Positive Outcome After Intentional Overdose of Dabigatran

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Abstract

Introduction Dabigatran (Pradaxa™), an orally active direct thrombin inhibitor, was approved by the United States Food and Drug Administration for the prevention of stroke in patients with atrial fibrillation in October 2010. Life-threatening consequences from dabigatran therapy include hemorrhage and bleeding complications, but they typically occur after renal impairment. We describe the first case report of intentional, acute overdose with dabigatran.

Case Report A 57-year-old woman with a medical history of depression and atrial fibrillation presented to the emergency department after ingesting 11.25 g of dabigatran in a suicide attempt. Despite an ecchymosis indicative of prior trauma, there was no evidence of acute bleeding. After receiving gastric lavage and activated charcoal therapy in the emergency department, she was admitted to the ICU. On presentation, dabigatran blood levels measured 970 ng/mL

and thrombin clot times measured above the testable limits (>120 s) until 52 h post-arrival. The remainder of her clinical course was uncomplicated, and the patient was transferred to an inpatient psychiatric unit for depression follow-up.

Discussion This case shows the clinical course of a patient with an acute, massive dabigatran overdose with no significant clinical consequences. Currently, there is no ideal method to monitor anticoagulation levels; there is no pharmacologic reversal method, and hemodialysis is an undesirable treatment option.

Keywords Pradaxa · Toxicity · Anticoagulation · Bleed · Hemorrhage

Introduction

Dabigatran etexilate mesylate (Pradaxa™), an orally active direct thrombin inhibitor, was approved by the United States Food and Drug Administration (FDA) for stroke prophylaxis in patients with atrial fibrillation in October 2010 [1]. Since then, it has also been used for the prevention of venous thromboembolism (VTE) after hip surgery and treatment of acute VTE. Formulations available include 75- and 150-mg capsules with standard therapy being 150 mg twice daily. Dabigatran represents a useful alternative to warfarin, which requires close outpatient monitoring due to its narrow therapeutic index, and low molecular weight heparin, which must be injected subcutaneously. Characteristics of dabigatran include peak plasma concentrations from 1 to 3 h, 35 % protein-bound, a 12–17h half-life depending on patient GFR, and elimination primarily through renal excretion (~85 % via urine) [2]. Pharmacologic strengths include a wide therapeutic index, oral pill formulation, and fast onset, while weaknesses include lack of reversal antidote and requirement of adequate renal function for drug elimination.

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The drug is converted to the active form through *in vivo* plasma and hepatic esterases and reversibly inhibits thrombin, the final step in the coagulation cascade.

One year after FDA approval, dabigatran has been prescribed 1.1 million times to treat over 371,000 patients in the USA [2]. While concern has grown over a growing number of anecdotal bleeding events, the FDA investigated the data 14 months after approval and preliminarily determined that there was no sufficient evidence of more frequent serious bleeding events compared to warfarin [2]. However, the FDA recommended further post-marketing surveillance.

There have been several documented cases of dabigatran-related bleeding complications, including intracranial hemorrhage after mild traumatic brain injury, spontaneous hemopericardium, postoperative bleeding complications, and significant GI bleeding after renal impairment [3–9]. Clinicians were neither armed with a reversal antidote nor with an evidence-based treatment protocol for managing the bleeding that was likely caused or exacerbated by dabigatran. The purpose of this case report is to describe a patient with acute, intentional dabigatran overdose who received conservative management that resulted in a positive outcome.

Case Report

A 57-year-old woman presented to the emergency department approximately 1 h after a suicide attempt by dabigatran and alprazolam overdose. The patient was the victim of intimate partner violence and proceeded to consume 75 dabigatran pills (a total of 11.25 g) and unknown quantities of alprazolam. The patient's medical history was notable for depression and atrial fibrillation. Her only outpatient medication was 100 mg metoprolol XL for atrial fibrillation rate control and 300 mg dabigatran for stroke prophylaxis. She had never had prior suicidal ideation.

On initial presentation, the patient somnolently reacted to voice and answered questions. Her Glasgow coma scale (GCS) was 14, blood pressure was 135/58 mmHg, heart rate was 72 beats per minute, respiration rate was 16 breaths per minute, temperature was 35.6 °C, and oxygen saturation was 100 % on room air. Over a 15-min period, the patient's mental status declined to a GCS of 4 (eyes opened to pain but no verbal or motor response). Naloxone was administered, but the patient's GCS did not improve. The patient underwent rapid sequence intubation for airway protection. A secondary survey for trauma was remarkable for old ecchymoses over her left eye, bilateral upper and lower extremities, and anterior chest wall and upper back—evidence of prior intimate partner violence. Skeletal survey showed no evidence of fracture or displacements. There were no signs of acute bleeding. The patient underwent

CT imaging of the head, cervical spine, abdomen, and pelvis, all of which were negative for acute findings.

Laboratory studies were obtained as follows: hemoglobin and hematocrit were 13.4 g/dL and 39 %, normal electrolyte panel except for creatinine of 1.5 mg/dL (reference range 0.4–1.0) with no previous baseline, glucose of 84 mg/dL (reference range 70–170), and normal liver function tests. Prothrombin time (PT) was 15.9 s (reference range 9.5–13.1), international normalized ratio (INR) was 1.3 (reference range 0.9–1.1), and activated partial thromboplastin time (aPTT) was 48.8 s (reference range 26.8–37.1). Thrombin clot time (TCT) registered above the testable limit at >120 s (reference range 16.6–24.3). Initial serum dabigatran level, a sendout laboratory test, was 970 ng/mL. Urine toxicology panel was positive for benzodiazepines. A 12-lead ECG revealed a normal sinus rhythm, with a pulse rate of 87 beats per minute and normal waveforms and intervals without an R' in the aVR lead.

Hematology specialists and the regional Poison Control Center were contacted for management recommendations. The patient received an orogastric tube for particle lavage and gastric decontamination with activated charcoal therapy. Renal specialists were consulted for consideration of prothrombin complex concentrate (PCC) administration or hemodialysis to decrease the blood dabigatran level. Because there were no acute signs of bleeding in the patient, the treatment team decided against hemodialysis or PCC administration. The patient was transferred to the medical intensive care unit for close monitoring.

Throughout the hospital course, the patient's TCT was measured serially as a surrogate marker for anticoagulation. The TCT remained above the test upper bound (>120 s) until 52 h post-arrival. At that time, the TCT was 94.2 s and continued to downtrend to 72.7 s at 71 h post-arrival. Daily hemoglobin and hematocrit levels showed no significant changes, and no blood loss or signs of hematoma were observed. After 4 days of inpatient monitoring, the patient was transferred to the inpatient psychiatry unit for suicide and depression follow-up.

Discussion

There are two difficulties when dealing with the management of acute dabigatran overdose: accurately measuring the degree of anticoagulation and reducing the level of anticoagulation. In this early stage of novel anticoagulant therapy, the lack of compelling data complicates clinical decision making. It is still unclear whether the risks outweigh the benefits of rapidly lowering dabigatran anticoagulation in different patient scenarios.

Standard coagulation laboratory tests such as PT, INR, and PTT are typically unreliable when measuring the

anticoagulation levels of patients receiving dabigatran [10, 11]. Studies indicate that plasma-diluted thrombin time assay, ECT, TCT, and aPTT are useful for confirming the degree of anticoagulation [12]. This patient consumed 38 times her daily dose (11.25 g vs. 300 mg) and arrived with a dabigatran level equal to 970 ng/mL. While loading doses of up to 600 mg have been administered without major bleeding events, in a 7-day trial of healthy adults, a 300-mg dose per day corresponded with plasma concentration=130 ng/mL [13]. The dabigatran blood level is a sendout test and thus offers minimal diagnostic utility in the acute setting. Within many emergency departments, only TCT and aPTT are rapidly accessible, but no study shows the relationship between the results of these tests and the risk of clot formation. TCT is a highly sensitive test for determining the degree of anticoagulation, but it was not useful in trending high levels of anticoagulation (as exhibited in our patient), and aPTT has a nonlinear dose dependence curve, making it unreliable in determining the precise level of anticoagulation [11, 14, 15]. With no standard monitoring studies available to determine the extent of anticoagulation, it is difficult for the clinician to determine if decreasing the levels of dabigatran serum is even necessary. We were able to monitor the trend using TCT, but results remained above the test upper bound for more than 2 days after the initial overdose. As more physicians utilize dabigatran for their patients, further studies are required to identify laboratory tests that may aid in clinical decision making.

In acute overdose situations, the true history of the present illness must rely on bystander and emergency medical service (EMS) reports. The information presented by EMS regarding the acuity of dabigatran ingestion for this patient led the treatment team down the clinical path of attempting to neutralize the dabigatran prior to absorption. In vitro models show that activated charcoal can neutralize >99.9 % of dabigatran after 2 h [16]. These tests, though purely in vitro, may suggest that oral activated charcoal could neutralize dabigatran prior to gut absorption if given close to ingestion time. While gastric lavage was performed in this patient, it is not traditionally recommended in the management of poisoned patients [17]. However in 2012, the Thrombosis and Hemostasis Summit of North America released an expert opinion in support of gastric lavage and/or oral activated charcoal if given within a couple of hours of ingestion for dabigatran toxicity after recent overdose [18]. The clinical intent to reduce drug absorption drove the decision to recommend gastric lavage and oral activated charcoal; however, direct impact and efficacy of this protocol remains unclear. More conservative management options such as close observation could be considered in the future.

The treatment efficacy of dabigatran toxicity with blood products and factors is not well established. Some clinicians have utilized fresh frozen plasma (FFP), recombinant activated factor VIIa (rFVIIa), or PCC to varying degrees of

success [4, 18]. In vitro studies reveal conflicting efficacy results for the use of rFVIIa in reversing dabigatran anticoagulation [18]. Studies in healthy humans demonstrate PCC to have no effect on reversal of dabigatran activity, although in vivo mouse studies show PCC to be effective in preventing hematoma expansion and decreasing bleed time [18, 19]. In a mouse model, data suggested that FFP may be effective in decreasing dabigatran-associated serious bleeding, but further studies are required to correlate to human use [19]. With many conflicting data reports, as to which blood coagulation products are most efficacious in the bleeding patient on dabigatran remains unclear.

Hemodialysis has been shown to be efficacious in reducing dabigatran anticoagulation in trials, and it was successful in reducing hemorrhage in a postoperative cardiac patient on therapeutic levels of dabigatran [9]. Hemodialysis studies in patients with end-stage renal disease on dabigatran showed a drug blood level concentration decrease by 62 % at 2 h and an additional 68 % decrease at 4 h [20]. However, the initiation of dialysis access in an anticoagulated patient may cause further bleeding complications, and the decision to dialyze a non-bleeding or minor bleeding dabigatran overdose patient requires further debate. In our patient, no complications or bleeding complications were measured even in the setting of prior mild trauma and acute dabigatran overdose.

If the patient arrives to the Emergency Department soon after treatment, oral activated charcoal therapy can be considered to decrease drug gut absorption. With the lack of a primary dabigatran reversal antidote and only the presence of inconclusive data regarding blood product transfusion, the clinician can consider rFVIIa and PCC. Hemodialysis has been shown to be effective to decrease dabigatran anticoagulation. Nevertheless, conservative management can be considered if the patient is clinically stable without signs of uncontrollable bleed. This case report shows an example of a patient with acute, severe dabigatran overdose who was provided supportive care only and developed no bleeding complications.

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