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Selected Topics: Toxicology

INTENTIONAL OVERDOSE WITH TINZAPARIN: MANAGEMENT DILEMMAS

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□ **Abstract—Background: Low-molecular-weight heparin (LMWH) is increasingly being prescribed for prophylaxis and treatment of thromboembolic diseases. Despite the fact that its therapeutic use is considered to be safe, it can be complicated by major hemorrhage and, in contrast to unfractionated heparin, it can only partially be neutralized by protamine. Recent reports of LMWH overdose illustrate the need for a consensus on its management. Objectives: To describe a case of self-poisoning with a very large dose of tinzaparin and discuss management options in patients with LMWH overdose. Case Report: A 69-year-old woman was brought to the Emergency Department 2 h after injecting herself with 280,000 IU of tinzaparin subcutaneously in an attempt to commit suicide. Despite an unrecordable activated partial thromboplastin time (APTT > 180 s) and prolonged prothrombin time, there was no evidence of active bleeding. She was given an intravenous infusion of 100 mg protamine sulfate and was admitted to the intensive care unit, where further infusions of protamine were administered. Normalization of the APTT occurred 40–50 h post admission, reflecting normal tinzaparin clearance rather than neutralization by protamine. No hemorrhagic complications occurred during her hospitalization except for prolonged bleeding from venipuncture sites. Conclusion: In this case of massive tinzaparin overdose, conventional doses of protamine failed to rapidly normalize the deranged coagulation parameters. The favorable clinical outcome suggests that, regardless of the LMWH amount injected, no active treatment is needed in the absence of hemorrhage. This is in accordance with the limited published data concerning cases of overdose with other LMWHs.** © **2014 Elsevier Inc.**

□ **Keywords—tinzaparin; heparin; low-molecular-weight heparin; overdose; protamine**

INTRODUCTION

The use of low-molecular-weight heparins (LMWHs) for prophylaxis and treatment of venous thromboembolism is widespread. These compounds offer distinct clinical advantages over unfractionated heparin (UFH), including longer duration of action and easier administration. A number of studies have shown that home therapy with LMWH is equally safe and effective and probably more cost-effective than hospital treatment (1). Consequently, an increasing number of patients are being prescribed LMWH for self-administration at home. Tinzaparin sodium is a LMWH with long biologic half-life, approved for once-daily treatment and prophylaxis of deep vein thrombosis and pulmonary embolism. The availability of a range of unit-dose graduated prefilled syringes minimizes the probability of significant accidental overdose.

As with UFH, major, occasionally fatal, hemorrhagic complications, including intracranial bleeding, have been reported in association with therapeutic use of LMWH (including tinzaparin) (2). In contrast to UFH, which can be easily neutralized by protamine sulfate, there is no antidote that will reliably reverse the activity of LMWH. We report a case of self-poisoning with a very large dose of tinzaparin that highlights the

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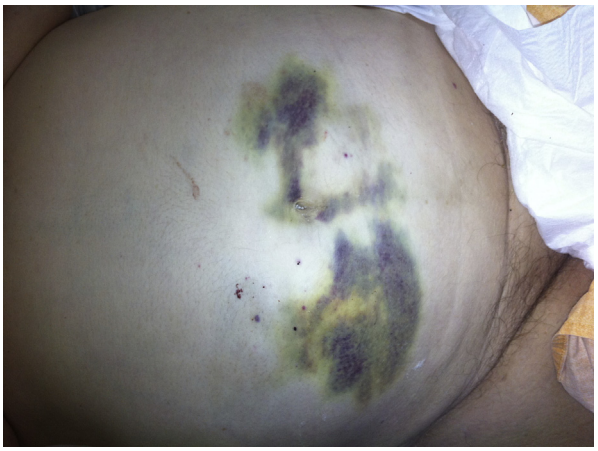

Figure 1. Multiple injection marks and old ecchymoses are visible in the periumbilical area.

therapeutic dilemmas faced by the emergency physician in the setting of LMWH overdose.

CASE REPORT

A 69-year-old white woman was brought to the Emergency Department after an intentional overdose with LMWH. Her relatives reported that she had injected herself subcutaneously with 20 prefilled syringes, each containing 14,000 IU of tinzaparin sodium (Innohep®; Celgene Corporation, Summit, NJ) 2 h prior to presentation in an attempt to commit suicide. She had a long-standing history of bipolar affective disorder treated by a psychiatrist, and had made another serious suicide attempt in the past. Her medical history was notable for Parkinson's disease, chronic obstructive pulmonary disease, and hypothyroidism. Her regular medication included citalopram, levomepromazine, lorazepam, a combination of levodopa and benserazide, levothyroxine, and inhaled bronchodilators. Tinzaparin 14,000 I.U. once daily had been prescribed for bilateral deep venous thrombosis of lower limbs occurring during hospitalization for a subcapital fracture of the left humerus 2 weeks prior to presentation.

On examination, the patient was fully alert and oriented, complaining only of pain in her fractured left arm. There was skin pallor and extensive old ecchymoses and hematomas in her left shoulder and upper arm, upper anterior thorax, and periumbilical area, where at least 14 injection marks were visible (Figure 1). Physical (including neurological) examination was otherwise normal. In particular, she was hemodynamically stable, with a regular pulse of 62 beats/min and arterial blood pressure of 120/80 mm Hg. There were no signs of active mucosal bleeding, and rectal examination was negative for blood or melena.

Laboratory investigations revealed an unrecordable activated partial thromboplastin time (APTT > 180 s) and prolonged prothrombin time (PT) at 23.1 s with an international normalized ratio of 2.02. Complete blood count showed hemoglobin of 7.9 g/dL with reticulocytosis and reactive leukocytosis and thrombocytosis. Biochemical profile was unremarkable and urinalysis was normal. No evidence of intra-abdominal or retroperitoneal hemorrhage was detected on ultrasound examination. After consultation with general and orthopedic surgeons, her anemia was ascribed to blood loss complicating the recent humeral fracture.

An intravenous infusion of 100 mg protamine sulfate was given over 30 min and the patient was admitted to the intensive care unit. Further infusions of protamine were administered as shown in Figure 2. Results of repeat estimations of APTT and PT are shown in the same Figure. Apart from prolonged bleeding from venipuncture sites, the patient experienced no spontaneous hemorrhagic manifestations during her stay in the hospital. She was transfused with three units of packed red cells and was discharged after being reviewed by a psychiatrist who modified her antidepressant medication. Tinzaparin therapy was resumed upon normalization of the APTT and arrangements were made for supervised administration of the drug at home.

DISCUSSION

To our knowledge, this is the first report of intentional tinzaparin overdose and one of the few cases of self-induced LMWH poisoning reported in the international literature (3–6). All but one case concerned dalteparin (Table 1)

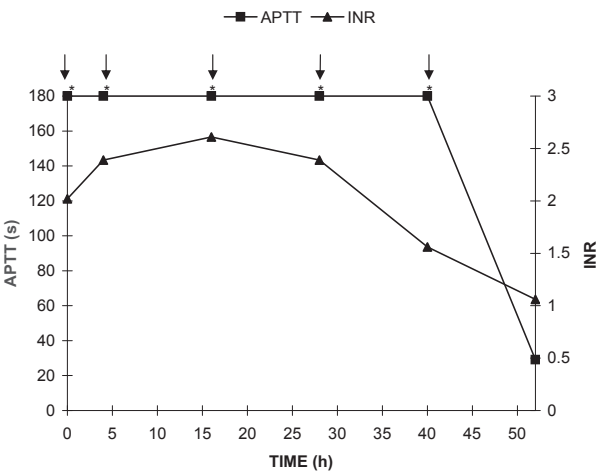

Figure 2. Coagulation test results from time of admission (0 h) to normalization of activated partial thromboplastin time (APTT) and international normalized ratio (INR). Vertical arrows indicate intravenous protamine sulfate 100 mg infused over 30 min. Stars next to APTT data points indicate values > 180 s, which is the instrument's measurement limit.