CASE REPORT

Fondaparinux therapy in a hemodialysis patient with heparin-induced thrombocytopenia type II

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Purpose. The successful use of fondaparinux in a hemodialysis patient with heparin-induced thrombocytopenia type II (HIT II) is reported.

Summary. An 85-year-old, 68-kg Caucasian woman came to the emergency department with shortness of breath and exertional chest pain radiating to the neck. Testing revealed non-ST-segment elevation myocardial infarction, severe coronary artery disease, mitral regurgitation, left ventricular dysfunction, an ejection fraction of 25–30%, and pulmonary arterial hypertension. I.V. unfractionated heparin was given for therapeutic anticoagulation per hospital protocol and discontinued on hospital day 3 before mitral valve repair and coronary bypass procedure. Postoperatively unfractionated heparin and low-molecular-weight heparin were avoided because of a reduction in the platelet count and suspicion of HIT. Instead, the patient was placed on sequential compression devices in addition to aspirin for prophylaxis of deep venous thrombosis. By postoperative day 6, the patient's platelet count dropped 76% from baseline, and the patient was found to have heparin-dependent platelet factor 4 antibodies. Argatroban infusion was initiated but discontinued after 2 days due to bleeding. Fondaparinux was ordered for anticoagulation therapy. By hospital day 8, the patient developed renal insufficiency requiring hemodialysis and adjustment of the fondaparinux regimen. During the 30-day course of fondaparinux, the patient did not experience thromboembolic events or bleeding and did not require transfusions. There was no clotting within hemodialysis membranes, and her hepatic function improved by the time of her discharge.

Conclusion. Fondaparinux was used in a hemodialysis patient with HIT II without the development of thromboembolic, hemodialysis-clotting, thrombocytopenic, or hemorrhagic complications. The patient's platelet count remained in the normal range during the 30-day course of fondaparinux.

Index terms: Anticoagulants; Argatroban; Aspirin; Dialysis; Dosage; Fondaparinux sodium; Geriatrics; Hemorrhage; Heparin; Platelet aggregation inhibitors; Thrombocytopenia; Toxicity; Venous thrombosis

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Fondaparinux is a synthetic pentasaccharide anticoagulant that inhibits thrombin by binding to antithrombin III and catalyzing the inactivation of factor Xa. The drug is labeled as contraindicated in patients with a creatinine clearance of <30 mL/min.[1] Fondaparinux is almost completely excreted unchanged in urine; however, in patients with impaired renal function, it has the potential to accumulate and increase the risk of bleeding.[1,2] There are presently no clinical trial data and little pharmacokinetic data on the administration of fondaparinux in patients receiving hemodialysis.

Unfractionated heparin remains the preferred anticoagulant in patients with severe renal impairment, but its use is complicated by its fluctuating pharmacokinetic features and the risk for heparin-induced thrombocytopenia (HIT).[3-5] The following case report describes fondaparinux

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use in a hemodialysis patient with subacute HIT type II (HIT II).

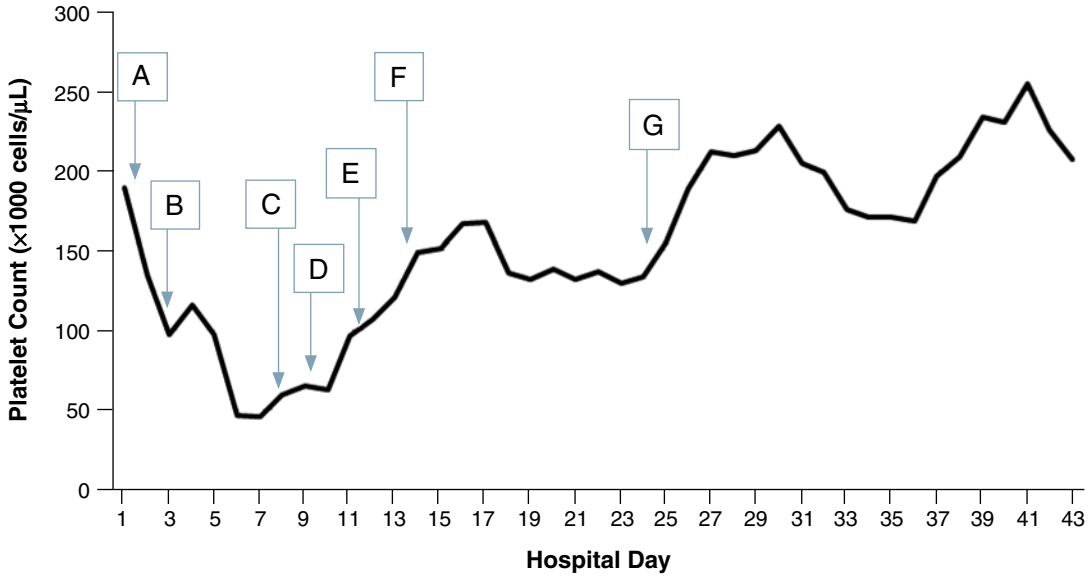
Case report

An 85-year-old, 68-kg Caucasian woman came to the emergency department with shortness of breath and exertional chest pain radiating to the neck. Her medical history included coronary artery disease, mitral regurgitation, unstable angina, hypertension, hyperlipidemia, and degenerative arthritis. Her surgical history included right total hip replacement, left-rotator-cuff repair, cataract surgery, and tonsillectomy. Her social history and family history were noncontributory to her condition. Her home medications included aspirin 81 mg orally once daily, clopidogrel 75 mg (as the bisulfate salt) orally once daily, rosuvastatin 10 mg (as the calcium salt) orally once daily, and extended-release metoprolol succinate 23.75 mg (equivalent to metoprolol tartrate 25 mg) orally once daily.

Upon admission to the hospital, her blood pressure was 120/70 mm Hg, heart rate was 78 beats/min, and respiration rate was 18 breaths/min. She had a serum creatinine concentration of 1.2 mg/dL, serum troponin concentration of 2.6 ng/mL, and platelet count of 189,000 cells/μL. An electrocardiogram revealed non-ST-segment elevation myocardial infarction. Cardiac catheterization performed on the same day revealed severe coronary artery disease, mitral regurgitation, left ventricular dysfunction, an ejection fraction of 25–30%, and pulmonary arterial hypertension. I.V. unfractionated heparin was given for therapeutic anticoagulation per hospital protocol and discontinued on day 3 before mitral valve repair and coronary bypass procedure. Unfractionated heparin was used intraoperatively and discontinued at the end of the procedures.

Postoperatively, the patient was treated with sequential compression devices, as well as aspirin 325 mg orally daily for prophylaxis of deep venous thrombosis. Unfractionated heparin and low-molecular-weight heparin were avoided due to a reduction in platelet count (Figure 1) and suspicion of HIT. By postoperative day 6, the patient's platelet count dropped approximately 76% from baseline, and an enzyme-linked immunosorbent assay (ELISA) was positive for heparin-dependent platelet factor 4 (H-PF4) antibodies. Argatroban infusion was initiated, but the dosage required adjustment (0.5 μg/kg/min) because the patient developed transient hepatic impairment (serum total bilirubin concentration, 6.7 mg/dL; serum direct bilirubin concentration, 5.3 mg/dL; aspartate transaminase [AST], 81 IU/L; alanine transaminase [ALT], 21 IU/L; albumin, 2.5 g/dL). Argatroban was discontinued after two days due to bleeding observed during endotracheal suction. Simultaneously, the patient's hemoglobin concentration decreased from 11.2 to 9.0 g/dL, and her hematocrit level decreased from 32.6% to 25.9%. Further anticoagulation was held for two days, during

Figure 1. Platelet counts during hospitalization. A, initiation of unfractionated heparin (UFH) (day 1); B, mitral valve repair and coronary artery bypass graft, discontinuation of UFH, and initiation of aspirin with sequential compression devices (day 3); C, initiation of hemodialysis every other day (day 8); D, initiation of argatroban (day 9); E, discontinuation of argatroban and aspirin (day 11); F, initiation of fondaparinux 2.5 mg every other day on days off of hemodialysis (day 13); and G, initiation of aspirin 81 mg daily (day 24).



which the patient's aPTT remained within the target range of 50–90 seconds.

Subsequently, fondaparinux was ordered for anticoagulation therapy. However, by hospital day 8, the patient developed cardiorenal syndrome, which led to renal insufficiency requiring hemodialysis. Therefore, the fondaparinux sodium regimen was adjusted to 2.5 mg subcutaneously every other day. The patient received hemodialysis on opposing days using a low-flux Polyflux 17-L dialyzer (Gambro), with acid citrate dextrose solution used for anticoagulation during each session. Warfarin was avoided for several reasons, including the hemorrhage experienced by the patient during argatroban therapy, an elevated International Normalized Ratio (up to 2.7 in the absence of warfarin and argatroban) during her hospital stay, and the use of antibiotic therapy. Eleven days after fondaparinux initiation, aspirin was reintroduced at a daily dose of 81 mg.

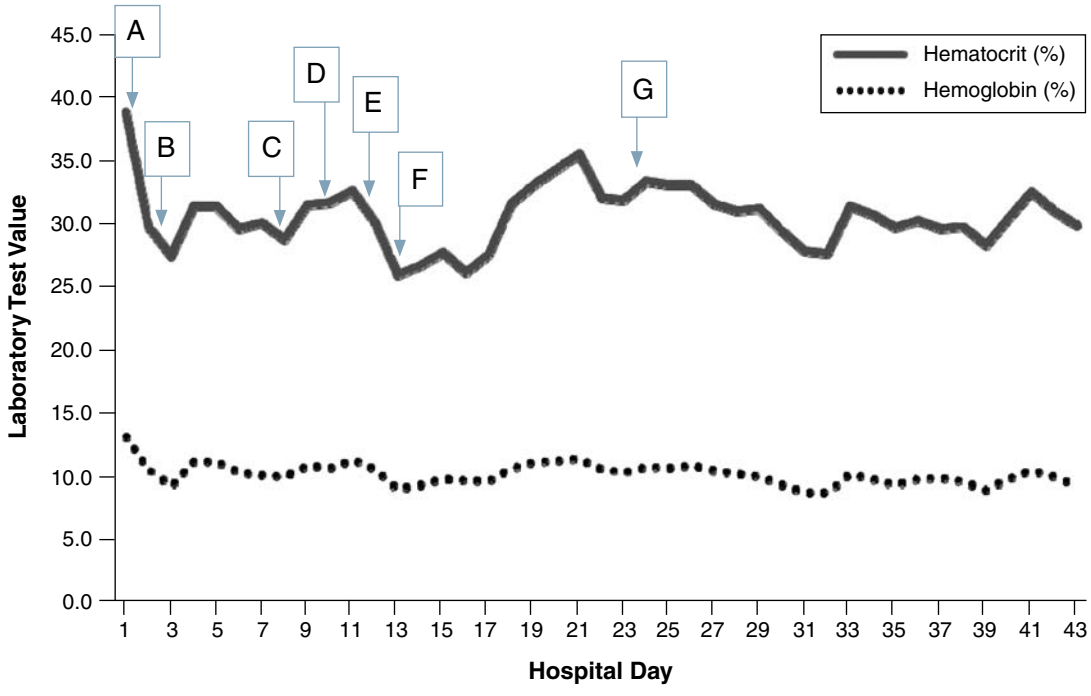
During the 30-day course of therapy with fondaparinux, the patient did not experience thromboembolic events, which was verified by ultrasound of the bilateral lower extremities and abdomen. The platelet count remained in the normal range (Figure 1). There was no clotting within the hemodialysis membranes, there was no evidence of bleeding, she did not require transfusions, her hemoglobin and hematocrit values remained stable (Figure 2), and her hepatic function improved (total bilirubin, 1.4 mg/dL; AST, 31 IU/L; ALT, 60 IU/L; albumin, 3.1 g/dL) by the time of her discharge to a long-term-care facility on hemodialysis.

Discussion

The first issue highlighted in this case report is the administration of fondaparinux in a patient receiving hemodialysis. Although data on the use of fondaparinux in patients receiving hemodialysis are limited, strategies in patients with renal impairment have included avoiding the medication, lowering the dose, extending the dosage interval, and monitoring antifactor Xa levels.[6-8] These methods have been explored in patients receiving hemodialysis and were discussed in several reports.[9-11]

Haase et al.[9] described a 52-year-old renal transplant recipient with a history of deep venous thrombosis who was given unfractionated heparin prophylactically. He was later diagnosed with HIT II after developing deep venous thrombosis and decreased platelets. Unfractionated heparin was discontinued, and fondaparinux sodium 2.5 mg was given for anticoagulation, instilled into the hemodialysis circuit every second day. A therapeutic antifactor Xa time

Figure 2. Hematocrit and hemoglobin values during hospitalization. A, initiation of unfractionated heparin (UFH) (day 1); B, mitral valve repair and coronary artery bypass graft, discontinuation of UFH, and initiation of aspirin with sequential compression devices (day 3); C, initiation of hemodialysis every other day (day 8); D, initiation of argatroban (day 9); E, discontinuation of argatroban and aspirin (day 11); F, initiation of fondaparinux 2.5 mg every other day on days off of hemodialysis (day 13); and G, initiation of aspirin 81 mg daily (day 24).



(70–110 seconds) was reached during the 10 weeks of hemodialysis, and the patient did not have any further thromboembolism, hemodialysis clotting, or bleeding.

Sharathkumar and colleagues[10] described the use of fondaparinux in a patient receiving hemodialysis after unsuccessful trials of enoxaparin for pulmonary embolism. Fondaparinux sodium was initiated at 5 mg daily (50% of the required dose), but the patient developed epistaxis and bruising at the injection site, with antifactor Xa levels of 1.65–2.5 mg/L. The dosage of fondaparinux sodium was further decreased to 2.5 mg daily and then to 2.5 mg every other day, leading to a drop in the antifactor Xa levels to 0.8 and 0.65 mg/L, respectively. No hemodialyzer clotting was observed, and the patient eventually underwent successful renal transplantation.

Sombolos et al.[11] studied fondaparinux use during hemodialysis in 16 patients. They concluded that fondaparinux sodium 2.5 mg i.v. can be successfully administered during hemodialysis in patients with low-flux polysulfane hemodialyzers, not with high-flux polyester-polymer alloy hemodialyzers, due to an increased risk of extracorporeal circuit and hemodialyzer thrombosis observed with the latter. They also observed in all study patients a sustained increase in antifactor Xa levels before hemodialysis sessions, indicating a potentially increased risk of bleeding.

In a pharmacokinetics study, patients undergoing long-term intermittent hemodialysis demonstrated a decrease in fondaparinux area under the serum concentration-versus-time curve by 20% during a four-hour hemodialysis session.[12] Another study suggested that although fondaparinux may be used to prevent circuit clotting during hemodialysis, it accumulates and increases antifactor Xa activity in the interdialytic period, potentially making it more suitable to be administered on days off of hemodialysis in patients requiring long-term systemic anticoagulation.[13] Our facility took this approach, administering the fondaparinux during the interdialytic period. Since we did not have access to antifactor Xa monitoring, we continued to monitor for complications, and the patient did not experience thromboembolism or bleeding during treatment.

The second issue highlighted in this case is the use of fondaparinux in a patient with HIT II. HIT type I is considered a harmless phenomenon characterized by a decrease in platelets 24–48 hours after exposure to heparin. On the other hand, the pathophysiology behind HIT II involves the binding of heparin to PF4, a peptide released from platelets during platelet aggregation. This results in immune complexes that bind to and destroy platelets. The destruction of platelets promotes thrombin generation, further platelet activation, thrombocytopenia 7–14 days after the start of heparin administration, and thrombosis. In vitro, fondaparinux does not cross-react with HIT-associated antibodies; this can be explained by the molecular characteristics of fondaparinux.[14] Its weight (2.4 kDa) and length (10 saccharide units) are too small for heparin-reactive antibody recognition.[15]

No recommendations are currently available for the dosing of fondaparinux in the treatment of HIT. According to a literature review performed by Blackmer and colleagues,[16] reported methods for fondaparinux administration in patients treated with HIT include weight-based regimens (5 mg for patients weighing <50 kg, 7.5 mg for patients weighing 50–100 kg, or 10 mg for patients weighing >100 kg), and non-weight-based regimens, ranging from 2.5 mg every other day (during hemodialysis) to 7.5 mg daily. While these reports favor the use of fondaparinux in the management of HIT, others advise caution.

Another consideration is the use of an ELISA in the diagnosis of HIT for this patient. A positive ELISA should be considered merely supportive of an HIT diagnosis in patients who present with clinical evidence and no other explanation for thrombocytopenia. This is because ELISAs have a relatively low specificity to detect H-PF4 antibodies, especially in patients undergoing open-heart surgery.[17] Despite the increased rate of false-positive ELISA results in cardiac surgery patients, our patient had a high pretest probability of HIT, according to the criteria from one clinical scoring system.[18] Thus, the positive ELISA in this patient served as supportive criteria for the diagnosis of HIT.

Conclusion

Fondaparinux was used in a hemodialysis patient with HIT II without the development of thromboembolic, hemodialysis-clotting, thrombocytopenic, or hemorrhagic complications. The patient's platelet count remained in the normal range during the 30-day course of fondaparinux.

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