

A rare case of fondaparinux-induced major bleeding in postmenopausal woman prescribed for non-ST segment elevation MI

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ABSTRACT

Fondaparinux sodium is a synthetic, sulfated pentasaccharide, selective factor Xa inhibitor, a safe and effective antithrombotic agent indicated for preventing thrombus formation in patients with acute coronary syndromes, including those with ST-segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), or unstable angina. Major bleeding is rarely known to exist with the use of fondaparinux and to best of our knowledge there exist no isolated case report presenting with fondaparinux-induced major bleeding prescribed for recently diagnosed NSTEMI. The case report highlights, a need for clinicians to have a sound understanding of anticoagulant pharmacology, dosing, toxicity, individualized approach, and predicting the risk of bleeding before they are prescribed to advancing age persons.

Key Words: Anticoagulant, antithrombotic, fondaparinux, low molecular weight heparin

INTRODUCTION

Fondaparinux sodium is a new synthetic, sulfated pentasaccharide, selective coagulation factor Xa inhibitor, a safe and effective antithrombotic agent, which is indicated for preventing thrombus formation in patients with acute coronary syndromes, including those with ST-segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), or unstable angina. It is a pure, unique chemical entity consisting of five saccharide units (pentasaccharide) obtained entirely by chemical synthesis. Therefore it does not contain any animal sourced component. Fondaparinux has no direct activity against thrombin. However, inhibition of factor Xa results in effective and linear dose dependent inhibition of thrombin generation, whether triggered by intrinsic or extrinsic pathways. Unlike conventional antithrombotics such as LMWHs (enoxaparin), which act on multiple targets within a coagulation cascade thereby, increasing the propensity of causing more bleeding complications. Thus Fondaparinux has a favorable tolerability profile, particularly with regard to the risk of major bleeding.^[1]

In the OASIS-5 trial, fondaparinux has been shown to reduce major bleeding with similar short-term efficacy as enoxaparin and lowers death and stroke during long-term follow-up in patients with acute coronary syndromes undergoing percutaneous coronary intervention.^[2]

Similarly, it has been shown superior to enoxaparin in reducing death or ischemic events at 9 days maintaining the efficacy up to 6 months in patients with unstable angina or NSTEMI with major bleeding occurring in fewer fondaparinux than enoxaparin recipients.^[3] On comparison with a heparin-based therapy, fondaparinux reduce mortality, ischemic events and major bleeding across the full spectrum of acute coronary syndromes.^[4] Thus, it is assumed and projected^[2-4] from the existing knowledge that fondaparinux being more selective in its action may prove safe and efficacious. There are few reports^[5,6] of heparin-induced thrombocytopenia (HIT) related to fondaparinux in a patient previously exposed to

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unfractionated heparin (UFH)^[5] and delayed-onset HIT caused during its prophylaxis.^[6]

In contrast, it is used sometimes off label in the management of HIT with thrombosis.^[7]

Major bleeding is known to exist with the use of fondaparinux in previously exposed heparin user^[5] but to best of our knowledge there exist no isolated case report presenting with fondaparinux-induced major bleeding in elderly postmenopausal women prescribed for recently diagnosed NSTEMI. Hence, the case is worth reporting.

CASE REPORT

We hereby report a rare case of fondaparinux-induced major bleeding in a 58-year-old postmenopausal woman, a known hypertensive and Type 2 diabetes mellitus (T2DM) patient prescribed for NSTEMI reported in our ADRM Centre.

The patient presented in the emergency with complaints of chest pain not relieved by sublingual nitrate. On examination there was no pallor, cyanosis, pedal edema, signs of atherosclerosis. Pulse rate was 94/min, regular, normal volume, no radio-femoral delay, and vessel wall not palpable. Blood pressure (BP) measured in both limbs was 160/90 mmHg. On auscultation of CVS and respiratory system showed no abnormality. Laboratory investigations revealed Hb 11g%, TLC 8400/cmm, platelet count 2.4 lacs/cmm, RBS 194 mg%, blood urea 29 mg, serum creatinine 0.9 mg, HbA1c 7.8%, serum cholesterol 245 mg%, serum triglyceride 185 mg%, HDL 35 mg%.

ECG was done immediately, which showed NSTEMI and a positive 10 hour troponin-T assay. Angiography was not done. Patient was treated with oxygen, morphine, beta blocker, ACE inhibitor, statins, aspirin, and clopidogrel, fondaparinux 2.5 mg once daily by subcutaneous route. Third day patient developed purpura and extensive ecchymosis in right arm and forearm [Figures 1 and 2]. The patient also developed epistaxis lasting >10 min, which required ENT intervention as well as macroscopic hematuria lasting for 3 days. Patient also presented with per vaginal bleeding, which continued till 7 days. Patient on subsequent investigations showed platelet count 45000/cmm. Hb was 6.9 g%. HIT antibodies were not done due to lack of facility. There were no signs of deep venous thrombosis, pulmonary embolism, gangrene, retroperitoneal, intracranial, or intraocular hemorrhage in the patients as suggested by USG abdomen and MRI brain. USG of pelvic organ revealed small postmenopausal sized uterus and normal adnexa. Based on clinical and

laboratory findings, a diagnosis of fondaparinux-induced major bleeding was established. Patient required four units of platelet fraction and three unit of blood transfusion. After which platelet count and Hb rapidly reestablished to 1.5 L/cmm and 8.9 g%. She was discharged in a satisfactory condition after 15 days of hospitalization and is now regular follow up and prophylaxis treatment of MI. Since the ADR was serious and most likely thought to be associated with fondaparinux because of its previous known few reports.^[5,6]

De-challenge of drug and blood/platelet transfusion caused ADR to ameliorate. Further re-challenge was not done with the fear of reappearance of ADR and due to ethical constrains. Thus, the appearance of major bleeding could not be explained by a concurrent disease as such, drug or chemicals and de-challenge improved the condition.

DISCUSSION

Hence, this ADR can be labeled 'Probable/likely' as per causality assessment with the score 6.^[8] Since this ADR



Figure 1: Extensive ecchymoses in right arm and forearm of a patient



Figure 2: Extensive ecchymoses in right arm and forearm of a patient (closer view)

was not studied for dose dependent response and was unpredictable/unusual as per mechanism of action is known, hence it could not be clearly labeled as Type-A or B class of ADR.^[9]

Anticoagulation, traditionally with UFH is a cornerstone of therapy for patients of unstable Coronary artery disease (CAD). However UFH exhibits unpredictable anticoagulant effect, which requires frequent monitoring and has low bioavailability due to high protein binding and induced thrombocytopenia. An effort to avoid this inherent limitation of UFH has led to introduction of low molecular weight heparin (LMWH). Enoxaparin, dalteparin, nadoparin, reviparin, and latest addition in the armamentarium in countering the thrombotic events in unstable CAD is fondaparinux. It is a synthetic pentasaccharide that acts as a selective inhibitor of activated factor X. The mechanism of action of fondaparinux involves high affinity (but reversible) binding to antithrombin III and a resultant conformational change in the serpin's reactive loop that greatly enhances antithrombin III's basal rate of factor Xa inactivation. Fondaparinux acts as an antithrombin III catalyst, with one molecule of fondaparinux leading to inhibition of many factors Xa molecules.^[1] Because of its selectivity, it is proposed to be devoid of major bleedings, unlike current report.

As longevity is constantly increasing, the numbers of elderly patients who require anticoagulation are also rising steadily. Managing elderly patients receiving anticoagulants is challenging because those patients are at high risk of both thrombosis and bleeding. Moreover, older patients are commonly frail; they have substantial chronic comorbid conditions including renal impairment and frequent acute illnesses and are often on many medicines.^[10] There remains a clear need to optimize the use of anticoagulant drugs in these patients as suggested by current case report.

CONCLUSION

The current case report highlights, a need for clinicians to have a sound understanding of anticoagulant pharmacology, dosing, toxicity, individualized approach, and predicting the

risk of bleeding before they are prescribed to advancing age persons.

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