

## Clinical Report

# Promise and challenges of anticoagulation with dabigatran

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### Abstract

Dabigatran, marketed as Pradaxa (Boehringer Ingelheim) in the USA, is a direct thrombin inhibitor that holds great promise. It has been shown to reduce the risk of stroke and venous thromboembolism with similar if not greater efficacy than warfarin and with far fewer side effects. However, like other anticoagulants, it can cause severe bleeding complications and lacks a specific antidote with proven efficacy. The patient presented here was on dabigatran and sustained a traumatic intracranial hemorrhage (ICH). The ICH continued to progress despite prompt initiation of 3 h of hemodialysis in an effort to remove the offending drug from the circulation. Through this case report, we highlight the challenges of anticoagulation with dabigatran including the lack of routine testing for monitoring its effect and of a specific antidote. We also discuss the potential role of dialysis in treating patients with life-threatening bleeding on dabigatran.

**Keywords:** bleeding; dabigatran; dialysis

### Background

Warfarin has been the mainstay of oral anticoagulation therapy for the prevention of thromboembolic stroke in patients with atrial fibrillation (AF). Its major drawbacks have been the need for frequent monitoring and numerous interactions with other drugs and food [1]. The Food & Drug Administration (FDA) in the USA approved dabigatran etexilate (DE) in 2010 for stroke prophylaxis in patients with non-valvular AF [2]. It does not need any monitoring [3] or dietary restrictions and has far fewer drug interactions. Dabigatran significantly lowers the risk of thromboembolic stroke and the risk of spontaneous intracranial hemorrhage is less than one-third the rate with warfarin [4]. Thus, it provides an attractive alternative to warfarin for prevention of thromboembolism. But the testing for its anticoagulant effect is not routinely available and not unlike some other anticoagulants, dabigatran does not have a specific antidote either. Both these factors limit our ability to effectively manage patients on dabigatran when they present with a life-threatening bleed. As we discuss here, dialysis may have an important role in clearance of this drug from the systemic circulation.

### Case report

A 64-year-old electrician presented with headache and mild confusion following a fall from his work truck. His

medical history was significant for non-valvular AF, hypertension, immune thrombocytopenic purpura and diabetes mellitus. He had no history of chronic kidney disease. The patient was taking Pradaxa (DE) 150 mg twice daily. Other medications included lisinopril, metoprolol, metformin and simvastatin. He had taken Pradaxa that morning. At presentation, he was mildly confused but otherwise neurologically and hemodynamically intact. Imaging revealed an occipital skull fracture, right subdural hematoma with 7 mm shift and bilateral subarachnoid blood. The basic metabolic panel and complete blood count were normal except for a platelet count of  $49 \times 10^9$  per liter (normal range  $140\text{--}440 \times 10^9$  per liter). The patient's platelet count 2 weeks prior to this admission was  $36 \times 10^9$  per liter. The prothrombin time (PT) was 14.9 s (normal range 9.6–12.4 s), the international normalized ratio (INR) was 1.4 s (normal <1.2) and the activated plasma thromboplastin time (APTT) was 44.3 s (normal range 22.3–34 s). Reversal of dabigatran's anticoagulant effect was imperative. Previous review of the literature confirmed that there was no proven antidote to dabigatran and that dialysis was probably the only reliable means of drug removal from the systemic circulation. A temporary dialysis catheter was placed and the patient commenced heparin-free hemodialysis within 90 min of arrival. We used an Optiflux 200 dialyzer for 3 h with a blood flow of 300–350 mL/min, dialysate flow of 500 mL/min and a 141 mmol/L sodium, 3 mmol/L potassium, 35 mmol/L bicarbonate and 2.5 mmol/L calcium bath. The patient tolerated the procedure well though he was intubated halfway through dialysis due to the

declining neurological status. Post-dialysis, repeat head computerized tomography showed worsening subdural hematoma with a 15 mm midline shift. He was then urgently taken to the operating theater for craniectomy and evacuation of hematoma. The patient received desmopressin and 2 units of platelets. Subsequent imaging showed extensive right intracerebral bleeding, bilateral hemispheric infarction and signs of herniation. Given the poor prognosis, the family made the decision to initiate 'comfort measures only' for the patient and he passed away soon thereafter. Table 1 trends his coagulation profile pre- and post-hemodialysis.

## Discussion

For over 50 years, warfarin has been the mainstay of oral anticoagulation especially in the chronic management of thromboembolism. But difficulty in achieving the optimal anticoagulant effect, narrow therapeutic window necessitating frequent monitoring of the INR, significant interindividual variability in pharmacological response and numerous drug and food interactions are major limitations to its use [5]. Parenteral factor Xa inhibitors such as fondaparinux are not practical in chronic management of thromboembolism. Direct thrombin inhibitors such as argatroban and lepirudin suffer from the same handicap and are restricted to treatment of heparin-induced thrombocytopenia. Ximelagatran was the first direct oral thrombin inhibitor that showed similar efficacy to warfarin [6]. It had to be withdrawn due to significant hepatotoxicity.

DE is an oral prodrug that is rapidly absorbed from the gastrointestinal tract and converted by serum esterase to its active form—dabigatran. The latter is a synthetic, non-peptide, direct, competitive inhibitor of thrombin. It inhibits both clot-bound and circulating thrombin and decreases thrombin-stimulated platelet aggregation [7]. Peak serum concentrations are reached an hour after oral administration when fasting and 3 h after a fatty meal. It has a half-life of 12–17 h and does not undergo hepatic elimination. Eighty percent of it is excreted in the urine. Twice daily dosing provides a predictable and reliable anticoagulant effect that is not impacted by food or drugs and does not need frequent monitoring.

Dabigatran at a dose of 150 mg twice daily has been associated with lower rates of stroke, systemic embolism and hemorrhagic stroke than warfarin [4]. The RE-LY study reported a higher risk of major bleeding with warfarin when compared with dabigatran 110 mg and no difference in the dabigatran 150 mg group. Life-threatening bleeding was also not more common with dabigatran [4]. Moreover, in a subsequent independent analysis, the case fatality rate per major bleed was numerically lower in those treated with dabigatran than warfarin (although the number of deaths was too few to perform meaningful statistical analyses) [8]. This observation may be due to less severe bleeding on dabigatran or because, despite

effective reversal of warfarin, correction of coagulation parameters may not have a significant impact on patient survival. As would be expected, bleeding risk has been shown to be specifically higher in the elderly and those with low body weight [9, 10].

Renal impairment increases serum concentration of this drug and reduced dosing is advised. The dose should be reduced by 50% for those with a glomerular filtration rate (GFR) between 15 and 30 mL/min/1.73 m<sup>2</sup> and the drug should be avoided in those with a lower GFR. FDA guidelines recommend the assessment of renal function prior to starting dabigatran and annually in those >75 years and also those with a GFR of <50 mL/min/1.73 m<sup>2</sup> [11].

The widespread use of dabigatran may bring new problems to the forefront. First, monitoring of its anticoagulant activity is not widely available. APTT, thrombin time (TT), activated clotting time (ACT) and ecarin clotting time (ECT) have been advocated for monitoring dabigatran's anticoagulant effect. APTT and TT are both sensitive to the anticoagulant activity of direct thrombin inhibitors, but may underestimate their true anticoagulant activity. In our patient, the APTT actually increased after hemodialysis. This is probably a reflection on the reagent used rather than the test itself. Others have shown that this parameter was in the normal range in acutely bleeding patients on dabigatran [12]. TT is of limited value in an overdose as coagulometers are unable to measure it when dabigatran concentration exceeds 600 ng/mL (steady-state concentration is much lower at ~200 ng/mL after multiple doses of the drug) [13]. Similarly, ACT has no linear correlation with plasma concentration of direct thrombin inhibitors. Ecarin is a metalloprotease isolated from the venom of the saw-scaled viper *Echis carinatus*. This cleaves prothrombin to generate meizothrombin—an intermediate in the generation of thrombin. Meizothrombin is inhibited by direct thrombin inhibitors such as dabigatran. ECT has a linear relationship to dabigatran's serum concentration and is hence suitable for monitoring its anticoagulant effect. But this test is not widely available and the result takes several days to be reported [14, 15]. Rapid thromboelastography (rTEG) is a point-of-care test that has been used to assess the anticoagulant activity of dabigatran [12], but has not been validated for this purpose.

Another challenge in managing patients on dabigatran who are bleeding is the lack of a specific antidote. A dabigatran-directed neutralizing antibody is currently under development [16]. While vitamin K, fresh frozen plasma, factor VIIa and prothrombin complex concentrate can all be used to reverse the effect of warfarin, none of these have been proven to reverse anticoagulation due to dabigatran [17]. One study did recommend the use of recombinant activated factor VIIa for patient bleeding on dabigatran [18], but a subsequent systematic review demonstrated that this off-label use of the product does not lower mortality and indeed increases the risk of thromboembolism [19]. This review does not indicate if some or all of the included patients were on anticoagulants. However, in a critically ill patient such as ours, it may be prudent to use recombinant activated factor VIIa or prothrombin complex concentrates in tandem with dialysis.

The only strategy for hastening the removal of dabigatran may be dialysis [20, 21]. Sixty percent of the drug can be removed within 2–3 h of dialysis [20]. It is a small molecule with a molecular weight of only 628 g/mol [8]. A third of the drug is protein bound. Both these factors

**Table 1.** Pre- and post-dialysis clotting profile (all values are in s)

	Pre-dialysis	Post-dialysis
PT (range 9.6–12.4)	14.9	15.7
APTT (range 22.3–34)	44.3	49.3
ECT (range 22.6–29)	125.5	83.1

favor the removal at dialysis. But, the volume of distribution of dabigatran is 50–70 L [18], suggesting that some of it is distributed into the tissues and may not be immediately accessible at dialysis necessitating longer and repeated treatments. The few case reports where dialysis was instituted show mixed results from this intervention [21, 22]. The use of dialysis is also limited by the lack of universal availability. In patients with ICH, intradialytic hypotension may contribute to clinical deterioration. Three hours of hemodialysis seems to have improved the ECT in our patient and possibly reduced the risk of ongoing bleeding. That this patient had a preserved GFR and a decline in the ECT may be a reflection of normal renal excretion of dabigatran, but it is possible that the APTT that should have improved in tandem with ECT went up slightly due to administration of fluids and also because patients with major intracranial bleeding may sometimes develop disseminated intravascular coagulation. Thus, the role of dialysis in dabigatran-associated life-threatening bleeding needs further evaluation. It is possible that longer and repeat dialysis sessions may be more effective, but this remains to be proven. Continuous renal replacement therapies (CRRT) may also be more useful in this setting. This is because of their ability to provide sustained clearance and to minimize intra-dialytic hypotension—a major pitfall of intermittent hemodialysis. The availability of CRRT is even more restricted than that of intermittent hemodialysis. Thus, even though there is not enough evidence to support its use, dialysis should be considered in patients with life-threatening bleeding on dabigatran and those with dabigatran overdose especially if they have reduced renal function.

We conclude that dabigatran is a potent oral direct thrombin inhibitor that, despite lack of testing for monitoring its anticoagulant effect and a specific antidote, is a real, and potentially superior, alternative to warfarin. Given the current state of the evidence on treating patients with dabigatran-related bleeding, further work is needed to assess the role of currently available therapeutic modalities including dialysis and for the development of potential new treatments.

**Conflict of interest statement.** None declared.

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