Case Files of the Medical Toxicology Fellowship at Banner Good Samaritan Medical Center in Phoenix, AZ: A Non-Warfarin Anticoagulant Overdose

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CASE PRESENTATION

A 50-year-old man presented to the emergency department (ED) following an overdose of his "blood thinners." The patient had become increasingly depressed over financial concerns, prompting a suicide attempt. He declined to provide any details regarding his current medications or his past medical history. A review of the computerized medical record, however, revealed he had a Factor V Leiden mutation with multiple venothromboembolic events. He previously had an inferior vena cava filter placed, and had received tissue plasminogen activator (tPA) for a cerebrovascular accident. A toxicology consult was obtained in the ED.

What "blood thinners" are routinely available for outpatient therapy?

The term "blood thinners" is commonly used by laypersons to describe any xenobiotic that can impair platelet aggregation or prevent thrombosis. In past decades, salicylates and warfarin were the primary agents available for outpatient use for these purposes. However, as the importance of treating venothromboembolic disease has become more recognized, there has been a substantial growth in pharmacological therapies available to physicians to prescribe for patient use outside of the hospital setting [1]. These agents may inhibit platelets or affect the coagulation cascade; for simplicity, we will refer to all of these medications as anticoagulants. Depending on the particular drug, anticoagulants may be administered either orally or parenterally. Despite increasing outpatient use of these newer drugs for a variety of conditions, experience in overdose is limited, with few cases reported in the literature. Because salicylates and vitamin K antagonists, such as warfarin, have been used extensively and are widely reviewed in the past, we will not address them here further.

There are 3 main newer classes of drugs currently used in outpatient management of venothromboembolic disease. These include the adenosine 5'-diphosphate (ADP) receptor antagonists, the low-molecular-weight heparins (LMWHs), and the factor Xa inhibitors. The orally-administered thienopyridines, which include ticlopidine and clopidogrel, are ADP receptor antagonists. The parenterally-administered LMWHs, which include enoxaparin, have gained favor over the older, unfractionated heparins because of an improved safety profile and lack of need to monitor coagulation parameters [2]. The factor Xa inhibitors include both the parenterally-administered fondaparinux and idraparinux, and the orally-administered rivaroxaban. As of April 2009, rivaroxaban does not have Food and Drug Administration (FDA) approval and is not currently available in the United States; however, it does have approval by the European Commission for use.

The thrombin inhibitors constitute a fourth class of anticoagulants. These include ximelagatran, melagatran, and dabigatran. These act by blocking thrombin and substrates. These drugs are not currently available for use in the United States.

ADP antagonists

Adenosine 5'-diphosphate (ADP) is a crucial chemical involved in platelet aggregation, and can be expressed from platelet-dense granules and vascular endothelium [3]. Following platelet activation, ADP binds to the platelet at 1 of 3 unique binding sites, ultimately resulting in activation of the glycoprotein IIb/IIIa receptor with subsequent increased platelet aggregation [3–4]. The thienopyridines work primarily by antagonizing the P2Y12 ADP

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receptor [4]. Ticlopidine, and the second-generation thienopyridine clopidogrel, were approved for use in the United States in 1991 and 1998, respectively [5]. These 2 drugs are structurally similar, differing only by a carboxymethyl side chain on clopidogrel.

Both ticlopidine and clopidogrel are prodrugs that must be metabolized via CYP1A before platelet inhibition can occur [6–7]. Despite achieving a maximal drug concentration within 2 hours, maximal platelet aggregation inhibition does not occur for 8–11 days following ingestion of ticlopidine [8]. Clopidogrel has a therapeutic advantage over ticlopidine, including a lower incidence of adverse effects and achieving faster platelet inhibition. The clinical effects can be seen within several hours with clopidogrel. The rate of inhibition appears to be dose dependent, with higher doses achieving ADP inhibition faster than lower doses [6,9,10], However, there appears to be a ceiling effect with both thienopyridines at which a maximal degree of platelet inhibition occurs [8,10]. Newer P2Y12 antagonists that are currently under investigation include prasugrel and ticagrelor. Ticagrelor is an ADP antagonist, but rather than belonging to the thienopyridine class, it is a cyclopentyl-triazolo-pyrimidine class drug, which does not require metabolism to be active. It is also a reversible inhibitor of the P2Y12 receptor, unlike the other antagonists [4,11].

Ticlopidine has been associated with several adverse reactions, prompting the FDA to issue a "black box" warning surrounding its use. These effects include neutropenia, aplastic anemia, and thrombotic thrombocytopenic purpura (TTP) [3,8]. While these reactions can occur with clopidogrel, the incidence is substantially lower.

Low-molecular-weight heparins

Historically, unfractionated heparin was used as the principal pharmacological therapy for both treatment of and prophylaxis against venothromboembolic disease. Because of increased ease of administration, a more predictable dose response curve (and therefore lack of need to monitor anticoagulation parameters), and improved safety profile, the LMWHs are often preferred over the unfractionated heparins [2]. They are being used increasingly in the outpatient setting for treatment of venothromboembolic disease. Some patients may be on this therapy as a bridge to full anticoagulation with oral agents, while other patients will be placed on these medications as sole therapy. There are currently four LMWHs approved for use by the FDA: enoxaparin, dalteparin, tinazaparin, and ardeparin.

Unfractionated heparin binds to antithrombin III, and ultimately blocks thrombus formation via inhibition of factors IIa and Xa (*Figure 1*). The binding of the unfractionated heparin/antithrombin III complex ultimately causes a conformational change in factor Xa, resulting in its inhibition. LMWHs also bind to antithrombin III, but because of a difference in size, there is greater inhibition of factor Xa. Therefore, when comparing the LMWHs with unfractionated heparin, the LMWHs have a greater antifactor Xa:IIa ratio than unfractionated heparin. This ratio reflects the potency of the LMWH, because it is the antifactor Xa activity, rather than antifactor-IIa activity, that accounts for the therapeutic efficacy of the drug. The peak antifactor Xa and antifactor IIa activity occurs 3–4 hours following subcutaneous administration [2]. The degree of factor Xa inhibition exists in a linear dose-dependent fashion [12]. The various LMWH agents have different potencies, however, resulting in variable degrees of inhibition of factor Xa depending on the agent. Dosing of these agents are weight based and are based on total body weight, rather than ideal body weight, regardless of the patient's body habitus [13]. While much less common than with the unfractionated heparins, the LMWHs can cause heparin-induced thrombocytopenia (HIT) syndrome following routine usage [14]. It is unknown if HIT syndrome can occur following a single acute overdose of an LMWH.

Factor Xa inhibitors

Recently, there have been several drugs developed that can inhibit factor Xa, either indirectly (fondaparinux or idraparinux) or directly (rivaroxaban). Fondaparinux is a synthetic pentasaccharide that is structurally related to the antithrombotic binding sites of heparin. Unlike the LMWHs, which inhibit both factor IIa and factor Xa, fondaparinux binds selectively to the pentasaccharide binding site on antithrombin III, causing an irreversible conformational change in antithrombin III, which ultimately leads to inhibition of factor Xa without affecting factor IIa (*Figure 1*) [15–17]. In addition, the fondaparinux/antithrombin III complex can inhibit the tissue factor/VIIa complex. This *in vitro* inhibition is both dose and time dependent [16].

Idraparinux is a derivative of fondaparinux with a much longer half-life, which can be administered once a week. Because of its more negative charge, idraparinux can bind to antithrombin III with a much higher affinity than fondaparinux [18]. Compared with either placebo or warfarin, idraparinux is associated with higher rates of bleeding [19]. Furthermore, the risk of bleeding appears to be dose dependent [20].

Following therapeutic administration of fondaparinux, the antifactor Xa activity peaks at 3 hours. In patients with normal renal function, the elimination half-life is 17–21 hours, and the drug is largely eliminated unchanged within 3 days [15]. In contrast, because of the high affinity for antithrombin III, the half-life of idraparinux is 130 hours following subcutaneous injection [21]. Fondaparinux appears to be at least as effective as enoxaparin in prevention of deep vein thrombosis, but is associated with a slightly higher rate of bleeding [22]. Fondaparinux should not be used in patients weighing <50 kg or in those with renal failure, as the risk of hemorrhage is inversely related to renal function [23].

Rivaroxaban differs from the other factor Xa inhibitors in several ways. First, it is available orally. Second, rivaroxaban competitively inhibits both free and clot-bound factor Xa (*Figure 1*). Since it does not require the presence of antithrombin III, rivaroxaban is considered a direct factor Xa inhibitor. Following ingestion, the drug is metabolized via oxidative degradation and hydrolysis. The elimination half-life is 5–9 hours [24–25].

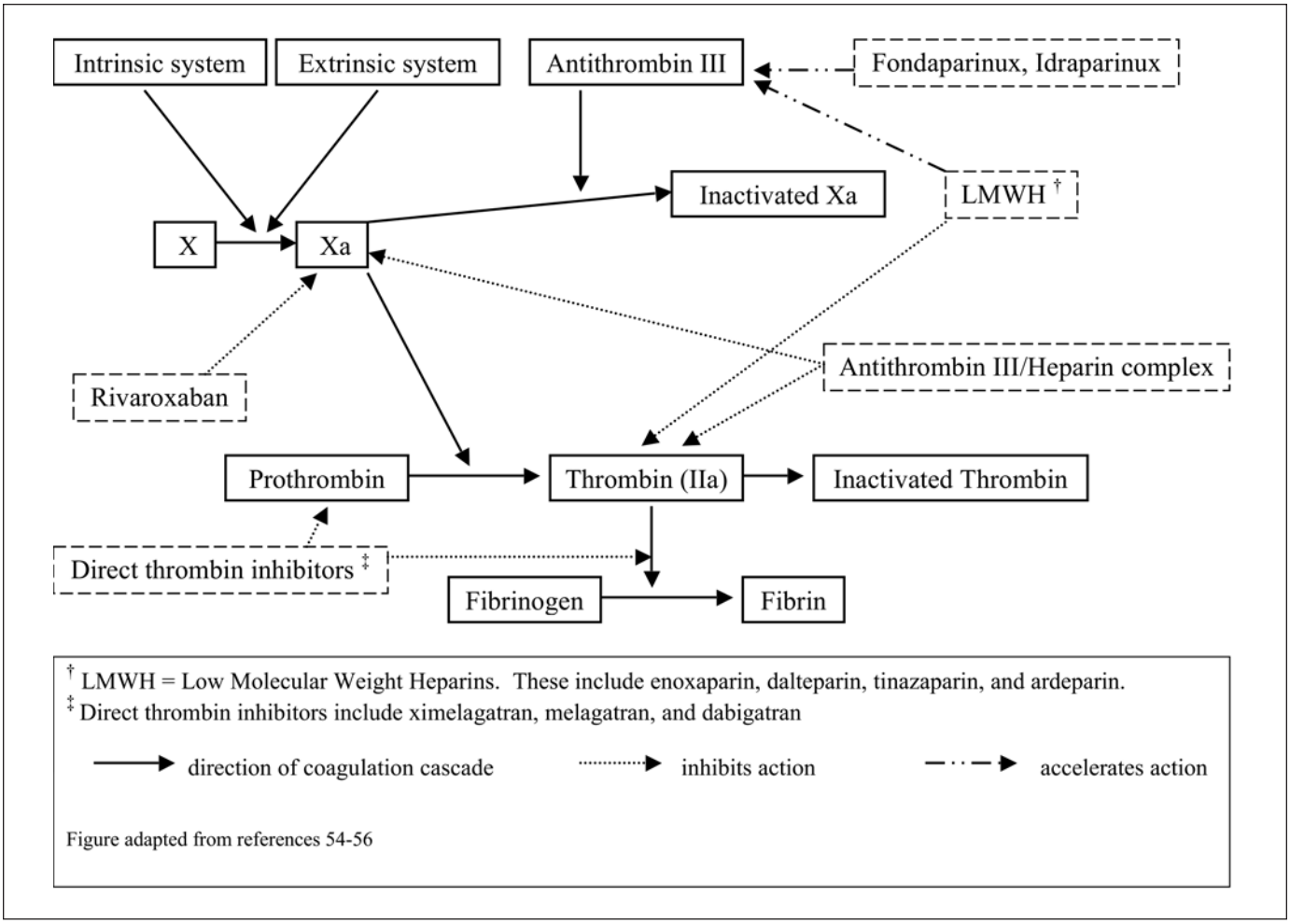

Figure 1: Site of action of newer anticoagulant drug classes.

CASE CONTINUATION

Upon further questioning, the patient reported that he injected himself subcutaneously with 1500 mg (17 mg/kg) of enoxaparin, approximately 3 hours prior to arrival. He denied taking any other medications.

Physical examination revealed a disheveled man in no acute distress. His vital signs included heart rate of 86 beats per minute, blood pressure of 130/83 mmHg, temperature of 36.9°C, respirations of 17 breaths per minute, and an oxygen saturation of 95% on ambient air. Pupils were 4 mm wide and equal, round and reactive to light. His intraoral exam was normal without gingival bleeding, and his neck was supple. His cardiopulmonary examination was normal. His abdomen was obese, with a periumbilical hernia that was nontender. There was no ecchymosis or fluctuance at the reported site of injection. Rectal exam revealed no gross blood, and stool tested negative for occult blood. He had no ecchymoses on skin exam, and neurological exam was normal, with intact cranial nerves II–XII, absence of focal deficits, and 5/5 strength in the bilateral upper and lower extremities.

Laboratory tests obtained in the ED revealed a normal complete blood count, with a hemoglobin of 14.7 g/dL and platelets of 218 k/mm^3. His electrolytes, liver function tests, blood urea nitrogen, and creatinine were normal, and acetaminophen and salicylate levels were nondetectable. A urine screen for drugs of abuse was also negative. Coagulation studies revealed a prothrombin time of 11.2 seconds and a partial thromboplastin time of 23 seconds. The patient was admitted by the toxicology service for continued monitoring and further workup.

What specific laboratory studies may be obtained to evaluate a patient for toxicity or potential adverse events following overdose of thienopyridines, LMWHs, or factor Xa inhibitors?

ADP antagonists

Currently, the 2 most common laboratory tests available to measure platelet activity after clopidogrel ingestion are bleeding time and platelet aggregation, the latter by both conventional optical

aggregometry and fully-automated aggregometry. Platelet aggregation is the most widely-used method to monitor ADP receptor antagonists [26]. The reference for platelet aggregation following in vitro addition of ADP, arachidonic acid, collagen, and ristocetin is normal aggregation. A clinical pathologist interprets the result of each test. There are other monitoring methods available, including point-of-care tests, which are presently undergoing evaluation [26–27]. The point-of-care tests, however, are expensive and not widely available.

The optimal time to assess for toxicity after clopidogrel overdose has not been established [28]. The time required for metabolism of this prodrug to its active metabolite, which is responsible for antiaggregating activity, varies greatly in the population. Maximum platelet inhibition is dose dependent as well. Following a therapeutic dose of 75 mg, platelet inhibition can be observed within 2 hours, although the maximum platelet inhibition will not occur for 5–8 days. Following a 300- to 400-mg load of clopidogrel, the peak platelet inhibition occurs within 2–5 hours [3,29]. Thus, following an overdose of at least 600 mg, it is reasonable to obtain the platelet aggregation tests as soon as 2 hours after the ingestion. While platelet aggregation tests can certainly be helpful, many centers do not routinely perform them. Furthermore, even if these tests are available in a timely manner, there is no data supporting or refuting their use to determine need for admission.

Clopidogrel levels, as well as levels of metabolites, may be obtained; however, it is not clear if these levels correlate well with bleeding risk. The parent compound can be detected in the serum for up to 12 hours post-therapeutic ingestion, while its principal inactive metabolite can be detected up to 48 hours [30]. There is great interindividual variation in both the plasma concentrations of the active metabolite and the degree of inhibition of platelet aggregation produced by ADP [28]. Furthermore, because 50% of patients consuming clopidogrel have less than 30% relative inhibition of ADP-induced platelet aggregation [31], interpretation of laboratory tests following clopidogrel overdose is significantly limited. Perhaps then, the only benefit of platelet aggregation studies and clopidogrel levels in an overdose setting would be to exclude an ingestion in a patient not already taking clopidogrel therapeutically.

Patients should have a complete blood count performed, primarily to obtain a quantitative assessment of platelet counts. Following therapeutic use of ticlopidine, thrombocytopenia occurs with an incidence of 1 in 1600–5000 patients treated [32]. The exact incidence of thrombocytopenia following clopidogrel is felt to be less, but not exactly known [33]. Previous studies have demonstrated that both clopidogrel fand ticlopidine have been associated with TTP. While this association has not been observed following overdose, the syndrome definitely occurs early in therapy [32–33], thus clinicians should follow platelet counts after an overdose of these agents. While there are no published recommendations regarding monitoring for TTP after clopidogrel overdose, we recommend rechecking a platelet count within 1 month.

Low-molecular-weight heparins

Generally speaking, laboratory monitoring of LMWHs is not necessary. However, instances in which monitoring is recommended include patients with renal failure, severe obesity, and iatrogenic overdoses [34]. The American College of Chest Physicians (ACCP) and the College of American Pathologists (CAP) recommend monitoring antifactor Xa activity with a chromogenic assay, which measures the inhibition of factor Xa [35–36] (*Table 1*). However, antifactor Xa levels are not available at most labs, frequently requiring sending the serum to a centralized reference laboratory. The results are usually not immediately available, and thus, would be unlikely to change acute management or disposition following a reported overdose. However, levels can be helpful in confirming or excluding an overdose in patients who are not using LMWHs therapeutically. Point-of-care monitors measuring anti Xa activity also exist, but these are not widely available [37].

When monitoring LMWH efficacy, it is recommended that the antifactor Xa sample be drawn 4 hours after the subcutaneous injection [36]. The therapeutic range, as recommended by the ACCP, is 0.6–1.0 IU/mL.[26] The CAP defines the therapeutic range for blood obtained four hours after the last injection as 0.4–1.1 IU/mL if the LMWH is administered twice daily, and 1.0–2.0 IU/mL for once-daily administration. Because each of the LMWHs appear to have similar pharmacokinetic properties, the therapeutic range is the same for all LMWH products [36,38]. Neither the prothrombin time (PT), activated partial thromboplastin time (aPTT), nor platelet count should be significantly affected under routine circumstances (*Table 2*).

Table 1: Consensus Recommendations from the College of American Pathologists for the Laboratory Monitoring of Patients Treated with Low-Molecular-Weight Heparin (LMWH)

1. Laboratory monitoring using an antifactor Xa assay may be useful in certain clinical settings (level 3)
2. Pediatric patients receiving LMWH should be monitored (level 2)
3. When LMWH is monitored, the sample should be obtained 4 h after injection (level 3)
4. The target concentration for the peak level in patients treated for venous thromboembolism should be 0.5–1.1 IU/mL when measured by an antifactor Xa assay (level 3)
5. The chromogenic antifactor Xa method is recommended for monitoring LMWH (level 2)
Levels of Evidence for Above Consensus Recommendations
Level 2: The recommendation is based on retrospective studies of multiple anecdotal studies or multiple anecdotal studies that reach consensus.
Level 3: The recommendation is based on isolated anecdotal studies of the consensus of expert practitioners.
Adapted from the College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy [36]

Table 2: Effect of Newer Anticoagulant Drug Classes on Laboratory Tests

	LMWH	Factor Xa Inhibitors	ADP Antagonists
PT	–	– / ↑	–
aPTT	– / ↑	↑	–
Bleeding time	–	–	↑
Platelet count	– / ↓	– / ↓	– / ↓

LMWH: low molecular weight heparin
PT: prothrombin time
aPTT: activated partial thromboplastin time
– : no change – / ↓ : change unlikely, possible decrease
↑ : increased – / ↑ : change unlikely, possible increase

Factor Xa inhibitors

As with the LMWHs, antifactor Xa levels can be obtained, but these tests are not available at many institutions. Furthermore, it is important to use the appropriate calibrator; the antifactor Xa assay cannot use the same international standards as are used for the LMWHs [23,39]. The antifactor Xa level may be helpful in confirming an overdose if found to be above the therapeutic range. Furthermore, the level can be helpful in determining when it would be safe to restart the medication, assuming it is still indicated.

The factor Xa inhibitors should not affect the PT or the aPTT. There should not be an increase in the bleeding time [16]. Thrombocytopenia may occur following use of factor Xa inhibitors, although the exact mechanism is not clear. In studies using fondaparinux, severe thrombocytopenia, defined as platelet counts <50,000/mm^3, occurred at rates of 0.04–0.2% [23] (*Table 2*).

What adverse events may occur after overdosing, either accidentally or intentionally, on ADP antagonists, LMWHs, or factor Xa inhibitors?

ADP antagonists

There is limited data on the toxic human dose of any of the ADP antagonists. Two cases of clopidogrel overdose have been reported. The first case involved a 34-year-old woman who was a participant in a clinical trial and ingested 1050 mg. She experienced no significant adverse effects and required no specific interventions [23]. A second case involved a 49-year-old man who took 1650 mg of clopidogrel in a suicide attempt. He developed mild platelet aggregation abnormalities, but clinically remained asymptomatic [40]. There are no published case reports of ticlopidine overdose. The package insert lists 1 case of an intentional overdose reported by a foreign post-marketing surveillance program and details are scant. It is described as a 38-year-old man who ingested 6000 mg of ticlopidine and developed an "increased bleeding time and increased SGPT." He received no interventions and recovered uneventfully [8]. To our knowledge, there have been no reports of bleeding following an intentional overdose of an ADP antagonist.

In rodent models, doses of clopidogrel exceeding 1500–2000 mg/kg have been lethal, while the lethal dose in baboons appears to be 3000 mg/kg. Specific signs or symptoms reported following nonlethal ingestion include vomiting, prostration, dyspnea, and gastrointestinal hemorrhage [23]. Similar to clopidogrel, the lethal dose of ticlopidine is also species specific. Doses of 1600 mg/kg were lethal to rats, while 500 mg/kg were lethal to mice [8]. The lethal dose for humans for any of the ADP antagonists is not known.

Following overdose of an ADP antagonist, platelet dysfunction may occur, placing the patient at risk for hemorrhage. While TTP can be observed with therapeutic dosing, it is unclear if this entity can occur following overdose as well.

Low-molecular-weight heparins

Despite their wide use, overdoses of enoxaparin or daltaparin are not widely reported in the literature. However, there are numerous reported cases of bleeding during therapeutic use, mostly when enoxaparin was used in the setting of renal insufficiency [41–43]. Bleeding is the major concern following an overdose of an LMWH. HIT is also a rare side effect of LMWH therapy. It is unclear if HIT syndrome can occur after LMWH overdose.

Factor Xa inhibitors

As with other anticoagulants, the primary concern after overdose is bleeding. To our knowledge, there are no reported cases of overdose involving factor Xa inhibitors.

How should patients who overdose on anticoagulant or antiplatelet medications be managed?

ADP antagonists

There are no published guidelines to help determine which patients can be watched at home and which should be referred to a healthcare facility. Furthermore, there is no data supporting a limited period of observation in the ED vs. admission to the hospital. Given the paucity of published clinical experience with overdoses of the newer ADP antagonists and the lack of previously-published guidelines, we propose the following conservative approach to evaluating pediatric ingestions and all intentional adult overdoses in the ED. A baseline complete blood count (CBC) should be obtained to check the hemoglobin and platelet counts. In addition, platelet aggregation studies may be obtained. After a period of 6 hours of observation, it would be reasonable for patients with small ingestions to be discharged home with close outpatient follow-up for signs of bleeding. It would be prudent to admit all patients with a large ingestion to the hospital for 24 hours of observation. A repeat CBC may be obtained as an outpatient to check for evidence of TTP.

In the event that clinically significant bleeding occurs, platelets should be transfused [44]. It should be noted, however,

that platelet transfusion has not clearly been shown to correct clopidogrel-induced coagulopathy. Another therapeutic option would be to administer desmopressin (DDAVP). Because DDAVP will increase factor VIII activity [47] and increase platelet adhesion [48] it may be beneficial in treating ADP antagonist–induced bleeding. In a small trial of volunteers receiving a single dose of 375 mg of clopidogrel, an increase in ADP-induced platelet aggregation was observed following DDAVP administration [48]. In addition, the use of the serine protease inhibitor aprotinin has been shown to reduce the bleeding time in rats given clopidogrel [49]. The exact mechanism by which this occurs is not known. Aprotinin has previously been used in patients undergoing coronary artery bypass graft. However, because of increased mortality in these patients, it has been voluntarily withdrawn from the US market by its manufacturer for all but very select indications. We would not routinely recommend the use of aprotinin in patients who have overdosed on clopidogrel.

Low-molecular-weight heparins

As with the ADP antagonists, there are no accepted guidelines regarding hospital referral or admission. We recommend that all pediatric patients and adults with an intentional overdose be evaluated in the ED. Baseline hemoglobin and platelet counts should be obtained. Following an observation period of 6 hours without signs of bleeding, it is reasonable to discharge all but large overdoses. Patients should be instructed to watch for signs of bleeding. Patients with a large overdose should be admitted to a monitored setting for 24 hours of observation. Serial neurological exams can be performed and serial hemoglobin levels obtained. In the absence of clinically significant bleeding, no specific treatment is required. There is a case report of a neonate receiving protamine sulfate following an overdose of LMWH [34]. Animal models, however, have demonstrated incomplete reversal of antifactor Xa levels following the administration of protamine sulfate [50–51]. In vitro studies have demonstrated effective reversal of LMWH following the administration of recombinant factor VIIa [52]. Following an overdose of LMWH, we would recommend protamine be administered only in the setting of clinically-significant bleeding. Blood products, including cryoprecipitate or fresh frozen plasma (FFP), can also be given in this situation.

Factor Xa inhibitors

There are no published reports of overdose on factor Xa inhibitors. Until further experience is gained, large or intentional overdoses should be referred to the ED for a baseline hemoglobin, platelet count, and coagulation studies.

The clearance of fondaparinux can be increased with hemodialysis [23], but it is not evident that the risk of bleeding from fondaparinux overdose exceeds the risks associated with hemodialysis. In human volunteers, recombinant factor VIIa has been shown to reduce the aPTT following the administration of fondaparinux [53]. However, the risk of inducing venothromboembolic events after the administration of recombinant factor VIIa needs to be weighed against the risk of bleeding. We would not recommend the routine use of recombinant factor VIIa. It could be considered, however, in the setting of clinically significant bleeding that is not reversed after the administration of cryoprecipitate or FFP.

CASE CONCLUSION

The patient's antifactor Xa level, obtained 4 hours following the reported self-injection, was < 0.1 U/mL (therapeutic range, 0.5–1.0 U/mL). Given the lack of inhibition, a repeat sample was obtained 8 hours after the reported injection, and was again <0.1 U/mL. Considering the history of Factor V Leiden deficiency, we opted to restart the patient on enoxaparin, although he refused. A psychiatry consultation was obtained to help assess his mental capacity.

A review of the patient's medical records clearly documented the IVC filter placement and prior tPA administration. An abdominal radiograph was obtained, which confirmed the presence of an IVC filter. However, the venothromboembolic events were always listed as part of the past medical history, and no radiographic study in the record ever confirmed the history of thrombotic disease. His previous MRI and CT scans were negative for both cerebrovascular accident and pulmonary emboli. At this point, the concern was raised that the patient might have Munchausen's syndrome. When the patient was confronted with these findings, he "fired" us as physicians and refused to answer any additional questions. He was ultimately transferred to an inpatient psychiatric hospital. Of note, serologic testing obtained during this hospitalization failed to confirm the presence of a Factor V Leiden mutation.

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