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CASE REPORT

Conservative Management of Intentional Dabigatran Overdose: Case Report and Review of the Literature

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Abstract

Background: Direct thrombin inhibitors and factor Xa inhibitors are gaining popularity as alternatives to warfarin for patients requiring anticoagulation. Toxicity due to these medications is difficult to manage because overdose experience is very limited and there is no clear guidance on when or whether to use antidote in this setting.
Case Presentation: A 50-year-old man with normal renal function ingested 10 to 25 tablets of dabigatran 150 mg. He denied any specific symptoms and had an unremarkable physical exam. No bleeding or bruising was noted and stool was guaiac negative on initial workup. Per recommendations from the Regional Poison Center, a single 100 g dose of activated charcoal was administered approximately three hours post-ingestion and the patient was admitted for monitoring. Baseline coagulation parameters of the patient (including aPTT) revealed coagulopathy. However, no sign of systemic or local hemorrhage was detected. Having received only supportive treatments during admission, aPTT restored to normal limits by hospital day 2. A dabigatran level revealed the drug to be almost completely eliminated by 34 hours after ingestion.
Discussion: Specific reversal agents for direct thrombin inhibitors are under final phases of development. The question of whether or not to use these antidotes is expected to come up in situations of accidental or intentional overdose with direct thrombin inhibitors. Similar to our observation, some scientists showed that dabigatran overdose can be managed conservatively with supportive treatments.
Conclusion: This case adds to the limited pool of literature regarding dabigatran overdose and outcomes, and suggests that a patient with an overdose of this magnitude may be safely managed without acute intervention. Literature review suggests that aPTT might be an appropriate method for monitoring anticoagulant effects related to this drug in the clinical setting.

Keywords: Antithrombins; Blood Coagulation Disorders; Dabigatran; Prescription Drug Misuse

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INTRODUCTION

Novel anticoagulants such as direct thrombin inhibitors (e.g. argatroban, dabigatran) and factor Xa inhibitors (e.g. rivaroxaban, apixaban) have found a niche in patients requiring anticoagulation; however, they have posed a new set of questions for health care providers and toxicologists because they are more difficult to monitor than warfarin, and moreover, specific reversal agents for them are still under development (1).

Dabigatran etexilate mesylate (commercially available as Pradaxa™) has been approved by the U.S. Food and Drug Administration since October 2010 for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (2). Later, in February 2011, the American College of Cardiology Foundation and American Heart Association added dabigatran to their guidelines for the same indications (3). Dabigatran is typically dosed twice daily without regard to meals, and is approximately 80% renally eliminated with a half-life in healthy subjects of 12-17 hours. Dose adjustments are required in renal impairment (4). During the first two years of introduction of dabigatran to the U.S. pharmaceutical market, 802 cases of overdose with this medicine were reported to the US National Poison Data System (5), accounting for 5% of exposures with anticoagulant medicines (n = 16044) in the same period (6,7).

Naturally, due to the inherent anticoagulant properties, poisoning and overdose with this class of medicines result in different extents of coagulopathy and hemorrhage. Bleeding related to dabigatran overdose is managed supportively with fluids, blood products, and concentrated blood factors as a last line option (8). Dabigatran is well removed by dialysis, although placement of a dialysis catheter in a patient with risk of severe bleeding is a concern (8). Recently, a specific antidote for dabigatran, idarucizumab, was approved, but has no specific indication for situations of dabigatran overdose (9). Overdose experience with dabigatran is very limited. In this paper, we present a case of successful management of

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acute dabigatran ingestion with supportive measures and close monitoring of coagulation parameters.

CASE PRESENTATION

A 50-year-old man with a history of atrial fibrillation and ischemic stroke presented approximately one hour after ingesting dabigatran 150 mg tablets in a suicide attempt. The patient estimated having ingested between 10-25 tablets. He had normal renal function and he had been taking dabigatran for two years prior to this event without incident. He denied taking any other medications in overdose and denied drinking alcohol. He stated that he had taken his other medications (pantoprazole, metoprolol, amlodipine, oxycodone) in their prescribed doses that morning. He denied any specific symptoms and had an unremarkable physical exam. No bleeding or bruising was noted and stool was guaiac negative on initial workup. Per recommendations from the Regional Poison Center, a single 100 g dose of activated charcoal was administered approximately three hours post-ingestion and the patient was admitted for monitoring.

Baseline coagulation parameters of the patient revealed impaired clotting (Table 1). However, no sign of systemic or local hemorrhage was detected. On the day following admission, the patient had a black stool which was attributed to the activated charcoal, although he also had a guaiac positive stool and a minor drop in hemoglobin/hematocrit. His hemoglobin/hematocrit were monitored every 8 hours and remained stable thereafter. No clinical symptoms associated with bleeding were observed. No blood product was given to the patient. The aPTT decreased to within normal range by hospital day 2. No significant adverse sequel occurred.

A dabigatran level was obtained 34 hours after presentation and was 11 ng/mL, well below levels expected in someone on just a therapeutic dose. The patient was discharged home 2 days after ingestion, having suffered no significant clinical effects from his overdose. He was restarted on dabigatran upon discharge.

DISCUSSION

This is a case of a patient with coagulopathy but no significant bleeding after dabigatran overdose. Unfortunately, the dabigatran level was drawn very late on this patient, and was not clinically useful. With a half-life of approximately 12 hours in adults with normal renal function (4), the majority of the dabigatran is expected to have been eliminated by the time our level was drawn. Thus, a correlation between the amount ingested, dabigatran level, and degree of anticoagulation is not possible in this case.

Assessing anticoagulation in patients with dabigatran overdose is a challenge. Douxfils et al recommended Hemoclot Thrombin Inhibitor® assay as the gold standard to evaluate anticoagulation due to dabigatran, but also stated that aPTT, with its wider availability, is a reasonable alternative (10). Thrombin Time (TT) was determined by two studies to be highly sensitive to dabigatran (10,11), although it is unlikely to be of use in acute overdose due to its exceeding the upper limit of detection at relatively low dabigatran levels. TT may be most useful for determining the presence of any dabigatran (i.e. ruling out dabigatran ingestion, such as a questionable pediatric ingestion or undifferentiated adult ingestion) (11). In any event, elevated coagulation values do not necessarily indicate risk for hemorrhage, as was observed in our patient.

A specific reversal agent for dabigatran was approved in November 2015 with an indication for uncontrolled or life/threatening bleeding or for patients requiring urgent procedures. Idarucizumab is a dabigatran-specific humanized monoclonal antibody fragment. It has been shown to rapidly reverse the anticoagulant effects of dabigatran after administration (9).

With a new antidote available, it will be important for healthcare providers to have data on which to base treatment decisions. The question of whether or not to use idarucizumab is expected to come up in situations of accidental or intentional overdose. Similar to our observation, some scientists showed that dabigatran overdose can be managed conservatively with supportive treatments (12,13). On the other side, some scientists recommended invasive interventions such as hemodialysis and plasmaphresis to accelerate drug elimination (8,14-16). Recombinant factor VIIa and prothrombin concentrate complexes are other therapeutic options proposed for dabigatran overdose (8,17,18).

Conway et al. reviewed 2.5 years of US National Poison Center data for dabigatran exposures and found that

Table 1. Coagulation and hematology parameters at various time points after ingestion

Parameter	Reference range	Time after ingestion		
		2.5 hours	17 hours	40 hours
aPTT (sec)	25.8-37.9	64.6	51.2	35.1
PT (sec)	9.2-12.3	17.0	-	-
INR	1-1.2	1.6	-	-
TT (sec)	11.7-15	>100.0	-	-
Hemoglobin (g/dL)	13.7-17.5	14.2	12.8	12.8
Hematocrit (%)	40-51	41	37	38

aPTT: activated Partial Thromboplastin Time; PT: Prothrombin Time; INR: International Normalized Ratio; TT: Thrombin Time

significant outcomes (coded as “major effect” or “death”) occurred in 4.5% of cases, most of which were related to adverse drug reactions as opposed to overdose (5). Only 1.3% of patients in the Conway study involved suicidal overdose, so applicability of results to such a population is limited. Interestingly, none of the 13 deaths reported involved intentional overdose (5). This further supports that patients with dabigatran overdose can benefit from favorable outcomes with conservative management and close monitoring rather than invasive interventions.

CONCLUSION

This case adds to the limited pool of literature regarding dabigatran overdose and outcomes, and suggests that a patient with an overdose of this magnitude may be safely managed without acute intervention. Literature review suggests that aPTT might be an appropriate method for monitoring anticoagulant effects related to this drug in the clinical setting.

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