count, history of exposure to heparin, and positive results on confirmatory assays. Laboratory tests for HIT consist of functional and antigenic assays. The functional assays available are serotonin release assay and heparin-induced platelet aggregation. The antigenic assay is the enzyme-linked immunologic serum assay (ELISA).^{1, 4, 9}

The goals of HIT therapy are to maintain effective therapeutic anticoagulation and prevent complications of HIT.¹¹ Treatment of HIT-II begins with immediate discontinuation of all sources of heparin, including flushes, heparin-coated catheters, heparinized dialysate, and any other drugs or devices containing heparin.^{1, 2} In addition, patients with HIT-II require an alternate form of anticoagulation, since 40–50% of patients without an initial thrombosis are at risk for a thromboembolic event up to 30 days after discontinuation of heparin.^{8, 12} Despite the low platelet count seen in patients with HIT-II, platelet transfusion should be avoided, as it may further increase the risk for thrombus formation.⁷

Patients with HIT-II also should not begin anticoagulation with warfarin, which has been shown to worsen thrombotic events.^{4, 8, 13} The length of time needed for the full anticoagulation effect of warfarin to be seen is approximately 5 days. This delay, coupled with warfarin's ability to inhibit synthesis of vitamin K-dependent clotting factors and the hypercoagulable state associated with HIT-II, can result in venous limb gangrene and limb amputation.^{4, 8, 13} Low-molecular-weight heparins should also be avoided in patients with HIT-II due to a high likelihood of both in vitro and in vivo cross-reactivity with HIT antibodies.^{6, 7}

Direct thrombin inhibitors (DTIs) are the anticoagulants of choice in patients with HIT-II.^{4, 6, 12–15} The DTIs available in the United States are lepirudin, argatroban, and bivalirudin. These agents inactivate both clot-bound and soluble thrombin.^{4, 7, 13} Unlike other anticoagulants, they are structurally different from heparin and lack cross-reactivity with HIT antibodies.⁶ Only lepirudin and argatroban have been approved by the United States Food and Drug Administration

for anticoagulation in HIT.

Approximately 69 patients have been treated with lepirudin at our institution. One of these patients developed antihirudin antibodies and experienced an anaphylactic reaction.

Case Report

A 45-year-old, 110-kg, African-American woman who was involved in a high-impact motor vehicle accident was transferred to our institution from another hospital for stabilization of her fractures. The patient was receiving heparin therapy for deep vein thromboses in both right upper and lower extremities. Her platelet count on the day of admission was $136 \times 10^3/\text{mm}^3$. Shortly after arrival, she developed shortness of breath, tachypnea, and pleuritic chest pain. A ventilation-perfusion coefficient scan confirmed the presence of a massive pulmonary embolism. The patient was transferred to the intensive care unit for more rigorous monitoring.

One day after admission (heparin day 10), the patient's platelet count decreased to $29 \times 10^3/\text{mm}^3$. Heparin was discontinued, an ELISA test for HIT was ordered, and argatroban $2 \mu\text{g}/\text{kg}/\text{minute}$ was started. Argatroban was discontinued after 5 days due to elevated liver function tests (doubled from baseline).

Lepirudin was started 4 hours after the discontinuation of argatroban. The patient received a bolus dose of lepirudin $0.4 \text{ mg}/\text{kg}$, followed by a continuous infusion of lepirudin $0.15 \text{ mg}/\text{kg}/\text{hour}$. The HIT assay confirmed that the patient had HIT antibodies. The patient continued with the lepirudin infusion for 13 days, at which time her aPTT increased to 194.2 seconds (goal 45–78 sec), although her renal function, as confirmed by blood urea nitrogen levels, serum creatinine levels, and urine output, remained normal. The lepirudin dosage was reduced based on the manufacturer's recommendations for an elevated aPTT until the patient was receiving only $0.001 \text{ mg}/\text{kg}/\text{hour}$ of lepirudin. Her aPTT remained supratherapeutic. Eventually, the lepirudin infusion was withheld for a total of 6 days; the patient's aPTT continued to be supratherapeutic. At the end of day 6, with her aPTT at 94.8 seconds, the consulting hematologist restarted lepirudin at $0.075 \text{ mg}/\text{kg}/\text{hour}$ (without a bolus dose) due to the patient's high risk for thromboembolic events.

Three hours after restarting lepirudin, the patient developed itching, chest pain, hypotension, and shortness of breath. The lepirudin infusion

was stopped, and the patient was treated with diphenhydramine, methylprednisolone, and alprazolam. The patient was rechallenged by restarting the lepirudin infusion 2 hours after the first reaction, and the reaction recurred. Lepirudin was discontinued permanently, and argatroban was restarted at 2 µg/kg/minute. The dosage was titrated to 1 µg/kg/minute, and the patient became stabilized. Her platelet count was $395 \times 10^3/\text{mm}^3$, and warfarin therapy was started. She was discharged from the hospital on day 37, while continuing to receive warfarin.

Discussion

Antihirudin antibodies are seen in approximately 40% of all patients treated with lepirudin.^{11, 13, 16} Development of these antibodies, which are of the IgG subtype, usually occurs 5–10 days after the start of lepirudin therapy.¹⁷ According to researchers who assessed data from two prospective studies, development of antihirudin antibodies leads to a drug-induced immune response that enhances the activity of lepirudin without affecting the rate of bleeding or thromboembolic events.¹⁶ The presence of antihirudin antibodies may be associated with a sharp increase in aPTT, requiring a decrease in the dosage of lepirudin. Another group of researchers speculated that antihirudin antibodies result in formation of antihirudin antibody–lepirudin complexes that are too large to be eliminated renally.¹¹ Thus, the rise in aPTT might be due to a prolonged half-life of lepirudin as a result of its decreased renal excretion.

With prolonged exposure to lepirudin and other hirudin analogs, patients may develop antihirudin antibodies. The presence of these antibodies may precipitate hypersensitivity or an anaphylactic reaction if the patient is reexposed to, or rechallenged with, these agents. A recent publication suggests that omitting the bolus dose of lepirudin may reduce the severity of the anaphylactic reaction.¹¹ However, switching to argatroban should be considered in patients who have recently been exposed to lepirudin.

Although bivalirudin is another DTI, it is not a good alternative for anticoagulation in patients with antihirudin antibodies. A research group suggested that renal elimination of bivalirudin is decreased in patients with antihirudin antibodies.¹⁸ In the same publication, the researchers also propose that patients who experience anaphylactic reactions due to antihirudin antibodies might develop similar reactions to bivalirudin, and vice

versa.

As of May 2003, 28 cases of allergic, anaphylactic reactions to lepirudin had been reported to its manufacturer (out of the 35,000–60,000 patients treated with lepirudin since 1994) (F. Almanakly, Berlex Laboratories Inc., written communication, May 21, 2003). Eleven of the 28 cases were identified as probable allergic reactions to lepirudin, with seven of these reactions being attributed to reexposure to lepirudin. Five of the reexposure cases resulted in death. As a result of these cases, “dear doctor” and “dear pharmacist” letters were sent to physicians and pharmacists in the United States and Europe, alerting them of changes in the package insert of lepirudin.¹⁹ This safety information emphasized the possibility of an allergic or hypersensitive reaction to lepirudin. It warned practitioners to watch for these reactions, especially in patients with past exposure to lepirudin, and to be prepared to manage patients appropriately if such a reaction should occur.

Conclusion

Although antihirudin antibodies were not objectively identified in our patient, her clinical presentation, length of therapy, and increase in the aPTT suggest their development. The drastic decrease in the dosage of lepirudin in light of normal renal function supports evidence that antihirudin antibodies may lead to decreased clearance of lepirudin, possibly due to the large size of antihirudin antibody–lepirudin complexes. In addition, the presence of antihirudin antibodies in this patient at the time when lepirudin was restarted could have led to the hypersensitivity reaction.

Health care providers must be educated about this reaction and make provisions for its management. In addition, hospitals and health care systems should develop systems to document exposure to lepirudin, both in the patient's chart and in the main pharmacy dispensing system. This will help identify patients at high risk for this allergic reaction.

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