Dabigatran Etxelilate 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 non-valvular 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 Additionally, the recommendations for monitoring coagulation parameters following dabigatran administration do not cite PT as a suitable marker of the drug’s efficacy [4].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...
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 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 function. 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.

**References**


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**Capsule**

**Plasmodium genetic loci linked to host cytokine and chemokine responses**

Both host and parasite factors contribute to disease severity of malaria infection; however, the molecular mechanisms responsible for the disease and the host-parasite interactions involved remain largely unresolved. To investigate the effects of parasite factors on host immune responses and pathogenesis, Pattaradilokrat and team measured levels of plasma cytokines/chemokines (CCs) and growth rates in mice infected with two *Plasmodium yoelii* strains having different virulence phenotypes and in progeny from a genetic cross of the two parasites. Quantitative trait loci (QTL) analysis linked levels of many CCs, particularly IL-1β, IP-10, IFNγ, MCP-1 and MIG, and early parasite growth rate to loci on multiple parasite chromosomes, including chromosomes 7, 9, 10, 12 and 13. Comparison of the genome sequences spanning the mapped loci revealed various candidate genes. The loci on chromosomes 7 and 13 had significant (*P < 0.005*) additive effects on IL-1β, IL-5 and IP-10 responses, and the chromosome 9 and 12 loci had significant (*P = 0.017*) interaction. Infection of knockout mice showed critical roles of MCP-1 and IL-10 in parasitemia control and host mortality. These results provide important information for a better understanding of malaria pathogenesis and can be used to examine the role of these factors in human malaria infection.

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