

What neurosurgeons need to know about dabigatran etexilate (pradax[®]/pradaxa[®]/prazaxa[®])

Christopher Michael Dwyer, Omprakash Damodaran, Michael Heckelmann,
Mark Michael Sheridan

Department of Neurosurgery, Liverpool Hospital, University of New South Wales, Sydney, New South Wales, Australia

ABSTRACT

Dabigatran etexilate is a novel oral anticoagulant that directly inhibits thrombin. It offers a number of substantial medical benefits over other oral and parenteral anticoagulants but its advent raises important neurosurgical considerations. Dabigatran has important potential benefits. Unlike warfarin, it does not require routine blood tests to monitor its anticoagulative effect and there is no need for dose titration. Drug interactions are greatly simplified when compared to warfarin as dabigatran is not metabolized by cytochrome p450 isoenzymes. As a result, dabigatran has been approved in many jurisdictions for DVT prophylaxis after orthopaedic surgery and also for the prevention of embolic events associated with non-valvular atrial fibrillation. There are, however, important neurosurgical challenges associated with regular dabigatran use. Unlike current anti-coagulants, there is no specific reversal agent for dabigatran. Known reversal options include activated charcoal (within one to two hours of intake) and renal dialysis. Protamine sulfate and vitamin K are unlikely to affect the activity of dabigatran. Platelet concentrates will not inactivate dabigatran's anti-thrombin properties. Assessing the degree of anticoagulation is difficult as conventional markers of serum coagulability are typically normal in patients taking dabigatran. The potential neurosurgical challenges of dabigatran were cast in sharp relief by a recent case report from the United States that is considered in this note. In the absence of a clear reversal pathway, we propose a treatment algorithm for chronic dabigatran use based on the replacement of any deficient factors and rapid access to renal dialysis.

Key words: Anticoagulation, dabigatran, heparin, reversal of anticoagulants, use in neurosurgical patients, warfarin

Introduction

A comprehensive knowledge of novel anticoagulants is an important part of current neurosurgical practice. While warfarin, heparin and its low molecular weight derivative, enoxaparin, have formed the mainstay of treatment for atrial fibrillation, valvular heart disease and the prevention of venous thromboembolism for over 30 years,^[1] new agents have recently been approved that promise to revolutionize the treatment of these conditions. There are compelling medical reasons driving the adoption of these agents and they will

have an important impact on neurosurgical practice. Here we review the risks and benefits of a novel direct thrombin inhibitor, dabigatran etexilate and consider its implications for neurosurgeons.

The benefits of direct thrombin inhibition

Despite the fact that heparin and warfarin are inexpensive and easy to reverse, they suffer from several well known limitations.^[2,3] These include parenteral administration for heparin, slow onset and offset of action for warfarin and variable pharmacokinetics for both agents, necessitating frequent monitoring with serum coagulation studies.^[1,2] These tests are inconvenient for patients and expensive for health care systems.

Dabigatran etexilate is a novel oral anticoagulant with stable pharmacokinetics – unlike warfarin, it does not require routine blood tests to monitor its anticoagulative effect.^[1] There is no need for dose titration. While drug interactions do affect dabigatran's absorption and metabolism, co-administration with other agents is greatly simplified when compared to warfarin as it is not metabolized by cytochrome p450 isoenzymes. Dabigatran is a direct thrombin inhibitor^[1] with a terminal half life of eight hours for a single dose and

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DOI:

10.4103/1793-5482.144156

Address for correspondence:

Dr. Christopher M. Dwyer, Department of Neurosurgery,
Liverpool Hospital, Elizabeth St., Liverpool NSW, 2170, Australia.
E-mail: cdwy0142@uni.sydney.edu.au

12 to 14 hours for multiple doses.^[4] Dabigatran is renally excreted and its half life can exceed 24 hours in patients with renal impairment.^[4]

Dabigatran has been approved in Europe, the United States, and Canada for the prevention of stroke in patients with non-valvular atrial fibrillation. In these patients, typical dosing is 150 mg per oral (PO) twice daily. In patients with reduced creatinine clearance, the dose is reduced to 75 mg PO twice daily. Patients should cease warfarin prior to conversion to dabigatran and dabigatran should only be started when the international normalized ratio (INR) is below 2.0.^[5]

In Europe, dabigatran has further been approved for use in the prevention of post-operative thromboembolic complications in patients undergoing hip or knee replacement surgery. In these patients, typical dosing includes one 110 mg oral dose taken one to four hours after surgery followed by 110 mg PO twice daily for 28 to 35 days in cases of hip replacement and for 10 days in cases of knee replacement. When converting from heparin or enoxaparin for venous thromboembolic prophylaxis, dabigatran should be started up to two hours prior to the time of the next dose of parenteral anticoagulant was to be administered.^[6] Importantly, dabigatran has not been approved for use as thromboembolic prophylaxis in settings other than orthopedic surgery.

In patients with normal renal function dabigatran should be stopped two to four days prior to surgery in order for serum levels to fall below five to ten percent.^[7] Table 1 compares the pharmacokinetics of dabigatran with other commonly used anticoagulants.

Surgical Pitfalls of Dabigatran

While dabigatran presents significant medical advantages, there are important surgical pitfalls. There is no specific reversal agent for dabigatran. Known reversal options include activated charcoal (within one to two hours of intake) and renal dialysis.^[2] When dialysis is not possible – for example, in surgical emergencies – recombinant factor VIIa, prothrombin complex and/or concentrates of coagulation factors II, IX, or X may be considered, but their use has not been evaluated in clinical trials.^[4] Protamine sulfate and vitamin K are not expected to affect the activity of dabigatran.^[5] Platelet concentrates can be given when thrombocytopenia is also present or long-acting antiplatelet agents have been used but these will not inactivate dabigatran's anti-thrombin properties.^[5]

In addition, there is no readily available assay for assessing the degree of anticoagulation with dabigatran.^[3] Conventional markers of serum coagulability are typically normal in patients taking dabigatran.^[3] The most sensitive test for assessing its activity is ecarin clotting time and this assay may not be

available in most hospitals.^[2] It is not currently available on-site at our large tertiary center in Sydney, Australia.

Garber *et al.* recently presented an alarming case of mortality related to dabigatran use that highlights the important neurosurgical issues related to this novel agent.^[8] An 82-year-old man presented to hospital after sustaining a minor fall. He was recently commenced on dabigatran 150 mg PO twice daily for atrial fibrillation. At presentation, his Glasgow Coma Scale (GCS) was 15 with no neurological deficits. The initial non-contrast computed tomography (CT) scan revealed a small intraparenchymal hemorrhage and associated subdural hemorrhage with no mass effect. Despite this reassuring finding, he experienced a rapid neurological decline to a GCS of 6 over the course of the next few hours. Recombinant factor VII was given without effect. Repeat CT brain showed a catastrophic extension of the intraparenchymal hemorrhage with significant mass effect. In light of a very poor neurological prognosis, the patient was palliated and passed away shortly thereafter.

This report casts in sharp relief the dangers of dabigatran in the AF population. These patients are typically elderly and more prone to falls. Even mild trauma can result in catastrophic bleeding. Dabigatran's action at the end of the clotting cascade – by direct inhibition of Factor II – renders typical approaches to reversal futile. In these cases, a high index of suspicion for progressive intracranial hemorrhage and low threshold for the initiation of dialysis might yield the best clinical outcomes. We propose the following treatment algorithm in patients presenting with intracranial bleeding in a setting of dabigatran use:

1. Cease all anticoagulant and antiplatelet medications;
2. Check all available coagulation parameters and reverse or provide replacement where necessary;
3. Proceed to renal dialysis if risk of bleeding is high;
4. Where emergency intervention is indicated, give platelets and available recombinant factors prior to surgery.

Dabigatran is approved for use in many Asian countries including Australia, Japan, Malaysia, Singapore, and South Korea.^[9] Its indications in these countries include stroke prevention in AF and thromboprophylaxis after orthopedic surgery.^[2,3] In addition to concerns relating to low-energy intracranial trauma, major gastrointestinal bleeding complications have been reported.^[3,10] As a result, warnings have been issued which advise caution when using dabigatran in the elderly, in patients with renal impairment and concomitantly with other anticoagulants, including aspirin.^[11]

Conclusion

As neurosurgeons, it's important to remain abreast of new developments in the area of anticoagulation. The compelling benefits of novel anticoagulants like dabigatran – for

Table 1: Citations for content in table provided below at end of title Comparison of Dabigatran etexilate and Other Commonly Used Anticoagulants[1-4,7,10]

	Dabigatran	Warfarin	Heparin	Enoxaparin
Route	PO	PO	IV or SC	SC
Mechanism	Direct inhibition of thrombin	Reduced synthesis of clotting factors II, VII, IX and X	Potentiates anti-thrombin, thereby reducing thrombin and Xa activity	Potentiates anti-thrombin, thereby reducing thrombin and Xa activity
Bioavailability	6.5%	~100%	~30%	~100%
Onset of action	30 mins	36-72 hours	IV: Immediate SC: 20-60 mins	3-5 hours
Half life	9-12 hours	20-60 hours	1-2 hours	4-7 hours
Pharmacokinetics	Stable	Unstable	Unstable	Stable
Metabolisation	Renal	Hepatic	Hepatic	Hepatic
Elimination	Renal	Renal	Hepatic	Renal
Drug interactions	Yes, PPIs reduce absorption	Yes; multiple with clinical significance	Limited, caution with other anticoagulants	Limited, caution with other anticoagulants
Diet interactions	Nil	Yes, clinically significant	Nil	Nil
Monitoring	None	Regular INR	Regular APTT	Regular anti-Xa
Reversal agent	None	Vit K; FFP; Prothrombinex-VF	Protamine sulfate	Protamine sulphate (limited efficacy)

physicians, patients and health care administrators – insure that their routine use will see rapid adoption. An understanding of the medical benefits and surgical risks of these agents is essential in obtaining valid consent for neurosurgical procedures and understanding the limits they place on emergency neurosurgical intervention.

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How to cite this article: Dwyer CM, Damodaran O, Heckelmann M, Sheridan MM. What neurosurgeons need to know about dabigatran etexilate (pradax®/pradaxa®/prazaxa®). *Asian J Neurosurg* 2015;10:66-8.

Source of Support: Nil, **Conflict of Interest:** None declared.