Hemorrhagic Complications in Emergency Department Patients Who Are Receiving Dabigatran Compared With Warfarin

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Study objective: Dabigatran is a reversible direct thrombin inhibitor recently approved for stroke prevention in patients with atrial fibrillation. An increasing number of patients receiving dabigatran present to the emergency department (ED) with bleeding complications. Unlike vitamin K antagonists, there are no accepted reversal agents for dabigatran and the data on course and management of bleeding complications are limited. The study objective is to describe the course of bleeding complications in patients admitted through the ED who are prescribed dabigatran in comparison with warfarin therapy.

Methods: This was a prospective observational study of ED patients under treatment with dabigatran or warfarin who were admitted with bleeding complications during a 6-month period. Patient demographics, laboratory results, bleeding site, interventions, and outcomes are reported.

Results: There were 15 and 123 patients admitted with dabigatran and warfarin-induced bleeding complications, respectively. Of the warfarin patients, 25 charts were randomly chosen for extraction. Patients with dabigatran-induced bleeding had a shorter length of stay (3.5 versus 6.0 days) and were older (77 versus 70 years). Patients receiving dabigatran were more likely to have gastrointestinal bleeding (80% versus 48%) and less likely to have intracranial bleeding (0% versus 32%) than those receiving warfarin. Of patients with dabigatran-induced bleeding, 53% presented with an acute kidney injury.

Conclusion: Our patients with dabigatran-induced bleeding had a more benign clinical course with a shorter length of stay compared with patients with warfarin-induced bleeding. As was the case in previous published reports, there were fewer intracranial hemorrhages in patients receiving dabigatran than warfarin. Sustaining an acute kidney injury potentially predisposes patients to bleeding while receiving dabigatran. [Ann Emerg Med. 2013;61:475-479.]

Please see page 476 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Importance

Dabigatran etexilate (Pradaxa) is a competitive direct thrombin inhibitor approved by the Food and Drug Administration in October 2010 for the prevention of embolic stroke in patients with atrial fibrillation. Use of dabigatran is increasing in the United States because of its ease of dosing and lack of need for monitoring. Further, the US anticoagulant market is expected to increase to more than $9 billion in 2014, from $6 billion in 2008. Direct thrombin inhibitors and factor Xa inhibitors are expected to compose more than half of this market.[1]

Background

Dabigatran has several characteristics that may make it preferable to warfarin. It does not undergo CYP 450 hepatic metabolism, so drug-drug and drug-food interactions are uncommon. The drug has standard, twice daily dosing and requires no international normalized ratio monitoring. Dabigatran has a short elimination half-life of 12 to 17 hours; however, it primarily undergoes renal elimination. Therefore, sustaining an acute kidney injury without altering the dose leads to increased serum dabigatran concentrations that may predispose the patient to bleeding.

Despite these potential advantages, little is known about the clinical course or optimal management of dabigatran-induced bleeding complications.[2] Additionally, there is no accepted reversal agent. There have been several recent reports describing clinical experiences with patients with bleeding in the setting of dabigatran use.[3,4] However, no study has yet examined the presentation, patterns of bleeding, and treatment course for emergency department (ED) patients admitted with hemorrhagic complications of dabigatran therapy. As dabigatran usage increases, emergency physicians are likely to encounter patients experiencing bleeding complications from it.

Editor's Capsule Summary

What is already known on this topic

Little is known about the clinical course or optimal management of dabigatran-induced bleeding complications.

What question this study addressed

The clinical characteristics of 40 patients presenting with dabigatran- or warfarin-related bleeding were compared in prospective observational study.

What this study adds to our knowledge

Patients with dabigatran-induced bleeding had a shorter hospitalization (3.5 versus 6.0 days). Dabigatran patients were more likely to have gastrointestinal bleeding (80% versus 48%) and less likely to have intracranial bleeding (0% versus 32%) than those receiving warfarin. Of patients with dabigatran-induced bleeding, 53% presented with an acute kidney injury.

How this is relevant to clinical practice

Although no immediate change in management is warranted, it is reasonable to monitor patients treated with dabigatran for deterioration of renal function.

Goals of This Investigation

We sought to describe our institution's experience with bleeding complications in patients admitted through the ED who are prescribed dabigatran in comparison with bleeding complications of warfarin therapy.

MATERIALS AND METHODS

Study Design and Setting

The study was a prospective cohort chart review of consecutive adult patients admitted through the ED with either dabigatran or warfarin on their medication list and a primary ED admitting diagnosis involving any type of hemorrhage. The study was conducted at an urban academic tertiary care hospital with 57,000 annual ED visits between June and December 2011. This protocol was approved by the institutional review board at the study institution.

Selection of Participants

We received a computer-generated daily report of all patients admitted with either dabigatran or warfarin on their medication reconciliation record. We reviewed the primary ED admitting diagnoses of these patients and included those whom the primary chart reviewer deemed had a hemorrhagic diagnosis (ie, included wording such as "hemorrhage" or "bleed").

Table 1. Definitions of bleeding episodes based on the RE-LY trial[5] and acute kidney injury based on Acute Kidney Injury Network diagnostic criteria.[6]

Term	Definition
Major bleeding	Reduction of hemoglobin ≥2 g/dL Necessitating a transfusion of ≥2 units PRBCs
Life-threatening bleeding	Reduction of hemoglobin ≥5 g/dL Necessitating a transfusion of ≥4 units PRBCs Bleeding requiring surgery Fatality
Acute kidney injury	Absolute increase of serum creatinine level ≥0.3 mg/dL *or* Percentage increase in serum creatinine level of ≥50%

PRBC, Packed RBCs.

Methods of Measurement

R.B. and M.G. designed a standardized data abstraction form to collect patient demographics, bleeding diagnosis, laboratory values, interventions, and outcomes. All variables were explicitly and unambiguously defined. We characterized bleeding episodes with criteria for major and life-threatening bleeding described in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial,[5] and we used the Acute Kidney Injury Network diagnostic criteria[6] for acute kidney injury. These definitions are presented in Table 1. The hematocrit nadir and peak creatinine levels were compared with the most recent hematocrit and creatinine levels before the day of admission.

R.B. performed the data collection and met regularly with M.G. to assess performance of the form and to address any potential issues. To ensure fidelity of data abstraction, M.G. analyzed 10% of included charts blinded to initial data abstraction. There was greater than 96% data concordance; the only discordance was in a subject's age because of the time difference between data abstraction by the investigators.

Primary Data Analysis

Descriptive statistics were used and 95% confidence intervals were calculated.

RESULTS

During the study period, 15 patients receiving dabigatran were admitted with a primary hemorrhagic diagnosis. During the same period, 123 patients were admitted to the hospital with warfarin-associated hemorrhage. To derive a comparable and representative cohort of warfarin patients, a random sampling of 20% of all days in the study period yielded 25 warfarin patients admitted with a primary ED diagnosis of hemorrhage or bleeding. The most common site of bleeding was gastrointestinal for both groups, representing 80% of dabigatran and 48% of warfarin cases. The distribution of bleeding sites is presented in the Figure. There were no intracranial hemorrhages