

Subcutaneous Lepirudin for Heparin-Induced Thrombocytopenia and When Other Anticoagulants Fail: Illustrative Cases

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Background

When a patient with malignancy fails to respond to or progresses during initial chemotherapy, she is often switched to a “second-line,” dissimilar treatment regimen. Failure to respond favorably to or progression despite second-line therapy prompts consideration of a “third-line” treatment approach. The choice of treatment sequencing usually depends on a combination of reported efficacy, safety, patient choice, and physician experience. A particular treatment, by virtue of being deemed other than “frontline” therapy, is not necessarily inferior in any way.

With regards to anticoagulant therapy for venous and arterial thromboembolic events, initial therapy almost universally consists of intravenous (IV) unfractionated heparin (UFH) or subcutaneous (SC) low molecular weight heparin (LMWH) followed by a variable duration of oral warfarin. Thrombosis progression and thrombosis recurrence despite documentation of target-intensity warfarin therapy, namely “warfarin failure,” prompts either attainment of a higher target international normalized ratio (INR) with oral warfarin or switching to long-term treatment with once-daily LMWH. In the event of thrombosis progression and recurrence during treatment-intensity LMWH, well established treatment options are limited.

Lepirudin is a recombinant hirudin that is identical to the naturally occurring medicinal leech peripharyngeal gland saliva-derived protein except for the substitution of leucine for isoleucine at the N-terminus and the lack of sulfation of the tyrosine at position 63.¹ Similar to the parent protein, lepirudin is bivalent and tightly binds to both the catalytic site and exosite of thrombin to exert its anticoagulant activity.¹ Because of its potency, lack of any molecular similarity to heparins, and lack of cross-reactivity with heparin-induced thrombocytopenia (HIT)-associated antibodies, lepirudin has been a trusted anticoagulant in patients with past or current HIT and those at risk for HIT. SC lepirudin has been

evaluated in HIT and several clinical situations where UFH is typically the treatment of choice. A limited number of case reports have illustrated the utility of SC lepirudin as a second- or third-line anticoagulant. We present 5 case reports that illustrate the special role of SC lepirudin in patients with HIT, warfarin failure, LMWH failure, fondaparinux failure, and refractory hypercoagulability.

Case 1

A 35-year-old woman with inflammatory bowel disease and chronic hepatitis C presented with a right upper-extremity, axillo-subclavian, catheter-associated deep venous thrombosis (DVT). She was initially treated with weight-based, SC enoxaparin 70 mg twice daily. Despite LMWH treatment, she developed extension of her DVT and a documented symptomatic bilateral segmental pulmonary embolism (PE). At the time of recurrent thrombosis diagnosis, it was noted that her platelet count had dropped from a baseline of 365,000/ μ L to 111,000/ μ L over the course of 5 days. Serological testing for anti-heparin:platelet factor 4 antibodies was positive. The patient was diagnosed with HIT with thrombosis (HITT). She was treated as an inpatient with IV lepirudin 0.15 mg/kg/hour for 8 days with a target activated partial thromboplastin time (aPTT) of 2.5 times median normal. Due to anorexia, abdominal pains, vomiting, and concomitant antibiotic therapy, she was not felt to be a good candidate for conversion to oral warfarin. She was switched from IV lepirudin to subcutaneous lepirudin 40 mg twice daily. Her aPTT ratio ran from 1.4 to 2.7 when drawn 6 hours after morning SC lepirudin doses. Her upper extremity swelling improved and when her oral intake stabilized, after 9 days of SC lepirudin, she was transitioned to oral warfarin with a target INR of 2.0–3.0.

Case 2

A 29-year-old man was diagnosed with acute portal vein thrombosis. Initial anticoagulation consisted of IV UFH. He was subsequently diagnosed with HITT following the development of extensive bilateral femoral vein thrombosis and right popliteal artery thrombosis in the setting of positive HIT serology. He was started on IV lepirudin and

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subsequently switched to once-daily SC fondaparinux prior to hospital discharge. Shortly after discharge, he developed testicular vein and artery thrombosis requiring orchiectomy. He was treated with SC lepirudin following surgery without recurrent thrombosis.

Case 3

A 64-year-old woman presented with extensive lower extremity superficial thrombophlebitis for which she was started on SC enoxaparin 1 mg/kg twice daily. Oral warfarin was begun 1 day after start of the enoxaparin with a target INR of 2.0–3.0. Three days later, and 1 day after the last dose of enoxaparin, she presented with thrombocytopenia (53,000/ μ L) and areas of what looked like classic warfarin-induced skin necrosis on both legs. She was felt to have both HIT and warfarin-induced skin necrosis. The enoxaparin and warfarin were stopped and the patient was treated with IV, and subsequently SC, danaparoid. Following successful skin grafting to the lower legs, she developed skin necrosis involving the skin graft harvest sites on the thighs. At this point in time, she was started on IV lepirudin. Laboratory testing uncovered an anticardiolipin antibody and cryofibrinogenemia. An attempt to gradually restart low dose (1 mg) warfarin after 1 month on IV lepirudin resulted in the patient developing new leg pain and new skin changes suggestive of early skin necrosis. She was given vitamin K and fresh frozen plasma. She was discharged on SC lepirudin 50 mg twice daily. After 1 year, the lepirudin dose was reduced to 25 mg twice daily. She was subsequently diagnosed with a large B-cell lymphoma and polycythemia vera. SC lepirudin was continued through chemotherapy without further documented thrombotic event.

Case 4

A 61-year-old woman with a history of rapidly progressive peripheral arterial occlusive disease and coronary artery disease presented with thrombotic occlusion of an aorto-bifemoral bypass graft 3 months after vascular surgery. She underwent repeat revascularization followed by warfarin thromboprophylaxis with a target INR of 2.0–3.0. Laboratory evaluation uncovered a persistent, high-titer anti-beta-2-glycoprotein I antibody, fasting plasma hyperhomocysteinemia, and platelet hyperaggregation (“sticky platelet syndrome”). She was started on triple vitamin therapy and aspirin 81 mg per day, and she had her target INR increased to 3.0–3.5 due to refractory transient ischemic neurologic events (TIAs). She subsequently developed recurrent lower extremity rest pain due to arterial graft thrombosis. Following successful thrombectomy, the target INR was increased to 3.5–4.0. Following repeat coronary artery bypass grafting, she was discharged on warfarin plus aspirin and clopidogrel. Recurrent claudication without documented graft or vessel occlusion prompted initiation of a new antithrombotic regimen consisting of SC dalteparin 5,000 units daily, clopidogrel 75 mg daily, and cilostazol 100 mg twice daily. She did well for 2 years until recurrent aorto-bifemoral graft thrombosis

was documented. Dalteparin was discontinued and replaced with SC lepirudin 20 mg twice daily. She has remained stable for 3 additional years.

Case 5

A 59-year-old woman with metastatic adenocarcinoma of unknown primary presented with recurrent thrombosis despite LMWH therapy. Her history was notable for acute left leg proximal DVT and left arm superficial thrombophlebitis treated with LMWH bridging to oral warfarin with a target INR of 2.0–3.0. LMWH and warfarin treatments had been overlapped for 7 days. Twelve days after discontinuation of LMWH, and with an INR of 2.51, she developed a symptomatic extension of her left leg DVT and a new proximal right leg DVT. She was deemed to be a “warfarin failure” and discharged on twice-daily, weight-based enoxaparin. Chest imaging 2 months later revealed the interval development of PE with associated pulmonary infarction. During placement of an inferior vena cava (IVC) filter, she was found to have infrarenal IVC thrombosis. Shortly after IVC filter placement, she developed acute left leg arterial thrombosis treated by catheter-directed thrombolysis. A patent foramen ovale was detected on echocardiography. She was viewed as a LMWH failure and started on IV lepirudin (Refludan, Berlex). She required a 0.075 mg/kg/hour (97.2 mg/day) infusion to maintain an aPTT between 45 and 60 seconds. She was switched to SC lepirudin 50 mg twice daily to facilitate hospital discharge and prevent further thrombosis.

Discussion

Lepirudin is a well established US Food and Drug Administration-approved direct thrombin inhibitor for the treatment of HIT.² IV lepirudin has been shown to reduce the composite endpoint of all-cause mortality, limb amputation, and new thrombosis in patients with serologically confirmed HIT compared to well matched historical controls.^{3–6} Lepirudin has been shown to be effective in HIT patients both with and without concomitant thrombosis. Efficacy in these patient groups with profound hypercoagulability and high rates of thrombosis in the absence of treatment substantiates our use of lepirudin in patients who fail to respond favorably to other anticoagulant agents. Our cases highlight the utility of lepirudin in general and SC lepirudin in particular in patients with LMWH-induced HIT and the inability to tolerate oral warfarin (case 1); HIT and fondaparinux failure (case 2); HIT and warfarin-induced skin necrosis (case 3); hypercoagulable states and recurrent arterial graft thrombosis despite standard anticoagulation (case 4); and hypercoagulability of malignancy and associated warfarin as well as LMWH failure (case 5). SC lepirudin has been formally studied in several clinical settings and has been recently reviewed.⁷ Lepirudin 1.25 mg/kg every 12 hours administered SC has been shown to be as effective and safe as IV UFH at reducing the incidence of subsequent thromboembolic events in patients with acute DVT.⁸ As an adjunctive therapy in acute myocardial infarction, lepirudin 0.2 mg/kg IV bolus before streptokinase (SK)

followed by SC lepirudin 0.5 mg/kg twice daily for 5–7 days was associated with a greater frequency of ST elevation resolution at both 90 and 180 minutes ($P \leq .03$) and a lower study-period-associated rate of reinfarction than patients treated with UFH plus SK.⁹ SC lepirudin was evaluated in a small prospective study of 19 patients with clinical and serologically confirmed HIT.¹⁰ Patients were separated into 3 treatment groups: HITT, $n=10$; isolated HIT, $n=5$; and HIT requiring interruption of oral warfarin, $n=4$. Patients in group 1 received a lepirudin 0.2 mg/kg IV bolus followed by 0.1 mg/kg/hour infusion for at least 10 days followed by SC lepirudin 25 mg twice daily. Groups 2 and 3 were each dosed with SC lepirudin 25 mg twice daily. This small study demonstrated that after thrombus stabilization, SC lepirudin appeared to be safe and effective for long-term treatment or prophylaxis in patients with HIT or HITT.

Additional experience with SC lepirudin has been published in case report format. Successful management of thromboembolic disease with SC lepirudin has been reported in patients with HIT in conjunction with heart transplantation and the need for frequent right-heart biopsies,¹¹ warfarin and LMWH “failure” in the setting of type I antithrombin deficiency,¹¹ and arterial plus venous thrombosis in association with Trousseau’s syndrome plus HIT.¹² Our 5 cases expand the published experience by illustrating the use of SC lepirudin in the setting of fondaparinux failure, in the setting of HIT, warfarin-induced skin necrosis, and refractory recurrent arterial graft thrombotic occlusion. SC lepirudin appears to be potent and safe at a broad spectrum of dosages. Further study of SC lepirudin and determination of the optimal and most cost-effective dose seem warranted.

Review

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Deitcher et al report their clinical experience in successfully treating 5 patients by SC administration of the recombinant hirudin lepirudin. These patients had a seriously enhanced risk for new thromboembolic complications and their comorbidities did not allow use of heparin or vitamin K antagonists.

The scientific value of such anecdotal case presentations is often questioned in the times of evidence-based medicine and megatrials involving thousands of patients. However, individual patients sometimes present with characteristics or complications, which are usually exclusion criteria in clinical trials, or as in the case of heparin-induced thrombocytopenia, the standard treatment caused the adverse events requiring alternative treatment. In the daily clinical practice these patients are often the most difficult to treat. This is especially true in patients with severe hypercoagulable disease.

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Deitcher et al compare in their introduction first- and second-line treatments in hypercoagulable patients with the different treatment approaches in patients with malignancies. In terms of short-term risk of lethality and in terms of quality of life, one should consider that patients with severe hypercoagulability are at least as seriously affected as patients with malignancies.

In patients with heparin-induced thrombocytopenia we do know that the natural course of the disease is associated with a 20% mortality and approximately the same number of patients being at risk to lose a limb or to develop stroke or myocardial infarction.¹ Also patients with severe antiphospholipid antibody syndrome are often very difficult to manage. Patients with malignancies, especially those with adenocarcinoma-associated thrombosis sometimes deteriorate after beginning of vitamin K antagonist treatment. In these patients the procoagulatory effect of the tumor together with protein C depletion by the vitamin K antagonist provoke further thrombosis.² The presented cases indicate that lepirudin might be a second-line treatment option in these patients. Another group of patients in whom alternative treatment with lepirudin usually facilitates management, also in my own clinical practice, are those with aPTT resistance.

Currently there are 4 alternative drugs available to substitute for heparin, low molecular weight heparin, or vitamin K antagonists: danaparoid, a heparinoid; fondaparinux, a synthetic pentasaccharide; argatroban, a synthetic monovalent direct thrombin inhibitor; and recombinant hirudins (lepirudin and desirudin). Danaparoid has been used in a large number of very complicated patients in a worldwide compassionate use program.³

It has a long half-life which makes it very suitable for SC application, but it is no longer marketed in the US. Fondaparinux is approved for post orthopedic surgery thrombosis prophylaxis and has been studied in patients with deep vein thrombosis and pulmonary embolism. It also has a long half-life but little data are available on its use in very complicated patients. Argatroban has such a short half-life that it cannot be used for SC treatment. It is too early to speculate on whether the oral direct thrombin inhibitors such as ximelagatran will offer an additional option in these patients in the future.

Lepirudin has been assessed in large clinical trials in patients with acute coronary syndromes,^{4,5} and in 3 prospective trials in patients with heparin-induced thrombocytopenia.⁶ The latter patients had severe comorbidities reflecting most likely most of the spectrum of complicated patients seen even in a large hemostasis unit.

In the clinical studies with lepirudin in HIT, patients were treated by continuous IV infusion of lepirudin. The safety and pharmacokinetics of SC lepirudin were established in pilot studies of 10 patients with deep vein thrombosis,⁷ and a dose-finding study of 121 patients with acute deep vein thrombosis.⁸ Here the dose of 1.25 mg/kg/12h was as efficacious as IV heparin. A pilot study of 15 patients suffering from HIT with and without thrombosis found that treatment with SC lepirudin for approximately 25 days resulted in no new thromboembolic or major bleeding events and indicated that SC lepirudin may provide a long-term thromboprophylaxis regimen in HIT patients.⁹ SC lepirudin has also been successfully used as an adjunct to streptokinase for treatment of thrombolysis in patients with acute myocardial infarction¹⁰ and postoperatively as an anticoagulant following cardiopulmonary bypass in open heart surgery¹¹ and on an outpatient basis for the long-term (3 months) management of venous thromboembolic disease.¹²

However, one must not generalize the experience made with low molecular weight heparins, which do not require monitoring due to a reasonably predictable dose-response relationship to the new anticoagulants. Lepirudin has to be monitored even when given subcutaneously, especially if given in therapeutic concentration.

When administered subcutaneously, lepirudin is completely absorbed.¹³ Bioavailability is greater than 85% as assessed from plasma/urine data. As lepirudin distributes into the extracellular compartment, in contrast to heparin, only 20% of lepirudin is found in the plasma, while the remaining 80% distributes in the extravascular compartment.

Pharmacokinetics of lepirudin is mostly dependent on renal function, as more than 90% of the drug are cleared by the kidneys. After the SC dose, pharmacokinetics is best described by a one-compartment model. In young healthy volunteers, maximum lepirudin concentrations are reached between 1.7 and 2.6 hours and the apparent terminal half-life is 1.8 to 3 hours. Area under the curve (AUC) values are proportional to the SC dose over the range of 0.05 to 0.5 mg/kg.¹⁴ During multiple dosing, steady state concentrations are achieved by the second BID dose with an accumulation ratio of 1.15. The mean values of renal clearance for subcutaneously administered lepirudin agreed well with IV studies. Similar to IV dosing, about 40% of a SC dose was recovered in urine in 24 hours, with the remaining 60% most likely degraded within the kidneys. However, this accounts only for patients with normal renal function. There are no published data on the pharmacokinetics of SC lepirudin in patients with renal insufficiency!

Converting from IV to SC lepirudin dosing involves a simple calculation based on the stabilized aPTT ratio achieved during the IV infusion prior to the conversion. For a patient whose aPTT ratio measures between 1.5 and 1.8 on IV therapy, the SC (BID) dose is 120% of the cumulative 12h dose obtained by IV infusion. For aPTTs 1.8 to 2.2, the SC dose is 100% of the cumulative 12h dose. Finally, for aPTTs 2.2 to 2.5, the SC dose is 50% of the 12h cumulative dose. Again, these recommendations for adjusting the SC dose based on aPTT ratios are based on a small number of trials using healthy volunteers with normal renal function.

Lepirudin elimination, and therefore lepirudin dosing, is highly dependent on renal function as at least 90% of lepirudin are cleared by the kidneys. Dose reduction combined with more frequent monitoring is mandatory in these patients. A recently published chart review analysis of 34 patients with renal insufficiency showed that 58% of the patients studied received a higher lepirudin dose than recommended by the manufacturer in the package insert.¹⁵ Not surprisingly, of the patients with an aPTT value above 2.5, 58% experienced bleeding. For patients who bled, 83% were receiving a higher lepirudin dose than appropriate based on renal function.

Also in patients who develop antihirudin antibodies pharmacokinetics of lepirudin may change. The polyclonal nature of antihirudin antibodies can result in variable biological effects. In most patients the antibodies have no effects of major clinical relevance.¹⁶⁻¹⁸ Data from 51 evaluable patients from the HAT studies showed that the effects of antihirudin antibodies on aPTT levels fell into 3 groups.¹⁶ No effect of antihirudin antibodies on aPTT was seen in 49% of antibody-positive patients, a neutralizing effect was seen in 5.9%, and an enhanced anticoagulation effect was seen in 45.1%. This is most likely caused by a decreased renal clearance of the lepirudin-antilepirudin-antibody complexes.

Antihirudin antibodies have also been detected following SC treatment with desirudin, another recombinant hirudin. No differences were observed in the occurrence rate of anti-

hirudin antibodies in patients treated with lepirudin IV or desirudin SC ($P=.113$), and there was 100% cross-reactivity for the two recombinant hirudins.¹⁹ In a study of 27 patients with HIT who had been treated long-term or recurrently with intravenously or subcutaneously administered lepirudin, patients mainly developed antibodies between the 10th and 30th days for both types of administration.²⁰ The biologic effects of antihirudin antibodies on anticoagulation can be easily compensated by changes in the lepirudin dose.

A review of lepirudin study databases from 1994 to 2002 found 9 cases of severe anaphylaxis that were associated with lepirudin use.²¹ Considering that lepirudin has been used in over 35,000 patients, the risk of anaphylaxis is rare (estimated at 0.015%) on first treatment and 0.16% upon re-exposure. All anaphylactic reaction occurred during IV treatment, but there is one report about mild anaphylaxis after application of the hirudin desirudin to an immunized volunteer.²² Thus, initiation of lepirudin treatment should be carried out in an environment where anaphylactic reactions can be readily treated.

Daily aPTT measurements are recommended at the beginning of lepirudin treatment as it is difficult to predict at what time steady state is reached in a patient with renal insufficiency and from Day 5 onward antihirudin antibodies may require dose adjustments.

As is known for reagents used to test prothrombin time (PT), reagents for the aPTT test can vary in their sensitivity to lepirudin and each laboratory should construct a dose-response curve using their own reagents. Additionally, caution must be exercised when interpreting the results of any functional assay in patients with low prothrombin levels as falsely elevated readings may result.²³

Patients with severe liver dysfunction, coagulopathy (eg, disseminated intravascular coagulation), or patients with acquired prothrombin deficiency due to treatment with vitamin K antagonists may have low PT levels. In these patients, the chromogenic substrate assay should be used to determine lepirudin levels as this assay is independent of PT levels.²⁴

In conclusion, a number of case reports and clinical trials with SC lepirudin demonstrate its feasibility in a variety of clinical settings. SC administration of lepirudin is likely to be especially valuable for patients in whom vitamin K antagonists are not practical for prevention or treatment of DVT or in those who have failed low molecular weight heparins. However, one has to know the pharmacology and pharmacokinetics of this powerful thrombin-inhibitor to dose the drug appropriately, especially in patients with severe comorbidities. The option to use lepirudin subcutaneously may allow for reduced hospital stays for less critically ill patients.

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