Dabigatran Etexilate Linked to Fatal Gastrointestinal Hemorrhage

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Thrombotic events remain a common cause of morbidity and mortality in the elderly population. As a result, thrombotic prophylaxis is an essential component of therapy. Older generations of anticoagulants have been associated with bleeding complications and poor patient compliance. In contrast, recent literature has shown dabigatran etexilate (Pradaxa®, Boehringer Ingelheim, Ridgebury, CT, USA), a newer drug, to have a side effect profile and efficacy similar to that of currently prescribed oral anticoagulants [1]. Moreover, the RE-LY study showed that compared to warfarin, dabigatran is associated with a lower incidence of stroke and thromboembolism in patients with atrial fibrillation.

Dabigatran etexilate is an oral prodrug that acts directly on thrombin via competitive inhibition. It is available in two doses, 110 mg and 150 mg, both taken twice daily. Owing to its predictable pharmacokinetics that does not require follow-up coagulation studies [2], dabigatran has become an attractive drug for patients with nonvalvular atrial fibrillation. Additionally, the risk of hemorrhage is decreased with the 110 mg dose, making it a suitable option for the elderly population. Over the past year, however, several case reports have documented severe bleeding associated with dabigatran use [3]. In most cases, prolonged prothrombin time had not been documented. Additionally, the recommendations for monitoring coagulation parameters following dabigatran administration do not cite PT as a suitable marker of the drug's efficacy [4]. In this report, we describe a 91 year old patient with prolonged PT and activated partial thromboplastin time who had been treated with dabigatran etexilate and died because of gastrointestinal hemorrhage.

PATIENT DESCRIPTION

In September 2012, a 91 year old woman was referred to our department for syncope and weakness. The patient had been prescribed dabigatran in June 2012 for presumably sick sinus syndrome with atrial fibrillation events. Her past medical history included dementia, chronic anemia, ischemic heart disease, congestive heart failure, type II diabetes, hypertension, a previous stroke, and a permanent cardiac pacemaker. On admission, the patient presented with altered mental status and was disoriented. Vital signs included temperature 36.5°C, blood pressure 100/60 mmHg, pulse 78 beats/minute and regular, weight 62 kg, and height 162 cm.

She appeared pale and slightly jaundiced with mild hematomas on her face. Lungs were clear to auscultation with vesicular breath sounds. On cardiac examination, a grade II/VI systolic murmur was heard in all areas of auscultation. Abdominal examination revealed no abnormalities. Peripheral vascular exam demonstrated bilateral +2 pitting edema. Digital rectal examination showed the presence of fecaliths without active bleeding, but according to the patient's caretaker she had had several recent black stools. Laboratory analyses on admission to the internal medicine ward were within normal limits, with the exception of hemoglobin 5.5 g/dl (normal 12–16), hematocrit 15.5% (normal 37–47), red blood cells 1.86 M/µl (normal 0–5.40), red blood cell distribution width 15.7% (normal 11.5–14.5%), urea 207 mg/dl (normal 10–50, baseline 100), creatinine 2 mg/dl (normal 0.5–1.2, baseline 1.5), glucose 324 mg/dl (normal 70–100), PT 44.4 sec (normal 12–18), and aPTT 69 sec (normal 21–32). Blood and urine cultures were taken. Urinalysis was negative for leukocytes, but urine cultures were positive for Enterococcus. Blood cultures were negative.

The patient was hospitalized for 7 days. During this time, her blood pressure remained low. Her PT, which was elevated at 44 seconds on admission, improved to 15.7 sec during the hospital stay. Importantly, at the time coagulation studies were done there had been no administration of anticoagulants other than dabigatran. Her hemoglobin level increased and remained stable at 9 mg/dl. It did not increase further despite multiple blood transfusions. Digital rectal examination did not reveal any signs of active bleeding until 2 days before she died. The patient received whole blood, vitamin K, and fresh frozen plasma in an attempt to restore circulating blood volume. Gastroenterology consultation determined that in view of the patient's condition diagnostic procedures would not be appropriate. The most likely site

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PT = prothrombin time

aPTT = activated partial thromboplastin time

of bleeding was presumed to be the small intestine or the proximal ascending colon.

On day 7 of hospitalization, she developed a fever of 39.9°C and her hemoglobin decreased to 6 mg/dl. Coagulation studies were not available at the time due to laboratory technical difficulties. A digital rectal exam revealed melena. The patient was treated with blood transfusions and amoxicillin/clavulanic acid. A chest X-ray showed an infiltrate in the base of the left lung, which was likely nosocomial in etiology. Blood cultures were positive for *Staphylococcus aureus*. Later that day, the patient died due to hemorrhagic and septic shock.

COMMENT

Our case raises several issues with regard to the prescription of dabigatran and demonstrates that this medication should be used with caution. Our patient was 91 years of age, 20 years older than the average patient studied in the RE-LY trial. That study demonstrated that patients over the age of 75 years had an increased risk of bleeding with doses of 110 mg and 150 mg compared to warfarin [1]. Secondly, with regard to drug clearance, the elimination half-life of dabigatran is twice as long in patients with severe renal impairment as in those without [3]. Using the Cockcroft-Gault formula, our patient's creatinine clearance was 23.9 ml/min, indicating markedly reduced function, classifying her as having stage 4 chronic renal failure. According to current international guidelines, creatinine clearance < 30 ml/min is an absolute contraindication for prescribing dabigatran. Given the significantly reduced creatinine clearance in our patient, this case emphasizes the need for caution when prescribing dabigatran to patients with decreased glomular filtration rate. Furthermore, despite the fact that vitamin K, fresh frozen plasma and packed red blood cells improved her PT to within normal limits, she continued to have melena. These measures were not sufficient to counter the patient's blood loss. As expected from the mechanism of action of dabigatran, all coagulation parameters are affected by thrombin inhibition. However, the literature does not recommend monitoring PT in patients taking the medication. As evident in this case, dabigatran greatly prolonged the PT, suggesting that PT can be a useful and necessary measure, particularly in elderly patients and those with renal impairment. Significantly prolonged PT may be an indication of excessive anticoagulation and should be used as a monitor to avoid adverse bleeding events. The literature suggests that dabigatran is a suitable anticoagulant for patients with healthy functioning kidneys, but our experience indicates it may not be as safe in elderly patients with impaired renal excretion. In light of the increasing incidence of dabigatran-related bleeding events, we call for more stringent and clearer guidelines for dabigatran use, taking into account the frail elderly and those with impaired renal function.

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