

Anaphylactic and Anaphylactoid Reactions Associated With Lepirudin in Patients With Heparin-Induced Thrombocytopenia

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Background—Lepirudin (Refludan) is a hirudin derivative. It is a direct thrombin inhibitor obtained by recombinant technology from the medicinal leech and is approved for treatment of heparin-induced thrombocytopenia complicated by thrombosis. Because 3 cases of fatal anaphylaxis possibly associated with use of lepirudin have been reported, we initiated an investigation of putative lepirudin-associated anaphylaxis.

Methods and Results—Aided by the manufacturer (Schering AG, Berlin, Germany), we used the lepirudin study databases to identify all patients in whom possible anaphylaxis/severe allergy was recorded from 1994 to September 2002. The 26 possible cases identified were reviewed independently by 2 investigators. After excluding patients with mild skin reactions, reactions likely caused by concomitant medications, poorly documented cases, and reactions that did not correspond temporally with lepirudin use, there remained 9 patients judged to have had severe anaphylaxis in close temporal association with lepirudin. All reactions occurred within minutes of intravenous lepirudin administration, with 4 fatal outcomes (3 acute cardiorespiratory arrests, 1 hypotension-induced myocardial infarction). In these 4 cases, a previous uneventful treatment course with lepirudin was identified (1 to 12 weeks earlier). We recorded high-titer IgG-anti-lepirudin antibodies in an additional patient with anaphylaxis. Because lepirudin has been used in $\approx 35\,000$ patients, the risk of anaphylaxis is $\approx 0.015\%$ (5 of 32 500) on first exposure and 0.16% (4 of 2500) in reexposed patients (7.5% estimated reexposures).

Conclusion—Lepirudin can cause fatal anaphylaxis, particularly in patients who are treated within 3 months of a previous exposure. The overall risk/benefit assessment of lepirudin as a treatment for heparin-induced thrombocytopenia remains favorable. (*Circulation*. 2003;108:2062-2065.)

Key Words: hirudin ■ antibodies ■ anticoagulants ■ shock, anaphylactic

Heparin-induced thrombocytopenia (HIT) is a prothrombotic syndrome that can be associated with thromboembolic complications.¹ Affected patients require alternative anticoagulation. The first approved anticoagulant not cross-reacting with HIT antibodies was the recombinant hirudin, lepirudin (Schering AG, Berlin, Germany).²

Although hirudin is a nonhuman protein, there are few reports on immune reactions toward it.³ In the major clinical studies of acute coronary syndromes, patients were usually treated with hirudin for 2 to 3 days only, a period too short for a B-cell response to develop. However, in patients receiving lepirudin for HIT, we and others have found a high incidence of anti-hirudin antibodies (44%).⁴⁻⁶ However, until now, only 2 patients with allergic reactions to hirudins have been reported.^{7,8}

In 2002, 3 patients with potential anaphylactic reactions associated with lepirudin treatment were identified by the

manufacturer's (Schering AG) pharmacosurveillance system. We therefore reassessed the risk of allergic and anaphylactic reactions potentially caused by lepirudin.

Methods

As part of the ongoing lepirudin pharmacosurveillance program, a review of the safety database, including clinical investigations and postmarketing reports, was initiated. The reporting period ranged from March 1994 until September 2002.

All cases reported to the manufacturer or the marketing authorization holder as anaphylactic or severe allergic reaction in conjunction with lepirudin treatment were identified, as were all cases in which such reactions were noted in the case narrative.

In addition, the adverse event database was screened for 289 terms potentially related to allergic, anaphylactic, or shock reactions (eg, hypotension, tachycardia). This initial screen retrieved 345 reports, which were reviewed by medical experts for cases representing or mentioning possible anaphylactic or anaphylactoid reactions irrespective of causality. The resulting case records were then independently assessed by 2 different

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Patients With Anaphylactic Reactions

Age, y/Gender	Outcome	Preexposure	Latency as Reported	Symptoms Reported	Medical Situation
64/M	Recovered "after withdrawal of lepirudin"	None known	Immediately after bolus	Choking sensation, pruritus palms and soles, cold and clammy, hypotension 70/20 mm Hg, pulse increase 72–92/min	Admitted with chest pain, history of myocardial infarction, angina pectoris, hypertension
62/F	Recovered	None known	Immediately after bolus	"Severe allergic reaction" with urticaria and broncho constriction	Admitted with unstable angina; medical history not given
57/F	Recovered within 30 minutes	None known	2 Minutes after bolus	Hypotension 30 mm Hg systolic, bradycardia 20/min, anaphylaxis with bronchospasm	HIT, history of chronic heart failure, coronary artery disease, ventricular cardiac arrhythmia, arterial occlusion left arm
67/F	Recovered within 60 minutes	Unknown	After bolus	Allergic shock, marked arterial hypotension, nausea vomiting	History of atrial fibrillation, torsades, pacemaker
72/M	Recovered	None known; positive rechallenge	Twice "after start of infusion" (no bolus given during rechallenge)	Hypotension 70 mm Hg systolic, generalized erythema, heat sensation	Acute HIT developed after colon carcinoma surgery; artificial aortic valve
81/M	Fatal decompensated cardiovascular failure	8 Days	5 Minutes after bolus	Hypotension 60 mm Hg, unresponsive, electromechanical dissociation	Pneumonia; troponin-positive acute coronary syndrome; underwent coronary angiography with new proximal stenosis and medial occlusion of LAD shown; history of RCA occlusion and chronic heart failure, EF 35%
67/F	Fatal decompensated cardiovascular failure	Twice, last 1 month prior	5 Minutes after bolus	Blood pressure decreased, cardiovascular collapse, went into cardiac arrest	History of coronary bypass surgery and HIT 10 months prior to event, chronic heart failure
63/M	Fatal, 1 hour after onset; myocardial infarction secondary to anaphylaxis suspected	3 Months	Minutes after bolus	Hypotension 70/40 mm Hg, generalized "pins and needles" sensation, erythema and pruritus, nausea, ventricular tachycardia, ventricular fibrillation, "huge histamine release phenomenon" in blood workup	Acute coronary syndrome; history of coronary bypass surgery, myocardial infarction, HIT, arterial hypertension
62/M	Fatal cardiorespiratory arrest	2 Months	Unknown, but same day	"Severe anaphylactic response followed by cardiorespiratory arrest"	Admitted for femoropopliteal bypass graft; history of coronary artery disease, diabetes mellitus, peripheral arterial occlusive disease
82/F*	Recovered	Start of dialysis with lepirudin 3 weeks before anaphylaxis	In the first minutes of dialysis; symptoms reoccurred after rechallenge with lepirudin	Bronchospasm, fever	HIT, end-stage renal failure

LAD, left anterior descending artery; RCA, right carotid artery; and EF, ejection fraction.

*This patient was identified in December 2002 after the end of the analyzed period.

medical experts aiming to identify cases with a reasonable probability of representing severe allergic reactions to lepirudin.

One additional patient was identified in December 2002 in whom anti-hirudin antibodies were tested as described.⁴

Results

Twenty-six cases were reported as likely being the result of severe allergic or anaphylactic reactions in conjunction with lepirudin treatment. Of the 26 reports, 17 were excluded for the following reasons: insufficient informa-

tion (n=4); lack of temporal association with lepirudin use (1 resolved when lepirudin was continued, 2 occurred 10 hours and 4 days after discontinuation of lepirudin); mild or moderate allergic reactions (2 skin reactions, 1 skin reaction, facial and pharyngeal edema with tachycardia but no drop in blood pressure); probable reaction to other drugs (3 streptokinase, 3 contrast medium); and unclear clinical presentation and negative test for anti-hirudin antibodies (1 patient).

The remaining 9 patients were considered to have experienced severe anaphylactic reactions (Table). All occurred within minutes of treatment initiation (time of onset unknown in 1 patient).

The 4 patients who experienced the event during reexposure to lepirudin suffered from severe cardiac disease and died shortly after the onset of the anaphylactic event (3 acute cardiorespiratory arrests, 1 secondary myocardial infarction).

The time interval to the preceding treatment course with lepirudin ranged from 1 to 12 weeks. Allergic symptoms were not reported for the preceding treatment courses in any of these patients. Only the additional patient (identified in December 2002) was tested for anti-hirudin antibodies. She showed high-titer anti-lepirudin antibodies of the IgG (1:5000) but not of the IgE or IgM class and had a positive rechallenge test.

Despite increasing use of lepirudin, the number of reports on anaphylaxis per year did not increase since 1994. All fatal cases occurred during the last 18 months.

Discussion

This study shows that Refludan, containing lepirudin as an active ingredient, has been associated with severe anaphylactic reactions, and recent preexposure seems to be related to reactions with fatal outcome. The patients who died were suffering from severe cardiac disease, which could have contributed to the fatalities. Because we had serum from 1 patient only to prove the anti-lepirudin antibodies, this study highly implicates but does not conclusively prove that all anaphylactic reactions observed were immune mediated.

Approximately 35 000 patients have been treated with lepirudin so far. If one extrapolates the reexposure rate of $\approx 7.5\%$ observed in 2 prospective trials assessing lepirudin in HIT,^{9,10} then ≈ 2500 patients will have been reexposed. Thus, the risk for severe anaphylactic reactions during lepirudin treatment is $\approx 0.015\%$ (5 of 32 500) on first treatment with lepirudin and 0.16% (4 of 2500) in reexposed patients.

In the known reexposure cases, the time period between last treatment with lepirudin and reexposure ranged between 1 and 12 weeks, and the anaphylactic reactions manifested within minutes of initiation of lepirudin therapy. This strongly suggests that in these patients, circulating anti-hirudin antibodies were already present at the start of lepirudin treatment. This was most likely the case in the dialysis patient in whom immunization was triggered by previous treatment with lepirudin, although contact with leeches, hirudins in ointments, or naturally occurring antibodies have not been formally excluded as causes.

It is known that not only IgE antibodies but also IgG antibodies can cause allergic reactions to drugs such as protamine,¹¹ thiamine,¹² and dextrans.¹³ This could also be the case for hirudin, because we could demonstrate high-titer anti-hirudin antibodies of the IgG class but no IgE antibodies in 1 of the patients. This is in line with a report by Bircher et al⁷ on a volunteer who received several uneventful intravenous injections of the r-hirudin desirudin. Five years later, this patient again received 15 mg desirudin subcutaneously twice within 1 week and devel-

oped a prickling cutaneous sensation, generalized urticaria, and slight respiratory depression controlled by steroids. No specific IgE antibodies to hirudin or candida or *S cerevisia* were detected, although high-titer (1:1600) anti-hirudin IgG antibodies were present directly before the injection, which were boosted after the injection (titer 1:12 800 at 2.5 weeks) and then declined.

Recombinant hirudins are produced in yeast, and small amounts of yeast proteins are found in the commercial preparations ($<0.001\%$). Yeast proteins or other compounds such as mannitol could have been responsible for some of the anaphylactic reactions, because in 5 of the 10 patients with anaphylaxis, no evidence for previous hirudin treatment was found.

Anti-hirudin antibodies can also be induced by other hirudins and low-dose subcutaneous injection, eg, by 15 mg desirudin subcutaneously twice a day.¹⁴ Currently, besides lepirudin, the recombinant hirudin desirudin (Aventis, Frankfurt, Germany) and bivalirudin (The Medicines Co, Parsippany, NJ), which shares the thrombin-exosite-binding amino acid sequence with hirudin, are approved or under trial in various countries for thrombosis prophylaxis after orthopedic surgery or for cardiac intervention.

To put the risk of anaphylaxis caused by lepirudin into perspective, it should be emphasized that the death rate of $>20\%$ in patients with HIT before lepirudin became available has been reduced to $<10\%$ in lepirudin-treated patients.²

In conclusion, lepirudin could be associated with anaphylaxis, and patients who have been preexposed to the drug, especially within recent months, could be at an increased risk for severe anaphylactic reactions. Omission of the bolus might reduce the severity of anaphylaxis. Alternative treatment options should be considered before reexposure to lepirudin. Treatment with lepirudin should only be started in an environment where treatment for anaphylactic reaction is readily available. The overall risk/benefit assessment of lepirudin as a treatment for HIT remains favorable.

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References

1. Warkentin TE, Chong BH, Greinacher A. Heparin-induced thrombocytopenia: towards consensus. *Thromb Haemost*. 1998;79:1–7.
2. Greinacher A, Lubenow N. Recombinant hirudin in clinical practice: focus on lepirudin. *Circulation*. 2001;103:1479–1484.
3. Close P, Bichler J, Kerry R. Weak allergenicity of recombinant hirudin CGP 39393 (Revasc) in immunocompetent volunteers. The European Hirudin in Thrombosis Group (HIT Group). *Coron Artery Dis*. 1994;5:943–949.
4. Eichler P, Friesen HJ, Lubenow N, et al. Antihirudin antibodies in patients with heparin-induced thrombocytopenia treated with lepirudin: incidence, effects on aPTT, and clinical relevance. *Blood*. 2000;96:2373–2378.

5. Song X, Huhle G, Wang L, et al. Generation of anti-hirudin antibodies in heparin-induced thrombocytopenic patients treated with r-hirudin. *Circulation*. 1999;100:1528–1532.
6. Huhle G, Hoffmann U, Song X, et al. Immunologic response to recombinant hirudin in HIT type II patients during long-term treatment. *Br J Haematol*. 1999;106:195–201.
7. Bircher AJ, Czendlik CH, Messmer SL, et al. Acute urticaria caused by subcutaneous recombinant hirudin: evidence for an IgG-mediated hypersensitivity reaction. *J Allergy Clin Immunol*. 1996;98:994–996.
8. Harenberg J, Hoffmann U, Huhle G, et al. Treatment of an acute flush reaction caused by subcutaneous r-hirudin with pegylated hirudin. *Br J Haematol*. 2000;108:528–530.
9. Greinacher A, Volpel H, Janssens U, et al. Recombinant hirudin (lepirudin) provides safe and effective anticoagulation in patients with heparin-induced thrombocytopenia: a prospective study. *Circulation*. 1999;99:73–80.
10. Greinacher A, Janssens U, Berg G, et al. Lepirudin (Recombinant hirudin) for parenteral anticoagulation in patients with heparin-induced thrombocytopenia. *Circulation*. 1999;100:587–593.
11. Weiss ME, Nyhan D, Peng ZK, et al. Association of protamine IgE and IgG antibodies with life-threatening reactions to intravenous protamine. *N Engl J Med*. 1989;320:886–892.
12. Proebstle TM, Gall H, Jugert FK, et al. Specific IgE and IgG serum antibodies to thiamine associated with anaphylactic reaction. *J Allergy Clin Immunol*. 1995;95:1059–1060.
13. Kraft D, Hedin H, Richter W, et al. Immunoglobulin class and subclass distribution of dextran-reactive antibodies in human reactors and non reactors to clinical dextran. *Allergy*. 1982;37:481–489.
14. Greinacher A, Eichler P, Albrecht D, et al. Anti-hirudin antibodies following low-dose subcutaneous treatment with desirudin for thrombosis prophylaxis after hip-replacement surgery: incidence and clinical relevance. *Blood*. 2003;101:2617–2619.