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Chronic fondaparinux use in a hemodialysis patient with heparin-induced thrombocytopenia type II and extracorporeal circuit thrombosis—A case report and review of the literature

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Abstract

Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening condition that can develop after exposure to unfractionated or low–molecular-weight heparins. Treatment options appear to be limited in patients on concurrent intermittent hemodialysis. We report the case of an 88-year-old man newly initiated on high-flux hemodialysis who developed HIT and extracorporeal circuit thrombosis after 3 weeks of exposure to unfractionated heparin. Our patient was successfully treated with fondaparinux 2.5 mg subcutaneously three times per week and citrate during dialysis sessions. Antifactor Xa levels were measured on several occasions while receiving fondaparinux.

Key words: Heparin-induced thrombocytopenia, HIT, fondaparinux, Arixtra, hemodialysis, extracorporeal circuit thrombosis

INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is an uncommon, life-threatening condition that may occur after exposure to unfractionated heparin (UFH) or low–molecular-weight heparins (LMWH). Two types of HIT exist: type I (HIT I) and type II (HIT II). HIT I is more common, occurring in 10–20% of patients, but is a harmless condition that leads to a decrease in platelets in the first 24–48 hours after initiating heparins.[1,2] It is not associated with thrombosis and is unrelated to an immunological response.[2] Patients can remain on heparin and their platelets will recover with time.[2] HIT II is a potentially fatal condition occurring in 2–3% of patients exposed to UFH and 0.8% of patients exposed to LMWH.[3,4] Patients develop a reduction in platelet count of >50%, typically developing 5–10 days after first exposure to UFH. All exposure to heparin (including heparin catheter locks, heparin flushes, heparin priming of extracorporeal circuits [EC], and heparin-coated catheters, tubing, and dialyzers) and LMWH, because of its cross-reactivity, must be discontinued immediately, even before confirmatory lab testing.[1,5] Alternative safe anticoagulants should be initiated to reduce HIT-associated morbidity and mortality. Mortality rates in patients with both HIT II and thrombosis have been found to be as high as 30%.[5] Early detection and treatment is critical, as there is a 5–10% risk of thrombus formation within 48 hours after thrombocytopenia begins, and 50% of patients will develop thrombosis within 30

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days.[1,2,5] As the severity of thrombocytopenia increases, the risk of thrombosis also increases.[1] Thrombosis may present as ischemia of one or more limbs, or cerebral or myocardial infarctions.[2] However, the majority of the thrombi will develop in the venous system as deep vein thrombosis or pulmonary embolism.[2] Even with prompt and appropriate therapy, 5.6–10% of patients with HIT II will require amputation, 9.8–18.3% will experience a new thrombotic event, and 8.5–21.3% will die.[6]

Hemodialysis (HD) patients are repeatedly exposed to heparins during dialysis sessions to prevent thrombosis of the EC. Although it is fairly uncommon for HD patients to develop HIT II and thrombosis, this situation can be difficult to treat because many of the alternative, safe anticoagulants are predominately renally eliminated. Accumulation of these agents can occur, putting patients at increased risk for bleeding. Studies have shown that the incidence of major bleeding correlates with the degree of renal failure.[7] End-stage renal disease (ESRD) patients have an increased bleeding risk because of several factors including uremia-associated platelet dysfunction, which can be further exacerbated by anticoagulants used during dialysis sessions.[8] Conversely, HD patients are also at higher risk of thrombosis. Pulmonary embolism has been found to be more common in HD patients than in matched non-HD controls.[2] End-stage renal disease patients have deficiencies of protein C and S, leading to increased hypercoagulability as renal function declines.[2] Three of four studies have also shown that there may be an association between mortality and positive HIT II antibodies in HD patients.[5]

Alternative, safe anticoagulants for HIT II include direct thrombin inhibitors (DTIs) (e.g., argatroban, lepirudin, or bivalirudin), or danaparoid. Fondaparinux has not been officially approved for treatment of HIT II, but at least 67 reports have been published using fondaparinux off-label for this indication in non-HD patients because of fondaparinux's very rarely reported cross-reactivity with heparin-induced antibodies.[4,6] The treatment efficacy rate in these trials was 100%.[4,6] The bleeding rate with fondaparinux is approximately 2%; much lower than the ~12% rate with DTIs.[6]

This is the first published case report using subcutaneous fondaparinux and citrate during dialysis as chronic therapy in a confirmed HIT II patient on high-flux HD with EC clotting.

CASE REPORT

An 88-year-old, 62-kg, male Caucasian with ESRD was initiated on high-flux HD (Xenium 190 dialyzer; Baxter, Deerfield, IL, USA) three times per week for chronic renal impairment. Past medical history included prostate carcinoma, recurrent urinary tract infections, chronic urinary retention, abdominal aortic aneurysm, benign prostatic hypertrophy, renal cell carcinoma with a left nephrectomy, macrocytic anemia, depression, and gout. He was a resident of a long-term care facility, but received HD on an outpatient basis thrice weekly. Unfractionated heparin was used during the dialysis sessions. At the initiation of HD, his platelets were 166×10^9/L but declined over 3 weeks to 54×10^9/L and HIT was suspected, although evidence of thrombosis was not present. A HIT enzyme-linked immunosorbent assay (ELISA) was drawn and UFH was discontinued during HD, with saline flushes being used as alternative. Fondaparinux 2.5 mg subcutaneously was initiated postdialysis (i.e., three times per week) and his platelets recovered.

The patient's HIT ELISA results were strongly positive (optical density [OD] = 1.256) for HIT II, and a confirmatory serotonin-release assay (C-SRA) also was positive. The fondaparinux was discontinued when the platelets returned to 150×10^9/L, as there had been no evidence of thrombosis. Unfractionated heparin was held during dialysis sessions and the lines continued to be flushed with saline. Soon afterward, the patient began to develop EC thrombosis, leading to blood loss and resulting in underdialyzation. Intravenous fondaparinux 2.5 mg diluted in 20 mL normal saline was initiated at the beginning of each dialysis session. An anti-Xa level for fondaparinux was drawn on the day postdialysis and was found to be 0.45 μg/mL. Another anti-Xa level was drawn the following day during the dialysis session and was 0.27 μg/mL. Two months later, anti-Xa levels were repeated to check for accumulation. A trough level (i.e., just before the start of dialysis) was found to be <0.01 μg/mL. A level during dialysis was 0.51 μg/mL. However, the patient continued to have EC clotting. Administering two, 2.5-mg doses intravenously (IV) during one dialysis session was empirically tried. The anti-Xa level at the end of the session was 0.8 μg/mL. As IV fondaparinux did not appear to be beneficial and bleeding concerns were increased with a double dose, the fondaparinux was then modified to 2.5 mg subcutaneous at 2200 hours on the evenings before dialysis. Citrate was added to infuse throughout the dialysis session at 75 cc/hour and normal saline at 200 cc/hour. The patient was dialyzed with dialysate containing calcium 1.5 mmol/L. Both pre- and postfilter ionized calcium were tested, and although the levels were not sufficient to prevent clotting, it did seem to work synergistically with the fondaparinux. The patient continued on this same regimen for 4.5 more months without

complications. After 4.5 months, repeat anti-Xa levels were done immediately prior to dialysis and found to be 0.66 μg/mL and immediately postdialysis 0.55 μg/mL. A repeat ELISA was done 7 months after the first test to determine if the patient still had circulating HIT II antibodies and was now only weakly positive (OD = 0.772). A repeat C-SRA was not done. The patient was continued successfully on this fondaparinux regimen and citrate infusions for over 18 months and remains on it.

DISCUSSION

HIT II in HD patients

HIT antibody development in patients undergoing HD has been found to be quite common. At least 15 studies have examined this issue and determined HIT II antibodies were detectable in up to 17.4% of HD patients based on ELISA testing.[5] Higher specificity functional assays (e.g., C-SRA, heparin-induced platelet activation assay [HIPA]) determined ~3.7% of HD patients were positive.[5] Despite positive antibody tests, several studies have shown that not all of these patients develop thrombosis or thrombocytopenia. Greinacher et al. screened 165 HD patients for HIT II antibodies using HIPA, and found 4.2% were positive. However, the occurrence of thrombosis or hemorrhage in patients who were HIT II positive was not significantly greater than those who were HIT II negative.[9] Other trials have shown conflicting results and found HIT II-positive patients do develop thrombosis, thrombocytopenia, and frequent clotting of the EC.[5] A trial of 154 newly initiated HD patients found that six patients developed frequent EC thrombosis and thrombocytopenia approximately 2 weeks after starting HD. Five of the six patients had a positive ELISA and four of the six had positive functional assays. One of the HIT II patients developed subsequent myocardial infarction and stroke. The authors concluded that clot formation in the dialyzer or EC may be the first sign of HIT II in HD patients.[5,10] However, it is known that a number of other factors can contribute to increased EC thrombosis including low blood flow, high ultrafiltration rate, excess turbulence within the circuit, low arterial blood pressure, high hematocrit, or the need for intradialytic blood transfusion or lipid infusion.[11]

Fondaparinux

Fondaparinux is a synthetic antithrombin-mediated selective inhibitor of factor Xa in the coagulation cascade. It is considered contraindicated in patients with ESRD, as 55–85% of its elimination is renal.[7] In patients with normal renal function, the half-life is 17–21 hours, but this time is prolonged in those with renal dysfunction.[1] Fondaparinux is thought to be dialyzable during HD because of its low molecular weight (1.7 kd), as high-flux dialysis membranes can clear molecules up to 3.8 kd, and lack of binding to drugs or plasma proteins other than antithrombin.[7] The clearance of fondaparinux increases by about 10-fold during HD; however, the total clearance remains low and may result in drug accumulation and elevated anti-Xa levels.[12]

Anti-Xa levels for fondaparinux

Appropriate anti-Xa levels have not been conclusively established for fondaparinux. However, when monitoring fondaparinux, the anti-Xa assay must be calibrated with a fondaparinux standard curve, as calibration using UFH or LMWH is highly inaccurate.[13] Peak levels of fondaparinux are achieved approximately 3 hours after a subcutaneous injection.[13] When given at a prophylactic dose of 2.5 mg/day, peak anti-Xa levels of 0.2–0.4 μg/mL can be expected and when given at a therapeutic dose of 7.5 mg/day, levels of 0.5–1.5 μg/mL would be anticipated.[14]

In our patient, we did not measure peak anti-Xa levels, but instead measured levels predialysis and postdialysis. The predialysis level was taken approximately 14 hours after the subcutaneous fondaparinux dose was administered. A follow-up anti-Xa level was drawn after 4.5 months of this dosing regimen once the patient was at steady-state concentrations. The value obtained was 0.66 μg/mL, indicating the patient did not have extensive accumulation of fondaparinux. The postdialysis anti-Xa level was found to be 0.55 μg/mL, confirming at least a portion of the fondaparinux was being removed during HD. Although we did not measure peak anti-Xa levels, it was deemed that the levels obtained were slightly high, but not extreme. The patient was no longer experiencing EC thrombosis, nor bleeding. As the lowest available strength of prefilled syringe of fondaparinux is 2.5 mg, we decided for convenience to continue this dose.

Use of fondaparinux in HD patients

Only a few case reports have been published on the use of fondaparinux in HD patients and have indicated varying degrees of success (Table 1). Two small trials have also been reported. In a trial done by Sombolos et al., fondaparinux was administered to 16 chronic HD patients during a single 4-hour HD session at an IV bolus dose of 2.5 mg. Eight of the patients were using high-flux

Table 1 Summary of published case reports of use of fondaparinux in HD patients

Author	Description of patient	Type of dialysis	Management	Comments
Sharathkumar et al.[7]	15-year-old obese girl with postoperative PE	High-flux HD	Fondaparinux 5 mg daily was initiated, but accumulation of drug occurred based on anti-Xa levels of 2.05 μg/mL. The dose was decreased to 2.5 mg every other day and resulted in anti-Xa levels of 0.8 μg/mL on day 19 and 0.65 μg/mL on day 21. Fondaparinux was discontinued on day 29 because of poor tolerability.	This patient did not have HIT II and was receiving UFH as a bolus at the beginning of each HD session. It was not stated if the fondaparinux was being administered subcut or IV.
Haase et al.[16]	52-year-old man with a DVT 2 mo prior treated with tinzaparin. He was admitted to ICU, placed on HD, and developed a new DVT. After 17 d of UFH, he developed thrombocytopenia.	HD—specifics not reported	Fondaparinux 2.5 mg was instilled directly into the dialysis circuit on dialysis days only. Anti-Xa levels were measured, but not reported. The patient did not develop thrombosis or bleeding during the 10 wk of therapeutic fondaparinux therapy.	Serological tests for HIT II were repeatedly negative.
Tekgunduz et al.[6]	75-year-old man with acute on chronic renal failure who developed HIT II after 10 d of UFH with HD. He subsequently developed thrombocytopenia and a DVT at the site of the HD catheter.	HD—specifics not reported	Enoxaparin was used for 4 d and the platelets continued to decline. The patient was switched to fondaparinux 2.5 mg subcut daily. He was then transitioned to warfarin when the platelet count improved. The patient did not have further episodes of thrombosis in the 6 mo of follow-up.	ELISA and functional tests for HIT II were positive. It is unknown how long the patient remained on HD. Anti-Xa levels were not monitored.
Bermejo et al. (abstract only)[17]	59-year-old woman who developed HIT II at the start of chronic dialysis.	HD—specifics not reported	Fondaparinux was given as 1.87 mg instilled directly into the dialysis circuit on dialysis days only. The patient remained on this regimen for 18 mo and experienced no episodes of bleeding or thromboembolism.	HIT II ELISA was strongly positive. Functional assays were never done to confirm the HIT II diagnosis and anti-Xa levels were also not reported.
Wellborn-Kim et al.[18]	85-year-old woman who developed thrombocytopenia and cardio-renal syndrome after a coronary bypass procedure.	Low-flux polyflux HD	Fondaparinux 2.5 mg subcut every other day was given and acid citrate dextrose solution was used during each dialysis session. She remained on fondaparinux for 30 d and also received aspirin 81 mg daily. She did not develop any thrombotic events, clotting of the HD membranes, or evidence of bleeding.	HIT II ELISA was positive. Functional assays were never done to confirm the HIT II diagnosis and anti-Xa levels were also never done.

DVT = deep vein thrombosis; ELISA = enzyme-linked immunosorbent assay; HD = hemodialysis; HIT = heparin-induced thrombocytopenia; HIT II = heparin-induced thrombocytopenia—type II; ICU = intensive care unit; IV = intravenously; PE = pulmonary embolus; subcut = subcutaneously; UFH = unfractionated heparin.

polyester polymer alloy dialyzers and eight were using low-flux polysulfone dialyzers. These patients did not have HIT II; hence, the dialyzers were primed with normal saline containing 5000 IU of UFH. Clot formation at the end of the dialysis session was significantly greater in the high-flux HD patients than in the low-flux HD patients, and in two of the high-flux HD patients, the session had to be stopped early because of clots in the circuit and dialyzer. Postdialysis anti-Xa levels were significantly higher in the low-flux dialysis patients than in the high-flux HD patients (low flux = 0.46 ± 0.12 IU/mL vs. high flux = 0.16 ± 0.04 IU/mL, $P < 0.025$). Anti-Xa levels before the next dialysis session were also much higher in the low-flux HD group (0.25 ± 0.06 IU/mL vs. high-flux group 0.06 ± 0.04 IU/mL).[15] The authors concluded that fondaparinux 2.5 mg IV bolus was ineffective for high-flux HD patients potentially because of increased removal of fondaparinux during high-flux HD, resulting in an inadequate anticoagulation effect.[15] The median fondaparinux half-life was increased and was found to be 18.9 hours in the high-flux group and 52.5 hours in the low-flux group.[15]

A trial by Kalicki et al. studied the injection of fondaparinux at a dose of 0.05 mg/kg of body weight into the arterial line of the EC immediately before the start of HD in 12 non-HIT II patients. Most of these patients were also taking 100 mg/day of aspirin. If more than traces of coagulation were seen in the filter and/or drip chambers, the amount of fondaparinux was increased by 0.01 mg/kg with the majority of patients requiring a dose of 0.06 mg/kg.[12] Six of the 12 patients reported bleeding from the puncture sites between dialysis sessions. Aspirin did not have any effect on filter patency, but seemed to increase the bleeding risk. No bleeding episodes were seen when the anti-Xa levels were <0.7 μg/mL. In the second phase of this trial, patients received fondaparinux 0.05 mg/kg on nine consecutive HD sessions. In the first phase of this trial, it was found that successive increases in the dose of fondaparinux did not significantly lower the amount of clotting, indicating a possible ceiling effect of the dose–response curve. However, in the second phase of this trial, high-trough anti-Xa levels were linked to improved filter patency rates, indicating greater benefit at higher fondaparinux concentrations.[12]

Regional anticoagulants

Citrate works by chelating calcium and magnesium after being infused into the arterial line and decreases the activation of the coagulation cascade in the EC.[2] The ionized calcium deficit only occurs in the EC, as calcium is added to the venous line to return to a normal ionized calcium level before reinfusion of the blood.[2] In this case, we infused citrate prefilter and dialyzed against a dialysis bath with calcium. However, regional anticoagulation such as citrate is not sufficient to use alone during HIT II or if there is still thrombocytopenia or evidence of thrombosis.[2]

Other potential options

Other options were considered for this patient, but were not deemed to be superior to fondaparinux. Direct thrombin inhibitors such as lepirudin and bivalirudin are not well cleared in a patient with renal impairment. Argatroban may have been an option because of its hepatic clearance but all of the DTIs need to be continuously infused by IV, are very expensive to use chronically, and have an increased risk of bleeding compared with non-DTIs. Although danaparoid is the agent with the most evidence for use in HD and HIT II, it currently has very limited availability in North America.

Warfarin is also not a favored option. Ziai et al. showed that vitamin K antagonists alone with a target International Normalized Ratio between 2 and 3 are insufficient to prevent clotting during HD. An increase in the D-dimer plasma level and clotting in the EC still occurred with use of a vitamin K antagonist alone.[8]

There are currently no published case reports of the use of new oral agents (e.g., dabigatran, rivaroxaban, or apixaban) for the treatment of HIT II. However, all of these agents have some degree of renal elimination and are not recommended in patients with renal impairment.

CONCLUSION

Development of HIT II antibodies in HD patients may be more common than previously suspected. The evidence appears to be inconclusive as to whether this leads to a higher incidence of thrombosis. Our case report is the first in which a new HD patient with HIT II and EC thrombosis was successfully treated on a chronic basis with subcutaneous fondaparinux and regional citrate. Several different doses, administration times, and routes of administration of fondaparinux were tried. The greatest success was found with fondaparinux 2.5 mg subcutaneously thrice weekly at bedtime on the night before HD in combination with citrate during dialysis. Our patient did not experience any excess bleeding and anti Xa levels appeared not to be excessive, indicating substantial accumulation of fondaparinux was not a concern at this dose.

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