Author/s:
Chan, M;Wong, A

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Chan Michael (Orcid ID: 0000-0003-3918-935X)
Wong Anselm (Orcid ID: 0000-0002-6817-7289)

Management and Monitoring of Large Enoxaparin Overdose treated with Protamine

Authors and affiliations:
Michael Chan *(Corresponding Author)*
MBBS (Hons)
General Medicine Department, Royal Melbourne Hospital
300 Grattan Street, Parkville, Victoria 3050, Australia
Email: Michael.chan4@mh.org.au
Tel: +61(3) 9342 7000
Fax: +61(3) 9342 7802

Associate Professor Anselm Wong
MBBS, DipTox PhD, FACEM, FAACT, FACMT
Victorian Poisons Information Centre and Emergency Department, Austin Health, Victoria, Australia
Department of Medicine, School of Clinical Sciences at Monash Health, Monash University, Victoria, Australia
Centre for Integrated Critical Care, Department of Medicine and Radiology, Melbourne Medical School, University of Melbourne, Victoria, Australia

Author contribution statement:
Both MC and AW analysed the patient data. MC wrote the manuscript under the supervision and with the feedback from AW. All authors read and approved the final manuscript.

Ethical Statement
The patient involved in this case report gave their informed consent prior to writing of this case report.

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Figures: Figure 1 (see attached)

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Reporting of enoxaparin overdose in the literature is rare and few examine the therapeutic use of multiple doses of protamine sulfate (1,2). We present a case of enoxaparin overdose treated with multiple doses of protamine.

Case report:

A 37-year-old female presented to the emergency department after administering 20 vials of 100mg injections of enoxaparin (total 2g) into her abdominal wall in a self harm attempt. She had a past history of epilepsy, recurrent unprovoked venous thromboembolism. On assessment, she was somnolent, but easily rousable with a Glasgow Coma Score of 13 (E3V4M6), respiratory rate 24, heart rate 82 bpm and blood pressure 120/88 mmHg. Physical examination revealed bruising over the upper abdomen at the sites of enoxaparin injection, with no signs of active bleeding.

Initial investigations taken 3 hours post overdose revealed a normal full blood count and renal function, and an elevated aPTT of 107 seconds (normal range 23-36 seconds) with a high anti-Xa level (Figure 1). She was administered 50mg of protamine over one hour and a further 2 infusions were given during her admission. The anti-Xa level gradually decreased with minimal effect from the protamine boluses observed.

The patient was monitored in hospital for 5 days without any signs of active bleeding, and was discharged from hospital with a staged supply of her medications.

Discussion

The management of a large enoxaparin overdose presents a challenge in regards to both its reversal and monitoring. The enoxaparin (Clexane®) prescribing information recommends neutralisation of enoxaparin with protamine at a 1:1 ratio if taken in the previous 8 hours, and a ratio of 0.5:1 if enoxaparin was administered more than 8 hours prior. However, protamine sulfate has been described to only partially neutralise the anticoagulant activity of low-molecular-weight heparins, such as enoxaparin, the consequences of which have been described in a patient in whom bleeding complications have been exacerbated by the inability to attain complete neutralisation (1). In addition, excess use of protamine is associated with reduced platelet function, inhibition of coagulation (reduced thrombin generation, factor V and VII activation, factor VIII clotting activity), and enhanced fibrinolysis (3). While protamine is effective in fully reversing the anti-IIa component of low molecular weight heparin, only a partial effect is seen on the anti-Xa component (1,4). Supporting this, the anti-Xa level in our case remained elevated 24 hours after normalisation of the aPTT.

In regards to the management approach, a case series described by Monte et. al. suggests that in cases of low-molecular-weight heparin (LMWH) overdose, observation seems to be appropriate in the absence of clinically significant bleeding (2). However, the overdoses in these cases were of smaller doses (72,000 units of dalteparin and 480mg enoxaparin), and there is a paucity of evidence regarding the safety of this approach in patients with larger overdoses (2). In our case, the patient received 150mg of protamine sulfate over 3 doses, however, this had little effect on rapidly decreasing anti-Xa levels. With this degree of overdose, one would have had to administer 2g of protamine (40 times the recommended manufacturer dose) in attempt to neutralize the LMWH, which could have led to a significant risk of bleeding as a side effect of the treatment. Indeed in the setting of protamine use for heparin reversal in cardiac surgery patients, recommended dosing can potentially worsen coagulopathy and bleeding in some patients (5). Given the absence of overt bleeding in the case, the lack of significant reversal from the manufacturer recommended dosing of protamine and the absence of safe guidelines in the setting of overdose, higher dosing was not pursued. Other therapies such as recombinant VIIa has been used previously in the case of bleeding secondary to LMWH (6). In the setting of bleeding secondary to enoxaparin overdose, clinicians should be aware of the limited efficacy of protamine to reverse anticoagulation and the risks associated with its use.

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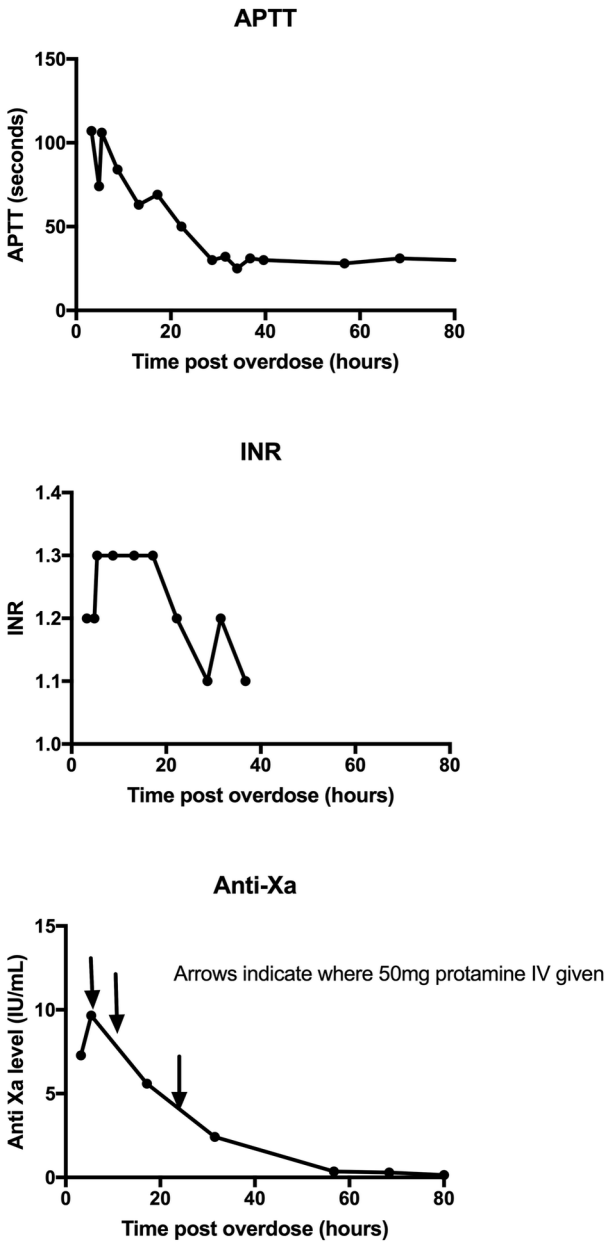
Figure Legend

Figure 1. aPTT levels and Anti-Xa levels post large enoxaparin overdose. Arrows indicate where 50mg protamine IV given.



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