

Low Molecular Weight Heparin Overdose: A 10 Year Case Series

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Abstract

Background: Low molecular weight heparin (LMWH) is used for the treatment and prevention of coagulative disorders. Few patients receiving therapeutic doses of LMWH develop major hemorrhage. Currently there are few reports in the literature on acute overdose on adults. In this study, clinical profile, treatment and outcome of 21 patients who acutely overdosed enoxaparin are described.

Methods: A retrospective chart review of California Poison Control System (CPCS) database: Visual Dot Lab during 1997 to 2007 was obtained. All patients with a definite reported overdose of subcutaneous injection of LMWH were included.

Results: In total, 21 patients who were all exposed to enoxaparin were studied. The reasons for overdose included medical miscalculation (3 cases, all infants), intentional misuse (2 patients), accidental overdose (7 cases), suicidal attempt (7 cases) and unknown in 2 patients. 7 cases were documented to have overdosed more than 2 times the therapeutic dose. The overdose ranged from 50 mg to 1300mg (0.1-80 times the therapeutic range). No patients were documented to experience bleeding or have thrombocytopenia although complete follow-up was only available for 11 patients.

Reassurance was given to patients with less than 0.14 times the therapeutic dose. The 2 patients who received protamine were overdosed with more than 2.5 times the therapeutic dose of enoxaparin.

Conclusion: Most patients had no complications and were not treated with protamine. This study suggests that a large dosage of LMWH is unlikely to result in any life threatening complications, though further studies are needed to certainly conclude about this. The use of protamine in LMWH overdose seems to remain controversial.

Keywords: Low molecular weight heparin; Enoxaparin; Protamine; Overdose

INTRODUCTION

Low molecular weight heparin (LMWH) is a class of medications which has been used for treatment and prevention of several disorders including deep vein thrombosis, pulmonary embolism, unstable angina and myocardial infarction. These medications are given as subcutaneous injection and contrary to unfractionated heparin, do not require laboratory monitoring, thereby they are allowed for self-administration and outpatient use (1,2). Their anticoagulant effect creates the potential for bleeding (3). In several studies, the risk of major bleeding from anticoagulant dose of LMWH medications was shown to be 0.5-4% within therapeutic dosage (4-6). However, there have been few reports in the literature on acute overdose to date. Protamine has been suggested as a possible antidote for heparin and LMWHs overdose. However, there is a paucity of information on its use on LMWH overdose in the literature. Hence, there has not been a consensus on treatment of LMWH overdose. In this study, clinical profile, treatment and outcome of 21 patients who acutely overdosed enoxaparin are described.

METHODS

The California Poison Control System (CPCS) has been consulted on several cases of LMWH overdose. We reviewed our computerized database for a 10-year period (1997-2007) to find cases of reported parenteral overdose of LMWH including ardeparin (Normiflo®), dalteparin (Fragmin®), anaparoid (Orgaran®), enoxaparin (Lovenox®), fondaparinux (Arixtra®), nadroparin (Fraxiparine) and tinzaparin (Innohep®). Diagnosis was confirmed with patient's clinical history or medical records as reported to the CPCS. Cases were excluded if therapeutic doses of LMWH were administered or if there was uncertainty in the occurrence of LMWH overdose. Cases were included if the dose administered was more than that which was prescribed therapeutically. The typical dose of enoxaparin for thromboembolic prophylaxis was taken to be 30 mg to 40 mg given subcutaneously in adults. For the treatment of thromboembolism, the typical dose is taken to be 1 mg/kg given twice daily. The dose is adjusted for patients with severe renal impairment.

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RESULTS

In total, 21 patients who overdosed on LMWH were found during 1998 to 2007. All cases were involved with enoxaparin overdose. Seven patients were female, 13 were male and one was an infant. Age of patients ranged from 25 days to 92 years, while the median age was 41.5 years.

The reasons for overdose included medical miscalculation (3 cases, including the infant), intentional misuse (2 cases), accidental overdose (7 cases), self-harm attempt (7 cases) and unknown for 2 cases. The overdose ranged from a given dose of 50 mg in a 5 months old infant to 1300 mg in an adult. Seven cases overdosed on more than two times the therapeutic dose. No patients were reported to have clinical evidence of bleeding, although complete follow-up data was only available for only 11 cases. One patient had arm bruising, but was otherwise asymptomatic. Two patients were treated with protamine sulfate because they had received more than 2.5 times the therapeutic dose of LMWH, although there was no evidence of bleeding.

Four patients had a documented prolonged partial thromboplastin time (PTT) of more than 40 seconds. One was mildly prolonged (60 seconds); while the 3 others were 143 seconds, 171 seconds and 200 seconds after overdosing on 630 mg, 960 mg and 1000 mg of subcutaneous enoxaparin respectively, in suicidal attempts. Although protamine sulfate was advised by the CPCS in all three of these cases, it was not administered in any of the patients. Two of the 3 patients remained asymptomatic up to 3 days after the overdose while one of them was lost to follow up.

DISCUSSION

Bleeding and possibly thrombocytopenia may be the main concerns of enoxaparin overdose. Among the coagulation enzymes, factors Xa and IIa are the key proteases that are involved in the regulation of the coagulation process. Monitoring the anticoagulant effect of LMWH is not proposed to be necessary in clinically stable patients and there are no clinical trials showing that measurement of the plasma anti-Xa levels correlates with outcome (7). However, dose-finding studies with LMWH showed that increase of dose is associated with a higher anti-Xa level, which increases the likelihood of bleeding (8,9). Thus, measurement of anti-Xa seems appropriate in cases of overdose. However, this investigation was not performed for any of the patients in our study. This may reflect resistance or low information of the treating physicians. However, the reason was probably that the treating physician thought the test was not clinically indicated based on the absence of evidence of bleeding. It should also be noted that performing the investigation is difficult due to lack of availability or cost issues in hospitals.

Since LMWHs minimally inhibit thrombin activity and cause only mild prolongation of the PTT, this test seems not to be appropriate for monitoring anticoagulant effects (7). The efficacy of protamine on reversal of anticoagulant effects has also been reported to be only partial to none (10-12). Although uncommon, the management of major bleeding still remains controversial. Protamine sulfate and

recombinant activated factor VII (rFVIIa) were administered in an effort to control bleeding in some studies with varying success (13,14). As such, thrombin clotting time might be useful for follow-up for such patients (13). However, most of the patients in our study recovered without any treatment. This is similar to the case series reported by Monte et al. whereby they concluded that watchful observation was appropriate for patients who did not have any bleeding complications (15).

In patients using LMWH therapeutically, major hemorrhage was associated with impaired renal function (defined as creatinine 1.5-1.8 mg/dL) and chronic liver disease (defined as a known persistent elevation of aminotransferase enzymes) (4,16). For such patients monitoring the anti-factor Xa assay seems appropriate in overdosed cases and should be performed 3 to 6 hours after overdose (7).

LIMITATIONS

This study is limited by its retrospective nature. Blood reports were not documented in many of the cases. There was also a lack of information on why CPCS advice was not followed in cases where protamine use was advised. There are no serum or blood levels to prove overdose; hence, diagnosis was based on history and physical examination, though it may be inaccurate. There was a paucity of documentation in the charts and only 11 of the 21 patients were followed up after the initial call was made to PCC.

CONCLUSION

Given the rarity of LMWH overdose, there is no clear consensus on its management. No patients in our study were reported to experience bleeding complications and only two were treated with protamine. Monitoring anti-Xa activity is recommended after severe overdose and in patients with renal or hepatic impairment or comorbid conditions with the risk of bleeding. The role of protamine for LMWH is yet uncertain.

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