Lepirudin Dose Recommendations for Treatment of Heparin-Induced Thrombocytopenia in Patients Undergoing Intermittent Hemodialysis

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Lepirudin, a specific inhibitor of thrombin, is indicated for anticoagulation in patients with type II heparin-induced thrombocytopenia.[1] The drug has been available on the Canadian market since November 1999. The manufacturer currently recommends that lepirudin's anticoagulation effects be monitored with activated partial thromboplastin time (aPTT). The goal is to maintain the aPTT at 1.5 to 2.5 times the patient's baseline value. However, the best method for monitoring lepirudin is currently under debate, and ecarin clotting time may prove more accurate once this test is widely available.[2]

Pharmacokinetic studies of IV lepirudin show that between 33% and 65% of lepirudin and its active metabolites are excreted in the urine.[3] Renal clearance is approximately 50% of systemic clearance.[3] In patients with renal impairment, lepirudin clearance decreases and half-life increases in proportion to creatinine clearance.[1] The manufacturer's recommended dose for patients without renal dysfunction is an IV bolus of 0.4 mg/kg followed by continuous IV infusion at 0.15 mg/kg per hour.[1] In contrast, the recommended dose for patients undergoing dialysis and those in acute renal failure is an IV bolus of 0.2 mg/kg followed by additional IV bolus doses of 0.1 mg/kg every other day if the aPTT falls below the lower therapeutic range.[1] However, a more recent report has recommended that IV doses of lepirudin in patients with renal impairment be limited to 0.05 to 0.1 mg/kg, without initial bolus dosing, to avoid overanticoagulation.[4] Avoidance of iatrogenic overanticoagulation is important, as these patients have a higher bleeding tendency than the normal population. The causes of this abnormal hemostasis include abnormal platelet adhesion and aggregation, decreased plasma concentrations of von Willebrand factor, and defective binding of von Willebrand factor, which results in impaired interactions between platelets and the blood vessel walls.[5]

The main advantages of lepirudin over other agents such as danaparoid include its lack of immunologic cross-reactivity with the antibodies associated with heparin-induced thrombocytopenia and its ease of monitoring through aPTT.[6] In contrast, danaparoid is associated with an *in vitro* cross-reactivity rate of approximately 10%, and there have been published reports of new and fatal episodes of heparin-induced thrombocytopenia during therapy with this agent.[7-9] Therefore, it is recommended that the patient's serum first be tested against danaparoid for cross-reactivity before use of this drug in the treatment of heparin-induced thrombocytopenia.[7] Another disadvantage of danaparoid is that anticoagulant monitoring must be performed using anti-factor Xa concentrations, a test that may not be readily available.[6]

This report describes a case of successful lepirudin anticoagulation in a hemodialysis patient with type II heparin-induced thrombocytopenia, without initial bolus dosing. Lepirudin dosing characteristics and considerations in the treatment of type II heparin-induced thrombocytopenia that are unique to the hemodialysis population are also discussed.

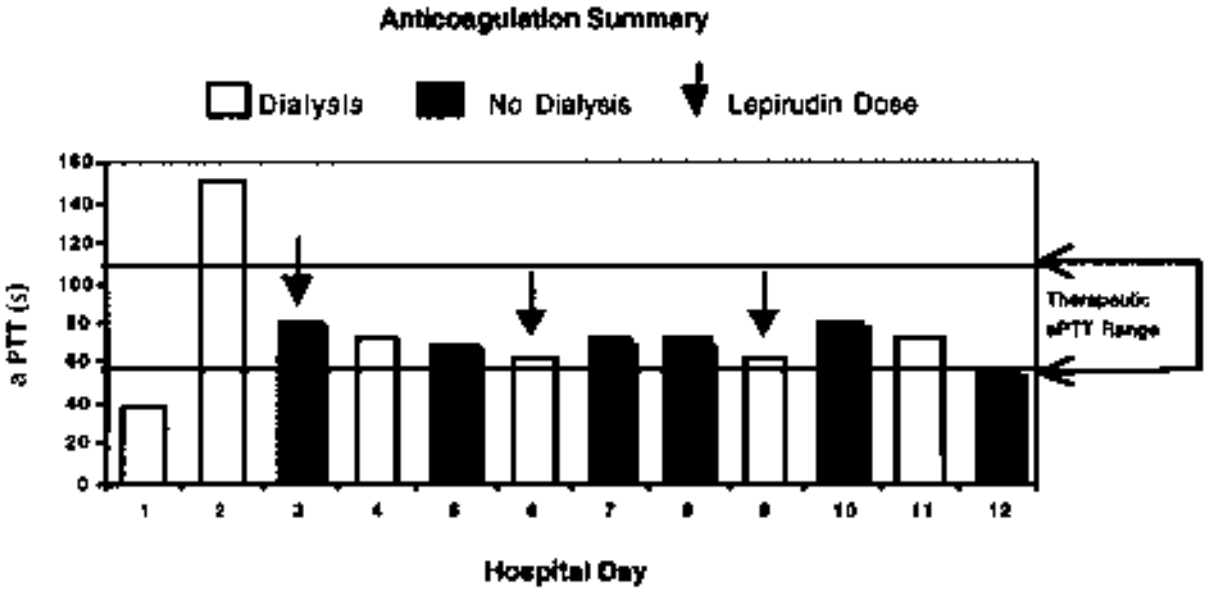

Figure 1. Activated partial thromboplastin time (aPTT) and dialysis history in a 50-year-old woman with heparin-induced thrombocytopenia who was treated with lepirudin.

CASE REPORT

A 50-year-old woman was admitted to the medical intensive care unit of the Medical College of Virginia Hospitals for hyperkalemia and volume overload, which had resulted when she missed her most recent scheduled hemodialysis session. Her medical history included coronary artery disease and hypertension-induced end-stage renal disease. She had been undergoing hemodialysis 3 times per week for the past 4 years, with access through a left forearm arteriovenous fistula; she was anuric. Pertinent laboratory values on admission were serum potassium concentration 7.0 mmol/L, blood urea nitrogen concentration 22.8 mmol/L, and serum creatinine concentration 929 mmol/L. The electrocardiogram indicated anterolateral ischemic changes, and the cardiac enzyme concentrations were elevated, consistent with myocardial infarction. At this time a heparin infusion was initiated. The patient underwent acute hemodialysis for 3½ hours with a low-flux (ultrafiltration coefficient 8.1 mL/h per millimetre mercury) polysulfone dialyzer (model F8, Fresenius, Bad Homburg, Germany). Subsequent dialysis sessions were performed with the same dialyzer according to the patient's regular thrice-weekly schedule.

Over the first 3 days of the hospital stay, the platelet count dropped significantly, from 172 x 10^9/L to 68 x 10^9/L. A hematology consult suggested that the sudden decline in platelets might have been due to type II heparin-induced thrombocytopenia, as the patient had prior exposure to heparin during hemodialysis and on hospital admissions during the previous 3 months. A heparin–platelet factor 4 enzyme-linked immunosorbent assay confirmed this diagnosis. All sources of heparin were discontinued. The hematology department consulted the clinical pharmacy department for a dose recommendation for lepirudin. The pharmacists (the authors of this paper) were aware of an earlier case report, which suggested that significant overanticoagulation may occur if the manufacturer's recommended bolus dosing regimen is followed in hemodialysis patients.[4] They were also aware of an *in vitro* study which suggested that low-flux dialyzers composed of polysulfone were impermeable to lepirudin.[10] On the basis of the available evidence, the decision was made to proceed cautiously, and intermittent 0.1 mg/kg dosing without the initial 0.2 mg/kg bolus was recommended. IV lepirudin 0.1 mg/kg was administered according to this recommendation on hospital day 3, approximately 90 min after the heparin infusion was discontinued. The first aPTT, obtained 6 h after the initial lepirudin dose, was within the therapeutic range (Figure 1). The patient remained adequately anticoagulated for 3 days after the initial dose (Figure 1). Repeat doses of lepirudin 0.1 mg/kg administered on days 6 and

9 maintained anticoagulation within the therapeutic range. The platelet count on day 9 was within the normal range, at 121 x 10^9/L. Warfarin therapy, with a target international normalized ratio of 2.0 to 3.0, in combination with saline flush dialysis, was initiated for long-term anticoagulation to prevent clotting on dialysis. No further doses of lepirudin were administered.

DISCUSSION

Factors Affecting Lepirudin Clearance in Patients Undergoing Hemodialysis

In deciding on an appropriate initial dose of lepirudin the patient's degree of residual renal function should be considered. Given that 70% to 90% of lepirudin is recovered in the urine after IV administration, even minor residual renal function (correlating to creatinine clearances of 2 to 3 mL/min) may significantly increase the clearance of lepirudin.[11-13] Because this patient was anuric, it was decided to proceed cautiously, with intermittent 0.1 mg/kg dosing and no initial bolus.

Another consideration is the type of dialyzer and the potential for drug removal by the membrane. Dialysis membranes are generally classified according to their ultrafiltration capacity or flux. Ultrafiltration is defined as the removal of water and other small solutes, and flux is a measure of ultrafiltration capacity. There is a direct correlation between flux and permeability to solutes, so a high-flux dialyzer can also be referred to as a high-permeability dialyzer and vice versa.[14] The specifications of any dialyzer must include the ultrafiltration coefficient. Low-flux dialyzers have an ultrafiltration coefficient of up to 12 mL/h per millimetre of mercury and can generally remove substances with a molecular weight of up to 500 daltons.[15] High-flux dialyzers have an ultrafiltration coefficient of more than 12 mL/h per millimetre of mercury and may remove substances up to 20 000 daltons or more in size.[15,16] Lepirudin appears to have characteristics that would enable its elimination by high-flux hemodialysis, as it is has a molecular weight of 6979 daltons, no relevant protein binding, a volume of distribution of 0.2 L/kg (which suggests extracellular distribution), and a renal clearance that contributes approximately 50% of the systemic clearance.[1]

Dialyzer membrane composition (Table 1) may also affect lepirudin removal. Although earlier studies using cuprammonium and high-flux polysulfone (PS 600, Bellco, Saluggia, Italy) membranes did not demonstrate removal of lepirudin, more recent evidence suggests that significant amounts of lepirudin are removed by certain types of membranes.[17] Bucha and others[10] performed in vitro testing on 19 different dialyzers. Only low-flux dialyzers with polysulfone or regenerated cellulose (including cuprammonium cellulose) membranes were impermeable to lepirudin. Other low-flux dialyzers, such as diethylaminoethyl cellulose, were partially permeable or, in the case of cellulose acetate membranes, almost completely permeable. All of the high-flux dialyzers tested allowed lepirudin to pass through the membrane. The authors concluded that, for hemodialysis patients undergoing treatment of type II heparin-induced thrombocytopenia, only low-flux polysulfone or regenerated cellulose membranes should be used. In a case report by Nowak and others,[18] administration of lepirudin as an anticoagulant during dialysis with a low-flux diethylaminoethyl cellulose membrane resulted in rapid decreases in lepirudin concentration in blood, and clots occurred in the bubble trap chamber and dialyzer. When the dialyzer was changed to a low-flux polysulfone membrane, a constant concentration of lepirudin in the blood was obtained and no further clots were observed. In the case reported here, a low-flux polysulfone membrane was being used, which would not be expected to remove significant amounts of lepirudin. An online searchable dialyzer database[19] is available for determining the ultrafiltration coefficient, flux, and membrane composition of various dialyzers, of which hundreds of different types are currently available worldwide.

Table 1. Composition of Common Dialyzer Membranes

Membrane Composition	Name
Cellulose	Regenerated cellulose Cuprammonium cellulose (Cuprophan) Cuprammonium rayon
Semisynthetic cellulose derivatives	Cellulose acetate Cellulose tracetate Diethylaminoethyl cellulose (Hemophan)
Synthetic polymers	Polyacrylonitrile methallyl sulfonate copolymer (AN69) Polyacrylonitrile (PAN) Polymethylmethacrylate (PMMA) Polysulfone

Other Case Reports

A recent case report[4] suggested that overanti-coagulation may occur if the manufacturer's recommended bolus dosing regimen for lepirudin is followed during hemodialysis. The authors reported

initial aPTTs of up to 6 times the patient's baseline value with no subsequent dosing required for 6 days after the 0.2 mg/kg bolus. Fortunately, no bleeding complications were observed. Although the authors stated that residual renal function may dramatically affect lepirudin elimination and duration of effect, they did not state whether their patient had any urine output. As the report described a patient in whom acute renal failure developed during a hospital stay and for whom hemodialysis was subsequently required, the degree of residual renal function or recovering renal function was an important issue. In addition, key factors related to the dialysis procedure itself, such as the type of dialyzer (high or low flux, membrane composition), the number of dialysis sessions, the duration of dialysis, and the days on which dialysis was performed, were not discussed. Finally, because the patient died after 13 days from complications unrelated to heparin-induced thrombocytopenia, the issue of intermittent anticoagulation for the hemodialysis procedure itself was not discussed. The case does, however, illustrate that lepirudin dosing in dialysis-dependent acute renal failure may involve more than simply estimating creatinine clearance.

A second report described the successful application of lepirudin infusion in 2 hemodialysis-dependent patients with heparin-induced thrombocytopenia.[20] The most interesting aspect of those cases was the fact that both patients received intermittent hemodialysis with high-flux polysulfone dialyzers (model F70, Fresenius). Lepirudin was initiated at doses of 0.01 and 0.005 mg/kg per hour for patients 1 and 2 respectively. Patient 1 achieved the target aPTT response (2.0 to 2.5 times control) with a dose of 0.015 mg/kg per hour. Patient 2 had an arbitrarily set lower target aPTT (1.8 to 2.1 times control) and maintained anticoagulation at doses ranging from 0.005 to 0.007 mg/kg per hour. The authors recommended measurement of aPTT 8 h after the initiation of infusion to allow for lepirudin accumulation before any dose adjustment. Unfortunately, the aPTT was not measured before and after hemodialysis, so the influence of the high-flux polysulfone dialyzer on aPTT and, hence, lepirudin clearance was unknown.

Monitoring Lepirudin Therapy

Because of the variability of lepirudin elimination in patients with renal impairment, frequent monitoring (every 4 h) of aPTT has been recommended when administering intermittent bolus doses.[4] However, there is debate that measuring aPTT may not be the best way to monitor lepirudin therapy. In studies examining lepirudin concentrations and corresponding aPTT values, considerable variation of aPTT values was observed between patients. The correlation of aPTT with plasma lepirudin concentrations was linear at low and medium lepirudin concentrations (0.1 to 0.5 μg/mL).[21] At high lepirudin concentrations (1 to 4 μg/mL), such as those required for cardiopulmonary bypass surgery and those that may be seen in overanticoagulation, the correlation with aPTT was poor.[2,21] Different aPTT reagents also differ in their sensitivity for detection of lepirudin's anticoagulant effects.[2,4] It has been recommended that the reagent used for patient monitoring be tested with samples containing various amounts of lepirudin (0.5 to 3.0 μg/mL).[2]

Ecarin clotting time has been used for monitoring lepirudin therapy in a limited number of patients. This test uses a snake venom fraction known as ecarin, which activates prothrombin to produce an intermediate known as meizothrombin, which is inhibited by lepirudin. *In vitro* studies of ecarin clotting time have demonstrated a linear dose–response curve to lepirudin at both high and low concentrations, with low inter-individual variability.[2,21] In addition, unlike aPTT, ecarin clotting time is not sensitive to heparin.[21] However, further studies are needed to validate the use of ecarin clotting time in the clinical setting.[22] As such, the test still used most often for laboratory monitoring is aPTT.[23] Nonetheless, in institutions with laboratories that can measure ecarin clotting time, it may be worthwhile to consider using this inexpensive test along with aPTT to improve the accuracy of monitoring of patients with significant renal impairment.

Because of the sensitivity of aPTT to both lepirudin and heparin, a potential confounding factor in the case reported here is the accuracy of the first aPTT measurement, which was determined 6 h after lepirudin administration (i.e., 7.5 h after heparin discontinuation). The half-life of heparin is approximately 90 min and is not prolonged in patients with renal dysfunction.[24] Therefore, it is unlikely that the heparin had a significant effect on this aPTT measurement, as more than 5 half-lives had passed between the discontinuation of heparin and the aPTT measurement. Furthermore, it seems unlikely that the patient would have remained therapeutically anticoagulated for another 3 days if heparin had been exerting a significant effect on this initial aPTT measurement.

Intermittent Anticoagulation During Hemodialysis

An issue that must be addressed in hemodialysis patients who have been treated for and recovered from an episode of heparin-induced thrombocytopenia is anticoagulation during the hemodialysis procedure itself. Obviously, the routine heparin infusion usually administered is no longer appropriate. Lepirudin has been given in doses ranging from 0.008 to 0.16 mg/kg to maintain anticoagulation during conventional thrice weekly hemodialysis.[17,18,25-27] It should be noted that only low-flux dialyzers were used in these studies. No data are available regarding lepirudin administration during intermittent hemodialysis with high-flux dialyzers. Lepirudin has also been used to maintain patency of a standard double-lumen dialysis catheter, required for hemodialysis access in some patients in whom fistulas or grafts cannot be created.[28] A 0.5-mg IV dose was administered, and then each port was locked with a 0.5 mg/mL concentration of lepirudin. Unfortunately, lepirudin is available only in a 50-mg vial that is stable for no more than 24 h after reconstitution.[1] No other stability data are currently available (Aventis Pharma, personal communication). As a result, there is drug wastage, and additional drug acquisition costs are incurred for each hemodialysis session.

Danaparoid may also be considered for intermittent hemodialysis anticoagulation. Effective anticoagulation with this drug has been achieved with a single bolus dose of 34 units/kg at the start of hemodialysis.[29-31] Danaparoid is available in 750-unit ampules, which may allow for less wastage, although the caveat for cross-reactivity testing before use should still be heeded. The disadvantages of this agent include lack of an antidote should overanticoagulation occur and relatively high cost compared with heparin.[32] Because danaparoid was not available on formulary and there was a desire to avoid wasting lepirudin, it was decided to first attempt saline flush dialysis in combination with warfarin, to prevent clotting of the dialyzer. During saline flush dialysis, the dialyzer is flushed with 100 to 200 mL of saline every 15 to 60 min to prevent clotting. The treatment is useful, and severe clotting requiring termination of treatment or replacement of the dialyzer occurs in only about 5% of patients.[33]

Although no clinical trials have been performed evaluating warfarin as an anticoagulant for hemodialysis, warfarin has been added at this institution as an adjunct to saline flush dialysis in patients with heparin-induced thrombocytopenia, in a further attempt to prevent clot formation. Anecdotal evidence to support this assumption has come from trials of low-molecular-weight heparins given for anticoagulation during hemodialysis. In 2 studies of dalteparin as an anticoagulant for hemodialysis, patients treated with warfarin before the study had less frequent clot formation in the dialyzer and lower concentrations of plasma coagulation markers (thrombin–antithrombin and prothrombin fragment).[34,35] In addition, a recent case review recommended a trial of warfarin for the treatment of heparin-induced thrombocytopenia in hemodialysis patients because of its safety, reversibility, low cost, and availability.[32] Obviously the risks associated with long-term warfarin therapy must be considered before this option is recommended. In addition, warfarin therapy must not be initiated until the platelet count has returned to baseline, as both venous limb gangrene and skin necrosis have been reported.[36,37] Because warfarin reduces protein C (one of the body's natural anticoagulants) and because of continued thrombin generation secondary to heparin-induced thrombocytopenia, microvascular thrombosis and tissue necrosis may occur.[38] Other anticoagulants that have been used during hemodialysis, although less commonly, include citrate and prostacyclins.[39-41] The disadvantage of these therapies is that much more intensive monitoring is required. In patients with central venous catheters for dialysis access, tissue plasminogen activator and citrate have been studied as lock solutions to maintain catheter patency and would be safe for use in patients with heparin-induced thrombocytopenia.[42,43]

Overdose

Although lepirudin overanticoagulation did not occur in the patient described here, it is important for the clinician to be knowledgeable about treatment of this problem, as dialysis patients are at greater risk of lepirudin overdose and subsequent increased risk of bleeding. In addition, it has been reported that there is no antidote for lepirudin.[1,4] The authors agree that there is no specific pharmaceutical antidote, but lepirudin overdose has been successfully treated with high-flux dialysis with a polysulfone dialysis membrane (model F80 membrane, Fresenius).[44] In that case, lepirudin plasma concentrations were reduced to the therapeutic range after 2 dialysis sessions. Another investigation determined lepirudin clearance for a high-flux polysulfone membrane (F50 membrane, Fresenius) and a high-flux polyacrylonitrile methallyl sulfonate copolymer (AN69) membrane (Nephral 200, Hospal Cobe, Stockholm, Sweden).[45] The authors concluded that the polysulfone membrane was more

effective than the AN69 membrane in eliminating lepirudin and that high-flux polysulfone membranes should be considered in cases of overdose.

CONCLUSIONS

This case illustrates that, in anuric patients undergoing long-term hemodialysis with a low-flux polysulfone membrane, lepirudin doses of 0.1 mg/kg without an initial bolus dose allow maintenance of aPTT within the therapeutic range. Lepirudin dosing in hemodialysis patients must take into account the patient's residual renal function as well as the flux and composition of the dialysis membrane used. Consideration should be given to using a low-flux polysulfone or regenerated cellulose dialyzer during treatment with lepirudin to prevent unpredictable removal of the drug during hemodialysis. Many institutions use aPTT to monitor lepirudin therapy, but clinicians should be aware of the controversy surrounding this method of monitoring and the potential application of ecarin clotting time. Clinicians must also consider how intermittent anticoagulation during hemodialysis will be achieved over the long term for patients requiring such therapy. Finally, although no specific pharmaceutical antidote exists for the treatment of lepirudin overdose, dialysis with a high-flux polysulfone membrane has been used to rapidly decrease lepirudin concentrations in plasma.

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