

Severe Anaphylactic Reaction After Repeated Intermittent Exposure to Lepirudin

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Lepirudin, a recombinant DNA derivative of hirudin, is used to prevent thromboembolic complications caused by heparin-induced thrombocytopenia type II. Anaphylactic and anaphylactoid reactions have been reported with its use in patients both with and without known previous exposure to lepirudin. We describe the case of a 57-year-old woman who received five uneventful courses of lepirudin therapy before having a severe anaphylactic reaction during administration of the intravenous bolus dose that began her sixth course. The patient experienced cardiorespiratory arrest but recovered from the reaction. The decision to administer lepirudin to a patient who has previously received it should be reached with due consideration of the risk:benefit ratio and strategies to manage risk resulting from readministration. Risk factors for an anaphylactic reaction to lepirudin may include use of an initial bolus dose, intravenous rather than subcutaneous administration, length of any single course of therapy beyond 3 days, and repeat administration of lepirudin within 100 days.

Key Words: lepirudin, anaphylaxis, drug reaction.
(*Pharmacotherapy* 2007;27(5):760–765)

Heparin-induced thrombocytopenia (HIT) type II is an adverse reaction resulting from unfractionated heparin (UFH) and, less commonly, low-molecular-weight heparins. Two types of HIT exist: type I and type II. Type I occurs in up to 25% of patients and is not immune mediated.^{1–3} It results in a relatively rapid drop in platelet count 1–4 days after starting heparin and has less severe consequences than HIT type II. The immune-mediated HIT type II occurs much less frequently than type I, occurring in 1–3% of patients.^{1–3} The reaction involves formation of antibodies against the platelet factor 4–heparin complex, resulting in platelet aggregation and apparent thrombocytopenia, which may lead to limb gangrene, amputation, and death.^{1–3} When patients

without past exposure to heparin or who have not received heparin within the past 100 days start heparin, HIT type II typically emerges 5–10 days after starting the therapy.^{1, 3} In contrast, among patients who have received heparin within the past 100 days, the fall in platelet count may occur within hours after heparin is restarted.⁴

Lepirudin is used to prevent thromboembolic complications caused by HIT type II.³ It is a desulfated, recombinant DNA derivative of hirudin, which is obtained from the salivary glands of the *Hirudo medicinalis* leech. Lepirudin produces anticoagulation through direct inhibition of the fibrinogen-binding site of both free and clot-bound thrombin.^{1, 2, 5–7} Although lepirudin produces effective anticoagulation in the setting of presumed or confirmed HIT, a concern with its use is that anaphylactic and anaphylactoid reactions with the drug have been reported. Reports describe anaphylaxis with lepirudin in patients both with and without known previous exposure to lepirudin, but many of these reports lack significant clinical details.^{8, 9} We describe an anaphylactic reaction to lepirudin

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in a patient receiving an intravenous bolus dose at the start of her sixth course of therapy.

Case Report

A 57-year-old, 88-kg, 165-cm Caucasian woman was hospitalized for acute exacerbation of heart failure. Her medical history included coronary artery disease, three previous myocardial infarctions, ischemic dilated cardiomyopathy with severely reduced left ventricular systolic function, and nonsustained ventricular tachycardia. Her surgical history included four-vessel and three-vessel coronary artery bypass graft surgeries 16 and 2 years earlier, respectively; placement of a bileaflet mechanical valve in the mitral position 2 years earlier, multiple percutaneous coronary interventions (last intervention 5 mo earlier), and appendectomy. Her long-term drug therapy consisted of furosemide, metolazone, spironolactone, carvedilol, simvastatin, aspirin, pantoprazole, escitalopram, and magnesium oxide. In addition, long-term warfarin therapy was required after placement of the mechanical valve.

Vital signs and laboratory results on admission were within normal limits except for the following: serum sodium 133 mEq/L (normal range 135–145 mEq/L), blood urea nitrogen 23 mg/dl (6–20 mg/dl), serum creatinine 1.4 mg/dl (0.5–1.1 mg/dl), prothrombin time 45.5 seconds (11.5–14.7 sec) and international normalized ratio (INR) 5.0 (0.9–1.1). Intravenous furosemide was started, and her long-term drug therapy was restarted.

The patient's medical record documented hematologic reactions during heparin administration on several previous occasions. She had received short intravenous courses of lepirudin 3 times before this admission, but screening for heparin-induced platelet antibodies was negative. Her warfarin was temporarily withheld due to the supratherapeutic INR and was restarted after the INR decreased to 3.4. The patient's calculated creatinine clearance was approximately 40 ml/minute early in her hospital course but declined during treatment to approximately 22 ml/minute. Warfarin was again discontinued on hospital day 10 in anticipation of surgical insertion of a dual-chamber implantable cardioverter-defibrillator (ICD). Because of her presumed history of HIT, intravenous lepirudin 0.04 mg/kg/hour was started to maintain anticoagulation. After 4 hours, the lepirudin infusion was reduced to 0.02 mg/kg/hour and

subsequently discontinued due to consistently elevated activated partial thromboplastin times (aPTTs) and bleeding from the patient's femoral vein triple-lumen catheter. Lepirudin was restarted on hospital day 13 and continued until the patient underwent surgery on hospital day 16. Warfarin was restarted on hospital day 17.

The patient was stable after surgery but then suffered further decompensation of heart failure with hypotension on hospital day 19; she was transferred to the intensive care unit. After several days of hemodynamic support, she was scheduled for right-heart catheterization with further evaluation for cardiac transplantation. Warfarin was again discontinued on hospital day 28 in anticipation of this procedure. Lepirudin was restarted on hospital day 31 with a 0.2-mg/kg intravenous bolus dose. During administration, the patient experienced cardiorespiratory arrest. The incomplete lepirudin bolus was discontinued, and advanced cardiac life support measures were started. The ICD fired 10 times in response to ventricular fibrillation (confirmed by ICD interrogation). The patient was intubated, and hemodynamic support was provided with continuous infusions of amiodarone, dopamine, and phenylephrine. She recovered from the reaction to near-baseline function and was transferred to the medical ward. Evaluation for cardiac transplantation proceeded as planned, and the patient was deemed a suitable candidate for the procedure. She died of worsening heart failure on hospital day 62 before cardiac transplantation could be attempted. In accordance with hospital protocol, this event was reported to the Food and Drug Administration's safety and adverse event reporting program. Figure 1 outlines the time courses of lepirudin administration to the patient.

Discussion

Several published case reports have described varying degrees of allergic-type reactions to lepirudin, ranging from urticaria¹⁰ or flush reactions¹¹ and asymptomatic hypotension¹² to more severe responses, such as hemodynamic collapse.^{8,9} Our review of published case reports identified 11 patients who experienced anaphylaxis in a strong temporal association with lepirudin administration.^{8,9} In four cases, the patient died as a result of the reaction.⁹ It is interesting that in each of the four cases, the patient had received lepirudin within 3 months before the fatal exposure. Tests for antihirudin

antibodies were performed (and were present) in only one patient.⁹ Another patient who experienced anaphylaxis was not tested for antibodies, but the presence of antihirudin antibodies was strongly suspected due to an increased aPTT, which persisted 6 days after discontinuation of lepirudin.⁸ According to a case series review, the risk for anaphylaxis on first exposure to lepirudin was approximately five cases for every 32,500 patients treated.⁹ Reexposure to lepirudin was associated with a greater risk, affecting approximately four patients among every 2500 patients treated.

Several factors, including route of administration, use of an initial bolus dose, length of therapy, and time until repeat administration of lepirudin, may influence the development and persistence of antihirudin antibodies and thus affect the risk for anaphylaxis. In various studies, antihirudin antibodies were detected in 44–74% of patients receiving lepirudin through either intravenous or subcutaneous routes.^{13–15} The antibodies were predominantly of the immunoglobulin (Ig) G subclass, although IgA and IgM antibodies were also detected. No IgE antibodies were found.^{13–15} Whereas both intravenous and subcutaneous routes of lepirudin administration may be associated with formation of antihirudin antibodies, most reported cases of anaphylaxis with lepirudin involved intravenous treatment. In one study, 84% of patients undergoing exclusively intravenous administration of lepirudin developed antihirudin antibodies, versus 50% of

patients with exclusively subcutaneous administration.¹⁴ Rapid accumulation of lepirudin may occur with bolus dosing, especially in patients with renal insufficiency. In published reports, eight (73%) of 11 patients who had anaphylactic reactions to lepirudin had received a bolus dose, indicating a possible association between bolus administration and the occurrence of anaphylaxis.^{8,9}

Duration of lepirudin therapy may affect patients' risk for an anaphylactic reaction. Studies and case reports indicate that antibodies develop no earlier than day 4 of lepirudin treatment.^{12–15} This may explain the lack of immunogenicity reported in studies in which the length of lepirudin therapy was 1–3 days.⁹ The duration of earlier courses of lepirudin is known for only one patient described in previous reports; this patient received lepirudin for 13 days during the first course of therapy.⁸ Our patient's experience differs from other published case reports in that none of her six individual courses of therapy was longer than 3 days.

Persistence of measurable quantities of antihirudin antibodies in blood may influence the risk for a severe reaction with subsequent lepirudin therapy. Time intervals between first lepirudin exposure and reexposure in patients who experienced anaphylaxis range from 6–90 days in published case reports.^{8,9} However, it is unknown how long antihirudin antibodies persist in the bloodstream. In one study, 66.7% of patients had cleared antihirudin antibodies within 180 days after stopping lepirudin, but one

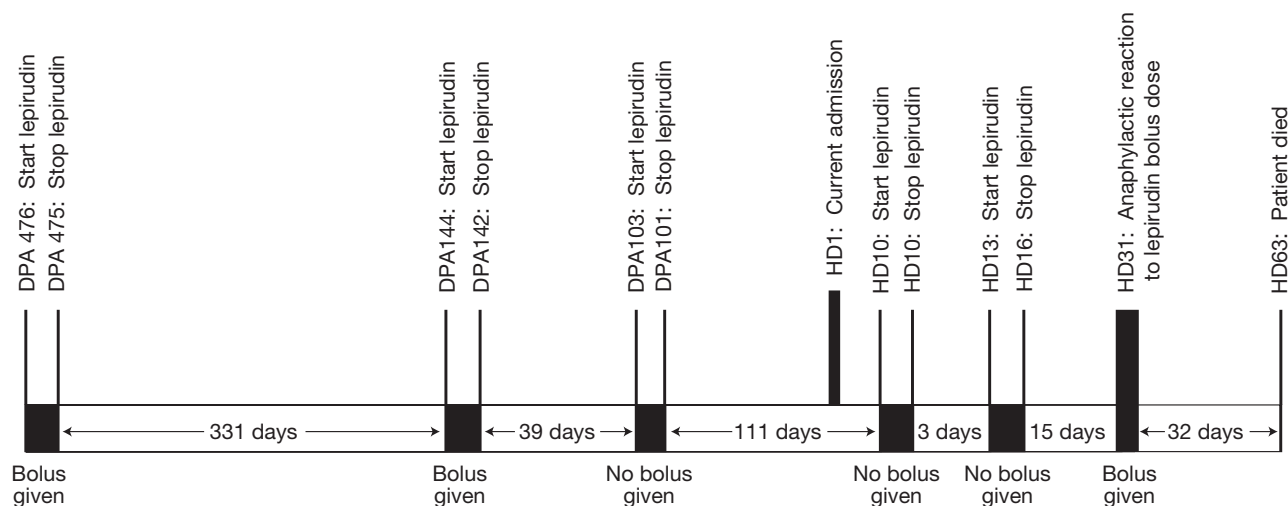


Figure 1. Time line of the patient's lepirudin administration. Black bars represent lepirudin infusion. DPA = days prior to admission; HD = hospital day.

patient had detectable levels of antihirudin antibodies 415 days after treatment with lepirudin.¹³ Another study followed antibody-positive patients for up to 490 days after discontinuation of lepirudin.¹⁵ Within this time period, antibody levels peaked and returned to undetectable levels in 22 of the 23 patients studied. However, patients have been reported to remain antihirudin antibody positive for as long as 2 years.¹⁶ One theoretical explanation for persistence of antihirudin antibodies is that clearance of lepirudin is reduced by the presence of antihirudin antibody-lepirudin complexes. Lepirudin is excreted renally by glomerular filtration, and antihirudin antibody-lepirudin complexes may be too large for glomerular filtration. Thus, the elimination half-life of the drug is extended and the antibodies persist. In addition, reduced clearance of lepirudin may result in enhanced anticoagulant effect. A subset of patients appear to experience enhanced anticoagulation after antihirudin antibodies develop, and increases in aPTT have been observed in antibody-positive patients.^{13, 14} Thus, unexplainable increases in aPTT values may indicate the presence of antihirudin antibodies and thus signal an increased risk for an anaphylactic reaction to lepirudin.

Our patient suffered a severe nonfatal anaphylactic reaction with reexposure to lepirudin. According to the Naranjo adverse drug reaction probability scale,¹⁷ lepirudin was a probable cause of this reaction. Unlike previous case reports, our report provides a detailed timeline of the patient's earlier courses of lepirudin therapy. It is significant that our patient received five short courses of lepirudin before having an anaphylactic reaction on her sixth exposure. No course of treatment resulted in more than 3 consecutive days of therapy. Antihirudin antibody testing was not performed in our patient, and all treatment courses were of short duration. Nevertheless, we believe that her increased aPTT values were a possible indication of the presence of antihirudin antibodies.

Our patient's experience is significant because it conflicts with past literature suggesting that courses of lepirudin must continue beyond 4 days to result in antihirudin antibody development.¹³ We believe that reduced renal function in our patient resulted in reduced elimination of lepirudin and a prolonged half-life, therefore simulating a lengthened course of therapy and resulting in antihirudin antibody development. Reduced elimination of lepirudin was signaled by

supratherapeutic aPTT values throughout several treatment courses. Bolus dose administration may have also contributed to anaphylaxis with the sixth exposure. Our patient's antihirudin antibody titer was likely boosted during her fifth course of treatment and remained elevated until the bolus readministration of lepirudin 15 days later. It is interesting that complications did not result from the third, fourth, or fifth exposures to lepirudin, even though these treatment courses were given within a relatively short time frame. None of those treatment courses was started with an intravenous bolus dose.

Considerations for Clinical Practice

Although anaphylactic reactions to lepirudin are rare, they are more likely to occur with repeated exposure to the drug.⁹ The amount of elapsed time required to safely administer a subsequent course of lepirudin therapy after previous exposure may be highly variable and is likely unpredictable. Moreover, it appears that administration of a bolus dose on reexposure to lepirudin increases the likelihood of a reaction. Therefore, the decision to administer lepirudin to a patient who has previously received it should be reached with due consideration of the risk:benefit ratio and strategies to manage risk resulting from readministration. These considerations should include a careful review of the patient's history of lepirudin administration and the length of each previous course of treatment. Clinicians should consider administering lepirudin in an intensive care unit, especially in patients with significant comorbidities. Consideration should be given to omitting the bolus dose at the start of therapy and perhaps to using a reduced infusion rate at the start to allow for gradual accumulation of lepirudin. Although no clinical evidence supports this practice, it may be particularly useful in patients with renal insufficiency. Routine testing for antihirudin antibodies is not recommended due to the high prevalence of antibody-positive patients and the very low frequency of serious adverse reactions to lepirudin.

Persistently elevated aPTT values in patients receiving stable or reduced doses of lepirudin may indicate drug accumulation due to the presence of antihirudin antibody-lepirudin complexes. Patients with renal insufficiency have a heightened risk for drug accumulation.¹⁸ A small retrospective study revealed that 58% of patients with renal insufficiency received either

Table 1. Manufacturer's Dosing Recommendations for Lepirudin Administration in Patients with Renal Insufficiency¹⁹

Creatinine Clearance (ml/min)	Bolus Dose (mg/kg) ^a	Initial Rate of Continuous Infusion (mg/kg/hr) ^a
> 60	0.4	0.15
45–60	0.2	0.075
30–44	0.2	0.045
15–29	0.2	0.0225
< 15 or receiving hemodialysis	0.1	Avoid infusion; give additional bolus dose of 0.1 mg/kg every other day if aPTT is supratherapeutic

aPTT = activated partial thromboplastin time.

^aBolus dose and infusion rate are dependent on patient's body weight up to a maximum of 110 kg.

Further dosage adjustments should be made in accordance with aPTT ratios over time.

bolus or infusion doses of lepirudin that were too high for their estimated creatinine clearance.¹⁸ Whereas it is unknown if supratherapeutic doses of lepirudin contribute to antibody development, clinicians must follow the manufacturer's dosing recommendations for patients with renal dysfunction to decrease bleeding risk. These recommendations are outlined in Table 1.¹⁹ Renal function and aPTT should be monitored daily in most patients and more frequently in patients with unstable conditions who receive lepirudin.

Because the risk for anaphylaxis on reexposure to lepirudin is unpredictable, alternatives may be considered for patients with a history of HIT and recent lepirudin therapy. Other direct thrombin inhibitors, such as argatroban, bivalirudin, or desirudin may be considered for these patients.³ However, bivalirudin and desirudin must be used cautiously in this patient population due to the threat of cross-reactivity. A study found that antihirudin antibodies from approximately 51% of antibody-positive patients also bound to bivalirudin.²⁰ The authors also speculated that antibody binding to bivalirudin may inhibit its renal clearance and necessitate close monitoring. Fondaparinux, a pentasaccharide that increases antithrombin III activity and thus inhibits factor Xa, may be considered as an alternative to lepirudin.³

Conclusion

Anaphylaxis is a rare but serious possible adverse effect of lepirudin. Risk factors may include use of an initial bolus dose, intravenous rather than subcutaneous administration, length of any single course of therapy beyond 3 days, and repeat administration of lepirudin within 100 days. Our patient's case was unusual in that an

anaphylactic reaction to lepirudin occurred even though none of her treatment courses had exceeded 3 days. We believe that impaired renal function in our patient caused reduced elimination of lepirudin, thereby simulating a longer course of therapy and resulting in antihirudin antibody development.

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