CASE REPORT

Fatal gastrointestinal hemorrhage after a single dose of dabigatran

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Introduction. Dabigatran (Pradaxa) is a new oral anticoagulant approved by the Food and Drug Administration (FDA), available internationally and indicated as an alternative to warfarin for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Dabigatran does not require laboratory monitoring and its kinetics allow for a more rapid onset of action with a time to peak concentration of 1.25–1.5 h. We are reporting a fatality resulting from gastrointestinal bleeding after the ingestion of a single dose of dabigatran 150 mg. Case details. A 92-year-old man with a medical history of chronic obstructive pulmonary disease, hypothyroidism, and atrial flutter presented to the emergency department with complaints of weakness and rectal bleeding. He was seen by his Cardiologist the day before and was found to be in new atrial fibrillation. He was prescribed dabigatran 150 mg twice daily for anticoagulation therapy. He took one dose of dabigatran 150 mg at 2200 and woke up the following morning before 0900 with profuse rectal bleeding. The initial vital signs in the emergency department, approximately 11 h after ingestion, were heart rate 72 beats/min, blood pressure 62/30 mmHg, and lab work showed hemoglobin 9.9 g/dL, international normalization ratio (INR) 1.99, blood urea nitrogen (BUN) 66 mg/dL, and creatinine (SCr) 1.4 mg/dL. (creatinine clearance (CrCl) 24.2 mL/min). He was resuscitated with intravenous fluids, two units of packed red blood cells, two units of fresh frozen plasma, platelets, and vitamin K 10 mg intravenously. He was also given an unknown dose of erythromycin early in his hospital stay. An actively bleeding gastric ulcer was discovered and treated with local epinephrine injections. Approximately 48 h after his exposure, he received an additional two units of blood to treat his decreasing blood pressure (98/41 mmHg). On day three, his hemoglobin and hematocrit were stable at 10 g/dL and 30%, INR 1.6, he was extubated and off vasoactive medications. Day six of hospitalization, he began having maroon stools, his hemoglobin decreased to 8.1 g/dL and his platelets to 81 × 10⁰/mL. On day seven, the hemoglobin decreased to 6.4 g/dL. Despite aggressive resuscitative efforts and supportive care, he died. Discussion. This case demonstrates the potential of a single dose of dabigatran 150 mg to result in a fatal gastrointestinal hemorrhage. This patient was started on the maximum dose with a CrCl 33.9 mL/min and on admission CrCl 24.2 mL/min, suggesting underlying renal insufficiency.

Keywords Pradaxa; Gastrointestinal hemorrhage; Gastric ulcer; Renal insufficiency; Anticoagulation

Introduction

Dabigatran (Pradaxa) is a new oral anticoagulant approved by the Food and Drug Administration (FDA) on October 19, 2010.¹ It is available internationally and indicated as an alternative to warfarin for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.² Unlike warfarin, dabigatran does not require laboratory monitoring and its kinetics allow for a more rapid onset of action with a time to peak concentration of 1.25–1.5 h.³ Studies have shown noninferior effectiveness compared to warfarin.⁴ In patients ≥75 years, the risk of bleeding is greater with dabigatran when compared to warfarin (5.1% vs. 4.3%, respectively).⁵ Since the drug’s release, 50 deaths have been attributed to its use.⁶ We are reporting a fatality resulting from gastrointestinal bleeding after the ingestion of a single dose of dabigatran 150 mg.

Case details

A 92-year-old man with a medical history of chronic obstructive pulmonary disease, hypothyroidism, and atrial flutter presented to the emergency department with complaints of weakness and rectal bleeding. He was seen by his Cardiologist the day before and was found to be in new atrial fibrillation. He was prescribed dabigatran 150 mg twice daily for anticoagulation therapy. He took one dose of dabigatran 150 mg at 10 pm and woke the following morning before 9 am with profuse rectal bleeding. The initial vital signs in the emergency department, approximately 11 h after ingestion, were heart rate 72 beats/min, blood pressure 62/30 mmHg, and lab work showed hemoglobin 9.9 g/dL, international
normalization ratio (INR) 1.99, blood urea nitrogen (BUN) 66 mg/dL, and creatinine (SCr) 1.4 mg/dL (creatinine clearance (CrCl) 24.2 mL/min). He was resuscitated with intravenous fluids, two units of packed red blood cells, two units of fresh frozen plasma, platelets, and vitamin K 10 mg intravenously. He was also given an unknown dose of erythromycin early in his hospital stay.

He was started on an esomeprazole continuous drip and an emergency gastric endoscopy was performed. An actively bleeding gastric ulcer was discovered and treated with local epinephrine injections. Approximately 20 h after the exposure, his blood pressure was 85/40 mmHg, heart rate 90 beats/min and the hemoglobin and hematocrit were 7.4 g/dL and 22%. Being hemodynamically unstable, he remained intubated and was placed on norepinephrine and vasopressin continuous infusions. Approximately 48 h after his exposure, he received an additional two units of blood to treat his decreasing blood pressure (98/41 mmHg). On day three, his hemoglobin and hematocrit were stable at 10 g/dL and 30%, INR 1.6, he was extubated and off vasoactive medications. Dialysis was not considered for this patient at the time based on the medications short half-life (12 h) and the instability at presentation.

Day 6 of hospitalization, he began having maroon stools, his hemoglobin decreased to 8.1 g/dL and his platelets to 81 × 1000/mcL. On day 7, the hemoglobin decreased to 6.4 mg/dL. Despite aggressive resuscitative efforts and supportive care he died.

Discussion

This case demonstrates the potential of a single dose of dabigatran 150 mg to result in a fatal gastrointestinal hemorrhage. The manufacturer recommends a lower dose of 75 mg twice daily for patients with creatinine clearance (CrCL) 15–30 mL/min. This patient was started on the maximum dose with a CrCl 33.9 mL/min and on admission CrCl 24.2 mL/min, suggesting underlying renal insufficiency, which could have been expected in a person of this advanced age.

Dabigatran is a p-glycoprotein transporter substrate; therefore, concurrent administration of a p-glycoprotein inhibitor prolongs the effects of dabigatran. This patient had been on propafenone when he took dabigatran; after admission he was started on erythromycin. Both of these p-glycoprotein inhibitors may have contributed to the prolonged anticoagulation but the extent of this interaction is not known. The patient did not receive any known p-glycoprotein inducers at home or during his hospital stay.

Below, you will find the list of medications the patient was prescribed for home use. Propafenone 225 mg orally twice daily, prednisone 10 mg orally once daily, dabigatran 150 mg orally twice daily, omeprazole 20 mg orally once daily, digoxin 0.125 mg orally once daily, finasteride 5 mg orally once daily, tiotropium inhaled once daily, synthroid 0.100 mg orally once daily, fluticasone/salmeterol inhaled two puffs twice daily, folic acid 1 mg orally once daily.

In reviewing his home medications, he was on prednisone, fluticasone/salmeterol and omeprazole. Steroid therapy is known to cause gastritis and intestinal bleeding. This patient was on chronic proton pump inhibitor therapy and had a gastric ulcer. Despite dabigatran’s therapeutic effect and adverse effects being noninferior when compared with warfarin, the randomized evaluation of long-term anticoagulation therapy (RE-LY) trial demonstrated a significantly higher risk of gastrointestinal bleeding in the dabigatran group (17% dabigatran vs. 6% warfarin). Because of the grave potential if a bleed occurs, we believe that baseline renal function and occult stool studies should be performed prior to initiation of this medication.

There is no antidote for dabigatran. Patients should be given supportive therapy of vasopressors, blood products, fluid resuscitation, and bleeding site repair. Dabigatran is 30% protein bound with a volume of distribution of 50–70%, making it 60% dialyzable. Other possible interventions include the administration of recombinant activated factor VIIa or activated prothrombin complex concentrate but they have shown mixed results.

No reliable laboratory studies determine coagulation derangement related to dabigatran nor is it possible to obtain dabigatran blood concentrations in a reasonable time frame. Prothrombin time (PT) and activated partial thromboplastin time are insensitive at therapeutic doses. The INR can be elevated secondary to higher amount of inactive Factor VII, seen during toxicity but it is not specific to dabigatran.

In this case, the INR ranged from 1.1 to 1.73 after admission and his liver function tests were normal. Thrombin time (TT) is a more sensitive indicator to determine the presence of dabigatran activity but is often too sensitive to determine toxicity. Ecarin clotting time (ECT) may provide more sensitive and linear response to dabigatran but is not FDA approved for patient care and unavailable for routine testing.

The single dabigatran 150 mg dose may have interacted with the P-glycoprotein inhibitor (propafenone) to cause an increase in dabigatran concentrations. This, combined with his underlying renal dysfunction (CrCl 33.9) resulted in an increase in unchanged dabigatran causing his existing gastrointestinal bleed to persist uncontrollably and his eventual death 7 days later.

In older patients, who have renal insufficiency, potential for gastrointestinal bleed; the advantage over warfarin does not outweigh the risk of fatal bleeding and coadministration should be avoided with p-glycoprotein inhibitors.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

References


2. Product Information: PRADAXA(R) oral capsules, dabigatran etexilate mesylate oral capsules. Boehringer Ingelheim Pharmaceuticals, Inc.