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MANAGEMENT OF DABIGATRAN-ASSOCIATED INTRACEREBRAL AND INTRAVENTRICULAR HEMORRHAGE: A CASE REPORT

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☐ **Abstract—Background: Dabigatran is an oral, reversibly bound, direct thrombin inhibitor currently approved in the United States for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. In the phase III trial leading to approval of the agent, the incidence of life-threatening bleeding was 1.80%/year in the dabigatran 150 mg twice daily arm. Because there is no direct antidote or reversal agent for this drug, the need to manage life-threatening hemorrhages with procoagulant products will arise. Objective: To describe a case of dabigatran-associated intracerebral and intraventricular hemorrhage and subsequent management with activated prothrombin complex concentrate. Case Report: An 85-year-old man currently taking dabigatran 150 mg twice daily presented to the Emergency Department for incoordination, expressive aphasia, and weakness. A computed tomography image of his head demonstrated an intracranial hemorrhage. The last dose of dabigatran was approximately 14 h prior to arrival, and conventional coagulation assays (thrombin time and activated partial thromboplastin time) confirmed the presence of dabigatran in the patient's serum. The patient received 27.5 units/kg of activated prothrombin complex concentrate (FEIBA®; Baxter Healthcare Corporation, Deerfield, IL) after an initial intravenous fluid bolus. His activated partial thromboplastin time was not completely normalized by the use of FEIBA; however, the patient's neurological examination slightly improved and remained stable throughout his hospital course despite some intraventricular expansion of the hematoma. After discharge to physical rehabilitation, the patient developed an ischemic cerebrovascular accident and was discharged home on hospice. Conclusion: Due to lack of an available antidote, activated prothrombin complex concentrate was utilized as a nonspecific procoagulant to stabilize an intracerebral hemorrhage in a patient on dabigatran.** © 2014 Elsevier Inc.

☐ **Keywords—dabigatran; intracerebral hemorrhage; anticoagulation reversal; FEIBA; ischemic stroke**

INTRODUCTION

Dabigatran (Pradaxa®, Boehringer-Ingelheim, Ridgefield, CT) was the first novel oral anticoagulant alternative to vitamin K antagonists for the treatment and prevention of thromboembolic disease to be approved by the United States (US) Food and Drug Administration. This approval was based on data that demonstrated the superiority of dabigatran 150 mg twice daily over international normalized ratio-adjusted warfarin in preventing stroke or systemic embolism (1). The overall prevalence of major bleeding was not statistically different between the dabigatran group and the warfarin group (3.11%/year vs. 3.36%/year; $p = 0.31$); however, life-threatening bleeding, including intracerebral hemorrhage, was reduced with the use of dabigatran, compared to warfarin (1.45%/year vs. 1.80%/year; $p = 0.04$) (1). The incidence of bleeding may be reduced with the use of dabigatran, but the number is not nil, thus, it will be necessary to manage life-threatening bleeding events. Unlike warfarin, there is no

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specific antidote to reverse the coagulopathy associated with dabigatran (2).

Although animal data and small studies in healthy volunteers provide some direction to clinicians attempting to manage patients on dabigatran who present with life-threatening bleeding, there are few published reports of actual hemorrhaging patients managed with a procoagulant agent (3–18). In this case report, we present our experience managing a patient with an intracerebral hemorrhage currently taking dabigatran.

CASE REPORT

An 85-year-old, 75-kg man was brought to the Emergency Department (ED) for progressive right-sided weakness, paresis, and aphasia. His past medical history was significant for atrial fibrillation, hypertension, coronary artery disease, and a transient ischemic attack 2 weeks prior to admission ($CHADS_2$ = 4, HAS-BLED = 3) (19). After the transient ischemic attack, the patient was converted from rivaroxaban to dabigatran 150 mg twice daily. Other home medications included atorvastatin 10 mg daily, losartan-hydrochlorothiazide 50–12.5 mg daily, and omeprazole 20 mg daily. On the evening of presentation, the patient developed right-hand incoordination and weakness, which progressed to expressive aphasia. His last dose of dabigatran was approximately 14 h prior to arrival.

On arrival to our ED, the patient underwent computed tomography (CT) scanning of his head. This revealed an acute left basal ganglia and thalamic hemorrhage approximately 2.5 cm in diameter with mild left-to-right midline shift. His neurological examination at this time was pertinent for severe expressive and conductive aphasia, mild right facial droop, limited arousability, and no movement or resistance in either right arm or leg. His initial Glasgow Coma Scale (GCS) score was 9 (eye 3, verbal 2, motor 4), blood pressure was 182/98 mm Hg, and pulse 69 beats/min. Coagulation assays revealed a fibrinogen of 310 mg/dL, an activated partial thromboplastin time (aPTT) of 45.7 s (upper limit of normal 35.4 s), and a thrombin time (TT) of 195.6 s (upper limit of normal 20 s). His hemoglobin and hematocrit were 15.3 mg/dL and 43.5%, respectively, and his serum creatinine was 0.9 mg/dL, with an estimated creatinine clearance of 60 mL/min.

Due to his recent dabigatran exposure and coagulation assays consistent with dabigatran, the emergency physician initiated our dabigatran reversal protocol. A 1-L intravenous sodium chloride 0.9% bolus was rapidly administered. He then received 2064 units (27.5 units/kg total body weight) of activated prothrombin complex concentrate (APCC) (FEIBA®, Baxter Healthcare Corporation, Deerfield, IL) as nonspecific procoagulant to reverse the effects of dabigatran. The dose recommended in our dabigatran reversal protocol is 25 units/kg rounded up to the nearest vial size(s), which resulted in the 2064-unit dose. The patient received no other hemostatic agents or blood products. Dialysis was not initiated, as the patient maintained adequate urine output (0.65–1 mL/kg/h).

Over the next 12 h, the patient became more arousable, however, his neurological deficits remained unchanged. His blood pressure was managed with intermittent intravenous hydralazine and enalaprilat and ranged from systolic blood pressures 162–183 mm Hg over diastolic blood pressures 70–100 mm Hg. His aPTT decreased slightly to 39.4 s when measured 7.5 h after APCC administration. Hemoglobin and hematocrit did not change during hospitalization. A follow-up CT scan, obtained 10 h after the initial scan on hospital day 1, showed mild increase in the size of the left basal ganglia hematoma, with a small amount of blood dissecting into the lateral ventricles. Blood pressure control (goal systolic blood pressure < 150 mm Hg) was obtained over the following 24 h and a CT scan performed on the morning of hospital day 2 showed stabilization of the hematoma. The patient's GCS remained between 9 and 11. He never required mechanical ventilation or neurosurgical intervention, but he did require percutaneous gastrostomy tube placement due to unresolved dysphagia. After 6 days, the patient was discharged to intensive inpatient physical rehabilitation.

Seven days after admission to inpatient rehabilitation (total hospital day 13), the patient developed increased confusion and lethargy. A CT scan of the head was obtained, which revealed a new left middle cerebral artery stroke. Due to the new ischemic cerebrovascular insult, the patient's family wished to pursue hospice, and the patient was discharged with hospice after a 15-day hospitalization.

DISCUSSION

Major, life-threatening, or fatal hemorrhage is one of the most feared adverse effects of anticoagulation therapy. Until recently, the only oral anticoagulants available were vitamin K antagonists. The use of agents like warfarin is somewhat more cumbersome than the newer oral anticoagulants; however, the effect of warfarin can be rapidly neutralized by a direct antidote – vitamin K and infusion of vitamin-K-dependent clotting factors (20). This had led to evidence-based recommendations on the management of vitamin K antagonist-related hemorrhages (20–22). On the other hand, dabigatran has no direct antidote and the ability to rapidly eliminate the drug's effect does not currently exist (2). Therefore, practitioners have sought to use available nonspecific procoagulant products in an attempt to manage dabigatran-related hemorrhages (3–18).