Dabigatran, intracranial hemorrhage, and the neurosurgeon

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Dabigatran etexilate (Pradaxa) is a novel oral anticoagulant that has gained FDA approval for the prevention of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation. In randomized trials, the incidence of hemorrhagic events has been demonstrated to be lower in patients treated with dabigatran compared with the traditional anticoagulant warfarin. However, dabigatran does not have reliable laboratory tests to measure levels of anticoagulation and there is no pharmacological antidote. These drawbacks are challenging in the setting of intracerebral hemorrhage. In this article, the authors provide background information on dabigatran, review the existing anecdotal experiences with treating intracerebral hemorrhage related to dabigatran therapy, present a case study of intracranial hemorrhage in a patient being treated with dabigatran, and suggest clinical management strategies. The development of reversal agents is urgently needed given the growing number of patients treated with this medication.

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Key words • stroke • fatal outcome • tracheostomy • decompressive craniectomy • warfarin • Pradaxa • dabigatran etexilate

Anticoagulants are frequently used in the prevention and treatment of thrombosis. The most popular of these, warfarin, antagonizes the vitamin K–dependent coagulation factors. Although warfarin has been used extensively for many decades, its narrow therapeutic range, interactions with other medications and food, and the need for routine monitoring to check blood levels have led to the search for alternatives. This has resulted in the development of new oral anticoagulant medications that work via different mechanisms. These “novel anticoagulants” include direct thrombin antagonists such as dabigatran and factor Xa inhibitors such as rivaroxaban, apixaban, and edoxaban.1,2 Since there are few clinical studies about Xa inhibitors because of the very recent approval by the US Food and Drug Administration, the focus of this review will be on dabigatran etexilate.

Dabigatran etexilate (trade name Pradaxa; referred to in this article as dabigatran) is a novel anticoagulant approved by the FDA in 2010 for the prevention of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation.32 When compared with warfarin, dabigatran achieves similar, if not superior, efficacy with lower bleeding risk and fewer interactions with drugs and food.7,27 Also, there is no need for laboratory monitoring to follow therapeutic drug levels.7,27 Due to these advantages, dabigatran is becoming a widely popular drug.17

Although patients taking dabigatran do not need to have their blood levels monitored as is the case with the international normalized ratio (INR) for patients taking warfarin, this may be a “double-edged sword.” When hemorrhage occurs, physicians cannot reliably measure the level of anticoagulation. In addition, there is no pharmacological antidote available for dabigatran. These drawbacks are challenging for physicians in the setting
of intracranial hemorrhage. Although some management algorithms have been proposed, there is no available evidence on how to best care for patients taking dabigatran who experience intracranial hemorrhage. Herein, we provide an overview of challenges related to the novel oral anticoagulant dabigatran in the setting of intracranial hemorrhage.

**Intracranial Hemorrhage in Patients Taking Novel Oral Anticoagulants**

Upon initiation of anticoagulation therapy, the risk of hemorrhagic stroke weighs heavily on the minds of the physician and patient. Clinical trials such as the RE-LY trial demonstrate that intracranial hemorraghes are less common with dabigatran treatment than with warfarin. In the RE-LY trial, patients taking dabigatran 150 mg daily experienced a hemorrhagic stroke rate/100 person-years of 0.10 as compared with 0.38 in the warfarin therapy group. This corresponds to a relative risk of 0.26 for dabigatran compared with warfarin (95% CI 0.14–0.49, p < 0.001). The direct factor Xa inhibitors have also been compared with warfarin in head-to-head trials. In the ROCKET-AF trial, rivaroxaban was associated with less intracranial bleeding than was seen in the warfarin group. Similarly, apixaban, a medication approved by the FDA in December 2012, was associated with fewer instances of intracranial bleeding than warfarin in the ARISTOTLE study. The aforementioned trials made it evident that novel anticoagulants have decreased the incidence of intracranial hemorrhage as a complication in patients requiring anticoagulation therapy. However, the potential for catastrophic complications in patients on these agents may be magnified given their lack of rapid reversibility.

Several agencies have published reports of adverse events attributed to dabigatran. According to new data compiled by QuarterWatch, dabigatran accounted for 3781 serious events overall in 2011, including 542 patient deaths. Moreover, it surpassed all other regularly monitored drugs in reports of hemorrhage (2367 cases), acute renal failure (291), and stroke (644). Another database, compiled by QuarterWatch, dabigatran accounted for 3781 serious events overall in 2011 (worldwide) of serious bleeding resulting in death in patients receiving dabigatran therapy.

There are at least 3 published case reports of intracranial hemorrhage in patients being treated with dabigatran (Table 1). Garber et al. reported a case of an 83-year-old man who presented with intraparenchymal hemorrhage, subdural hemorrhage, and subarachnoid hemorrhage after falling down on the ground at home while taking dabigatran. In an attempt to stop the bleeding, the neurosurgical team administered recombinant human factor VIIa. Unfortunately, it was ineffective. The hemorrhage progressed extensively, and the patient died.

Chen et al. reported a case of an 80-year-old man who presented with a small subdural hematoma after hitting his head as a result of a mechanical fall while taking dabigatran. His neurological examination findings were nonfocal. Repeat CT scans revealed no hemorrhage progression, and he was discharged 2 days later.

In another recently published case, Chang et al. reported on a 94-year-old man who experienced a mechanical fall while taking dabigatran. A CT scan of the brain demonstrated a large right-convexity subdural hematoma with left midline shift and compression of the right lateral ventricle. Anticoagulation was effectively reversed by first administering a low dose of anti-inhibitor coagulant complex (FEIBA) and then following it with a 3-hour hemodialysis session. The patient’s course was subsequently uneventful, and he was discharged after 10 days of hospital observation with persistent mild left-sided weakness.

**Dabigatran**

**Mechanism of Action and Pharmacokinetics**

Dabigatran is a direct reversible inhibitor of thrombin, preventing the conversion of fibrinogen to fibrin, and as a result prevents thrombus formation (Fig. 1). Dabigatran etexilate is a prodrug that is converted to its active form, dabigatran, with a peak plasma concentration achieved within 2 hours after ingestion; it has a half-life of 8–10 hours and 14–17 hours with single and multiple dose administrations, respectively. The volume of distribution is 68.6 L/kg and it has a clearance of 155 ml/min. An individual with normal renal function needs 24 hours from the last dose before the anticoagulant action of dabigatran is removed. In contrast to warfarin, dabigatran is not metabolized by the liver cytochrome p450 system, so there are few drug interactions. Since it has predictable pharmacokinetics, dabigatran therapy does not require regular monitoring.

**Laboratory Testing**

Measuring the level of anticoagulation from dabigatran is not simple, especially in the emergency setting. Conventional coagulation assays, thrombin time and activated partial thromboplastin time, although usually considered sensitive, do not measure the effect of dabigatran very accurately. Many studies demonstrated that ecarin clotting time has a high sensitivity and specificity. Unfortunately, it is not widely available in clinical laboratories. The Hemoclot thrombin inhibitor assay (Aniara) has excellent linear correlation with dabigatran activity at all doses and is very accurate in determining anticoagulant activity. This assay allows for determination of plasma dabigatran levels. While it is approved for clinical use in Europe and Canada, it not yet approved in the US.

**Approval**

Prior to approval in the US, dabigatran was studied in clinical trials comparing it with warfarin. Notably, the RE-LY trial demonstrated that dabigatran at a dosage of 150 mg twice daily was more effective than warfarin in prevention of stroke or systemic embolization. Moreover, the RE-COVER study demonstrated similar efficacy of dabigatran 150 mg twice daily compared with warfarin in treatment of acute thromboembolism. Soon thereafter, the FDA announced in 2010 the approval of dabigatran for stroke prevention in people with atrial fibrillation. Late in 2012, the FDA announced that dabigatran should...
not be used to prevent stroke or thromboembolism in patients with mechanical heart valves.\(^3\) This announcement came after a clinical trial in Europe (the RE-ALIGN trial)\(^3\) was stopped because patients taking dabigatran experienced more strokes, heart attacks, and blood clots forming on the mechanical heart valves than were seen in the warfarin treatment arm. Additionally, there was also more bleeding after valve surgery in patients treated with dabigatran than in those treated with warfarin.

**Dabigatran Reversal**

In contrast to the situation with warfarin reversal, fresh frozen plasma and vitamin K are not expected to alter the anticoagulant effect of dabigatran. This is because dabigatran works by a different mechanism, direct thrombin inhibition, rather than antagonizing vitamin K–dependent factors. Unfortunately, there is no specific antidote that can reverse the anticoagulant effect of dabigatran yet. A monoclonal antibody targeted against dabigatran is under development. In preclinical studies, it specifically reversed the anticoagulant effect of dabigatran in human plasma in vitro and in small mammals.\(^3\)

The manufacturers of dabigatran, Boehringer Ingelheim, have provided general guidelines for the periprocedural management of dabigatran therapy in patients undergoing an invasive or surgical procedure.\(^3\) They suggest that for patients with a creatinine clearance rate of 50 ml/min or more, dabigatran should be discontinued at least 1–2 days before the procedure. For those with renal impairment (creatinine clearance rate of less than 50 ml/min) dabigatran therapy should be discontinued earlier, at least 3 to 5 days before the procedure. In addition, they suggest that longer times should be considered in patients undergoing major surgeries.\(^3\) However, clinical data supporting these recommendations have not been established.

**TABLE 1: Summary of reported cases of intracranial hemorrhage in patients treated with dabigatran***

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Mechanism of Injury</th>
<th>ICH Type</th>
<th>Reversal Mechanism Attempted</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garber, 2012</td>
<td>83, M</td>
<td>mechanical fall</td>
<td>IPH, SDH, SAH</td>
<td>rFVIIa</td>
<td>death</td>
</tr>
<tr>
<td>Chen, 2012</td>
<td>80, M</td>
<td>mechanical fall</td>
<td>SDH</td>
<td>phytonadione</td>
<td>stable hemorrhage, pt discharged 2 days later w/o further intervention</td>
</tr>
<tr>
<td>Chang, 2013</td>
<td>94, M</td>
<td>mechanical fall</td>
<td>SDH</td>
<td>FEIBA, followed by a 3-hr hemo- dialysis</td>
<td>stable hemorrhage, pt discharged w/ persistent mild hemiparesis</td>
</tr>
<tr>
<td>present case</td>
<td>85, F</td>
<td>mild head trauma</td>
<td>SDH</td>
<td>hemodialysis (attempt failed)</td>
<td>bur hole drainage, discharged neurologically intact</td>
</tr>
</tbody>
</table>

* ICH = intracranial hemorrhage; IPH = intraparenchymal hematoma; pt = patient; rFVIIa = coagulation factor VIIa (recombinant); SAH = subarachnoid hemorrhage; SDH = subdural hematoma.

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**Fig. 1.** Mechanisms of anticoagulant agents. New-generation anticoagulants such as rivaroxaban, apixaban, and dabigatran etexilate, have specific targets in the coagulation pathway. The dashed lines indicate inhibition.
One potential agent for reversing the effect of dabigatran is prothrombin complex concentrate (PCC). Weitz et al. reported that 40 IU/kg of PCC was very effective and promptly reduced blood loss in a patient taking dabigatran who presented with hematemesis and melena. In an animal model of intracerebral hemorrhage using dabigatran, PCC 100 U/kg dramatically reduced hematoma growth and decreased the 24-hour mortality after intracerebral hemorrhage, whereas recombinant human factor VIIa was ineffective. Another animal study demonstrated that PCC at a dosage of 50 IU/kg effectively reversed the effects of dabigatran. In contrast, Erenberg et al. conducted a randomized, double-blind, placebo-controlled study and concluded that PCC immediately and completely reverses the anticoagulant effect of rivaroxaban in healthy subjects but has no influence on the anticoagulant action of dabigatran at the dosage of 50 IU/kg (PCC dosage). The authors conclude that PCC is a viable option for reversing the anticoagulant effects of rivaroxaban, but is not effective in the reversal of dabigatran. However, PCC is not yet approved for use in the US.

Another potential dabigatran reversal agent is activated prothrombin complex concentrate. This commercially available concentrate known as factor eight inhibitor bypassing activity (FEIBA) has been found to successfully reverse the anticoagulant effect of dabigatran in human plasma ex vivo.

Because of the low percentage (approximately 35%) of plasma protein binding, dabigatran can be removed by means of dialysis. In an open-label study, dabigatran was given to 6 patients with end-stage renal failure who were being treated with hemodialysis. Investigators reported that 62% of the drug could be removed by dialysis within 2 hours. Wanek et al. reported that hemodialysis was safe and effective for dabigatran removal before cardiac surgery. In other separate reports, hemodialysis was the most effective treatment in reversing life-threatening bleeding in a patient who had been treated with dabigatran.

Management

There is no clear consensus regarding the emergency management of patients with intracerebral hemorrhage in the setting of dabigatran. The general principle of management, in addition to the basic tenets of arterial blood pressure management and ICP control with any intracerebral hemorrhage, is rapid reversal of the agent. In cases of life-threatening hemorrhage or lesions that are suspected to have a propensity to enlarge, hemodialysis should be instituted emergently. If neurosurgical intervention is required, dabigatran reversal with hemodialysis should be completed prior to the operation. Without reversal, intraoperative control of bleeding would be difficult, if not impossible.

Case Report

This 85-year-old right-handed woman presented to our institution's emergency department with progressive confusion, word-finding difficulty, and gait instability over the course of 2 days. She had sustained a mild head trauma 2 weeks previously and reported a mild right-sided headache on arrival. She had a history of atrial fibrillation and had been taking dabigatran. Her neurological examination on arrival revealed disorientation and mild word-finding difficulty, but full strength in all extremities. A head CT scan revealed a 2.2-cm acute-on-chronic right subdural hematoma with 1.5-cm of leftward midline shift (Fig. 2).

Given the size of her hemorrhage and her neurological deficits, urgent surgery was considered, but a consulting hematologist recommended delaying surgery 48 hours to allow for adequate renal clearance of dabigatran prior to operative intervention. A nephrologist was consulted to determine if dialysis should be performed. Placement of a hemodialysis catheter proved difficult, however, and the procedure was aborted. The patient was subsequently admitted to the neurosciences intensive care unit for close hemodynamic and neurological monitoring. She was treated with levetiracetam for seizure prophylaxis. Her blood pressure was controlled with antihypertensive agents.

On the morning of hospital Day 3, the patient was difficult to arouse, nonverbal, and unable to follow commands reliably. A repeat CT examination revealed an increase in the degree of acute hemorrhage within the right subdural space and in the size of the hematoma to 2.4 cm (Fig. 3). Given that sufficient time has passed since

Fig. 2. Axial (left) and coronal (right) CT images obtained in our patient on admission revealing a 2.2-cm acute-on-chronic right convexity subdural hematoma with 1.5 cm of leftward midline shift.

Fig. 3. Axial (left) and coronal (right) CT images obtained on hospital Day 3 demonstrating an increase in the degree of acute hemorrhage within the right subdural space and an increase in the size of the hematoma to 2.4 cm.
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Fig. 4. Follow-up axial (left) and coronal (right) CT images obtained at the 8-week clinic visit demonstrating near-complete resolution of the subdural collection.

her last dabigatran dose, she was taken to the operating room emergently for bur hole drainage of the right subdural hematoma. Postoperatively, she returned to her intact neurological baseline. A follow-up CT scan at the 8-week clinic visit demonstrated near resolution of the subdural collection (Fig. 4). She remained neurologically intact.

Conclusions

While there is good-quality evidence that the incidence of hemorrhagic stroke is reduced with the use of dabigatran compared with warfarin, the severity of these events is poorly described. The inability to rapidly reverse the anticoagulation profile is a clinical challenge that has catastrophic potential. The development of reversal agents is urgently needed given the growing population of patients treated with this medication.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Walcott, Awad. Acquisition of data: Awad. Analysis and interpretation of data: Walcott, Awad, Nabed. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: Walcott, Awad, Stapleton, Yanamadala, Coumans. Approved the final version of the manuscript on behalf of all authors: Walcott. Study supervision: Coumans.

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