



Case Report

Protamine sulfate for the reversal of enoxaparin associated hemorrhage beyond 12 h



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ABSTRACT

Clinical practice guidelines recommend protamine sulfate for reversal of enoxaparin associated bleeds dependent on the time from last administration and dose of enoxaparin. We present a case of a hemodynamically unstable patient with an enoxaparin induced abdominal wall hematoma/hemorrhage and the previous enoxaparin administration 21.5 h prior to presentation with a therapeutic anti-Xa assay (0.8 IU/mL) upon assessment in the emergency department. Along with resuscitative efforts, an interdisciplinary team collaborated to administer protamine sulfate 50 mg intravenous once (0.5 mg per 1 mg of enoxaparin) to reverse the therapeutic anticoagulation. Our case demonstrates the importance of monitoring renal function and the potential for accumulation of enoxaparin in patients with renal dysfunction leading to prolonged therapeutic anti-Xa assays. With the availability of anti-Xa assays, future reversal recommendations of enoxaparin associated bleeds using protamine sulfate should include the initial anti-Xa assay as a guide for the dosing regimen.

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1. Introduction

Bleeding is a serious complication associated with the use of anticoagulants, with the bleeding rate for patients receiving low molecular weight heparins of approximately 2% [1]. Protamine sulfate is currently the recommended reversal agent for enoxaparin associated hemorrhage [2,3]. If the previous enoxaparin administration was within 8 h, 1 mg of protamine sulfate should be administered for each 1 mg of enoxaparin (max 50 mg of protamine) [2,3]. Current clinical practice guidelines recommend that a reduced dose of protamine sulfate can be administered if the previous enoxaparin administration was greater than 8 h (0.5 mg protamine sulfate for 1 mg enoxaparin) [2,3] and within 12 h [3]. After 12 h from the previous enoxaparin administration, the clinical utility of reversal of enoxaparin has been suggested to be minimal [3] and is not recommended in our institutional guidelines. We present a case of using protamine sulfate for reversal of an enoxaparin associated hemorrhage outside the recommended reversal period in a therapeutically anticoagulated individual with new onset renal dysfunction.

2. Case report

A 65 year old female (100 kg), with a past medical history of factor V Leiden deficiency with multiple deep vein thrombosis was transitioned from warfarin to enoxaparin 1 mg/kg every 12 h as bridge therapy for a planned surgical procedure. Other significant past medical history includes chronic kidney disease stage III (baseline creatinine 0.95 mg/dL) and esophageal stricture. The patient presented to the emergency department with signs of Class II hemorrhagic shock and a new right flank-abdominal wall mass. A bedside ultrasound demonstrated a large fluid collection exterior to the abdominal wall measuring approximately 13.5 centimeters (cm) by 24 cm. Subsequent imaging with a computed tomography angiography of the abdomen and pelvis demonstrated a new large hyperdense fluid collection along the lower right flank measuring approximately 23 cm × 8.9 cm × 14 cm, consistent with a large abdominal wall hematoma/hemorrhage (Fig. 1). The patient was concurrently resuscitated with four units of packed red blood cells and intravenous crystalloid fluids. Initial hospital laboratory evaluation demonstrated a hemoglobin of 3.8 g/dL and serum creatinine 1.96 mg/dL on presentation. A review of the patient's medical administration record from the nursing facility found the most recent enoxaparin administration was 21.5 h prior to presentation. Based on initial laboratory results and clinical instability, further testing with an

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Fig. 1. Computed tomography abdomen demonstrating abdominal wall hematoma/hemorrhage.

anti-Xa assay was obtained which demonstrated a therapeutic level of 0.8 IU/mL, confirming our suspicion of residual enoxaparin presence in the setting of now onset renal dysfunction. With the patient being outside the normal recommended time frame to administer protamine sulfate (12 h), an interdisciplinary team collaborated and decided to administer protamine sulfate 50 mg intravenous once (0.5 mg per 1 mg of enoxaparin) due to the therapeutic anti-Xa assay and clinical instability. No further administrations of protamine sulfate occurred due to the patient's hemodynamic stability post resuscitation/protamine sulfate administration as well as the patient's coagulopathy history. The patient was admitted to the intensive care unit for further monitoring and management of the enoxaparin abdominal wall hematoma/hemorrhage. During hospitalization, the patient required an incision and drainage of the right abdominal wall hematoma (approximately 500 mL evacuated) and ligation of the right inferior epigastric artery. The patient's renal function improved over the duration of hospitalization back to baseline and the urine output was greater than 0.5 mL/kg/h throughout the hospitalization. The patient did not experience any thrombotic events during the hospitalization (5 days) and was reinitiated on anticoagulation prior to discharge.

3. Discussion

Our case demonstrates the importance of monitoring renal function and the potential for accumulation of enoxaparin in patients with renal

dysfunction leading to prolonged therapeutic anti-Xa assays. In individuals with enoxaparin associated bleeding events and renal dysfunction, reversal outside the recommended time frame (12 h) might be indicated based on the patient's bleeding source and clinical instability. When utilizing the Naranjo algorithm [4], the probability of the patient's abdominal wall hematoma/hemorrhage being related to enoxaparin was probable (8) for our patient case. Creatinine clearance and anti-Xa assays have previously been shown to be inversely correlated [5] and there have been multiple reports of prolonged therapeutic effects of enoxaparin requiring reversal with protamine sulfate outside the typical recommended reversal time frame [6,7]. Limitations of our patient case include being a single center retrospective chart review with a single patient. With the availability of anti-Xa assays, future reversal strategies of enoxaparin associated bleeds with protamine sulfate should incorporate the initial anti-Xa assay as a guide for dosing recommendations. Variability exists with response to protamine sulfate for hemorrhage cessation and further evidence is necessary to determine which laboratory parameter is most indicative of coagulation status after protamine sulfate administration [7]. Our case adds to the current evidence supporting the clinical utility of evaluating the initial anti-Xa assay to facilitate protamine sulfate administration in reversal of enoxaparin associated bleeds outside the recommended time frame, especially in patients with renal dysfunction.

Conflict of interest statement

Dr. Gibbons receives clinical trial support from Astra Zeneca. No other authors declare a potential conflict of interest.

References

- [1] Dhakal P, Rayamajhi S, Verma V, et al. Reversal of anticoagulation and management of bleeding in patients on anticoagulants. *Clin Appl Thromb Hemost* 2017;23(5): 410–5.
- [2] Garcia D, Baglin T, Weitz J, et al. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis 9th ed: American College of Chest Physicians Evidence-based clinical practice guidelines. *Chest* 2012;141(2 Suppl):e24S–3S.
- [3] Frontera J, Lewin J, Rabinstein A, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage. *Neurocrit Care* 2016;24:6–46.
- [4] Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30(2):239–45.
- [5] Chow S, Zammit K, West K, et al. Correlation of antifactor Xa concentrations with renal function in patients on enoxaparin. *J Clin Pharmacol* 2003;43:586–90.
- [6] Chawla L, Moore G, Seneff M. Incomplete reversal of enoxaparin toxicity by protamine: implications of renal insufficiency, obesity, and low molecular weight heparin sulfate content. *Obes Surg* 2004;14:695–8.
- [7] Van Veen J, Maclean R, Hampton K, et al. Protamine reversal of low molecular weight heparin: clinically effective? *Blood Coagul Fibrinolysis* 2011;22:565–70.