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REVIEW

Incidence and Management of Ischemic Stroke and Intracerebral Hemorrhage in Patients on Dabigatran Etexilate Treatment

Masaki Watanabe · Fazeel M. Siddiqui · Adnan I. Qureshi

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Abstract Dabigatran etexilate is an oral, reversible direct thrombin inhibitor and has been recently approved for the prevention of stroke in patients with non-valvular atrial fibrillation. This review describes the incidence and management of stroke and related complications in patients on dabigatran etexilate. Dabigatran is a rapidly acting, and highly selective and reversible inhibitor of thrombin. It also has a potent inhibitory effect on thrombin-induced platelet aggregation, making it effective in preventing both venous and arterial thrombosis. The activated partial thromboplastin time, ecarin clotting time and thrombin time are sensitive tests to evaluate the anticoagulant effects of dabigatran. The rate of ischemic stroke is significantly lower in patients on 150 mg of dabigatran etexilate as compared to 110-mg dose or warfarin (9.2, 13.4, 12 per 1,000 patients, respectively). As there is no standard coagulation test for dabigatran; treatment of acute stroke in such patients is debatable. Careful clinical consideration is required before administering thrombolytic therapy in this patient population. The rate of hemorrhagic stroke was 1.2 and 1.0 per 1,000 patients treated on 110 and 150 mg of dabigatran, respectively. As there is no specific antidote, the only treatment option is discontinuation of the drug and supportive management. Other treatment options, though not clinically proven, include specific reversal agents, which can be individualized according to the severity of the hemorrhage. Dabigatran should be discontinued before invasive procedures depending on the degree of renal impairment and risk of bleeding.

Keywords Dabigatran · Dabigatran etexilate · Direct thrombin inhibitor · Stroke · Ischemic stroke · Intracranial hemorrhage · Atrial fibrillation

M. Watanabe · A. I. Qureshi (✉)
Zeenat Qureshi Stroke Research Center, University of Minnesota, Minneapolis, MN 55455, USA
e-mail: aiqureshi@hotmail.com

F. M. Siddiqui
Department of Neurology, Southern Illinois University Health Care, Springfield, IL, USA

Background and Introduction

Atrial fibrillation affects approximately 2.3 million Americans [1] and remains a major cause of severe disabling stroke [2]. For decades, warfarin, a vitamin K antagonist, was the only effective oral anticoagulant treatment for preventing embolic events in patients with atrial fibrillation [3]. Six randomized controlled trials and two meta-analyses have demonstrated the benefit of warfarin in reducing the risk of ischemic stroke in patients with atrial fibrillation [4–11]. However, warfarin use requires frequent drug level monitoring because of variable drug activity, narrow therapeutic index, and interactions with food and other commonly used medications (especially those that are metabolized through P450-cytochrome system). The relatively high risk of intra- and extracranial bleeding associated with warfarin also supports the need for developing alternate anticoagulants [12].

Dabigatran etexilate is a direct thrombin inhibitor (DTI) that is highly efficacious in the prevention and treatment of venous thrombosis [13–18]. After the recently concluded phase III trial RE-LY (randomized evaluation of long-term anticoagulation therapy) [19], dabigatran has been approved by U.S. Food and Drug Administration as a potential replacement to warfarin in patients with non-valvular atrial fibrillation, to reduce the risk of stroke and systemic embolism in 2010 [19]. RE-LY was a randomized

non-inferiority trial designed to compare two fixed doses of dabigatran with open-label use of warfarin in patients with atrial fibrillation who were at increased risk for stroke. Dabigatran was administered, in a blinded fashion, in capsules containing either 110 mg or 150 mg of the drug, to be taken twice daily. Warfarin was administered in an unblinded fashion and adjusted locally to an international normalized ratio (INR) of 2.0–3.0. The rate of the primary outcome (stroke and systemic embolization) was significantly lower with dabigatran at a dose of 150 mg twice daily (1.1%) than with either dabigatran at a dose of 110 mg twice daily (1.5%) [RR 0.73, 95% CI (0.58–0.91), $P = 0.005$] or warfarin (1.7%) [RR 0.66, 95% CI (0.53–0.82), $P < 0.001$ for non-inferiority < 0.001]. Dabigatran 110 mg twice daily dosing was not inferior but statistically not superior to warfarin.

Due to reliable pharmacokinetics, frequent monitoring of anticoagulant activity is not necessary in patients on dabigatran etexilate. However, an assessment of coagulation status becomes necessary in situations such as acute ischemic stroke, bleeding into critical organs, or emergent invasive procedures or surgery. Furthermore, there is paucity of systematic data synthesis with particular emphasis on the management of newly occurred hemorrhagic or ischemic stroke in patients on dabigatran. We provide a systematic review in anticipation of the new challenges expected to be seen with increasing use, discussing the incidence and management of ischemic and hemorrhagic strokes in patients receiving active treatment with dabigatran.

Mechanism of Action

Dabigatran etexilate is a small molecule with similar structure to α-NAPAP (N-alpha-(2-naphthylsulfonylglycyl)-4-amidinophenylalanine piperidide), a benzamidine-based thrombin inhibitor [20–22]. It is orally absorbed as a pro-drug, which is constituted by the addition of hydrophobic side chain to the original molecule [23]. In the body, the pro-drug is converted to active form "dabigatran" by esterase-catalyzed hydrolysis in plasma and in the liver [24]. Dabigatran is a rapidly acting, and highly selective and reversible inhibitor of thrombin [21, 25]. It also has a potent inhibitory effect on thrombin-induced platelet aggregation [25]. These unique properties make dabigatran effective in preventing both venous and arterial thrombosis [26].

Monitoring Therapeutic Activity

Two double-blind, randomized, placebo-controlled studies were performed to assess the effect of dabigatran etexilate on coagulation markers including activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time (TT) and ecarin clotting time (ECT) [27]. First, a single-dose and the second a multiple-dose, escalating regimens were evaluated [27]. Single, orally administered doses (10–400 mg) led to rapid, dose-dependent increases in mean INR, TT and ECT, with the maximum anticoagulant effect occurring at the maximum plasma dabigatran concentration indicating that thrombin inhibition by dabigatran is a direct effect linked to the central plasma compartment [27]. Coagulation parameter alterations were closely related to drug concentrations when healthy men were given dabigatran 50–400 mg three times daily. Maximum effects were achieved within 2 h of administration. Twelve hours after administration, blood coagulation prolongation was reduced to $\approx 50\%$ of its maximum [27]. Due to reliable pharmacodynamic and pharmacokinetic properties, routine coagulation tests are not necessary to monitor the effect of dabigatran etexilate [19]. However, there is a need to quantitate the intensity of anti-coagulation activity of dabigatran in settings of acute systemic or intracranial hemorrhage.

Pharmacokinetics of Dabigatran

Coagulation parameter alterations remained associated in almost a linear fashion with drug concentrations among healthy men who were given dabigatran 50–400 mg three times daily. Maximum effects were seen within 2 h of administration. Twelve hours after administration, blood coagulation prolongation was reduced to $\approx 50\%$ of its maximum effect [27]. Similar pharmacodynamic effects were observed in healthy older subjects [28]. If the last dose of dabigatran was more than 24 h apart from the time of evaluation, the anticoagulant effect was not present in patients with normal renal function (Creatinine clearance: CCr > 50 ml/min). In patients with impaired renal function (CCr < 50 ml/min), the last dose had to be at least 2 days before evaluation to assume normalization of coagulation profile. Therefore, for some situations where normal coagulation profile is required, use of dabigatran within the last 24 h in persons with normal renal function and within last 48 h in persons with impaired renal function is considered a contraindication.

Various Assays for Monitoring Therapeutic Activity

A brief description of each coagulation marker that could be useful in specific situations is provided.

a. The aPTT assay measures the integrity of the intrinsic pathway of the coagulation cascade. Prolongation of the aPTT occurs with increasing dabigatran plasma

concentration, which achieves a plateau effect at high serum levels (>400 ng/mL) [21]. Thus, while measurement of aPTT may provide a qualitative indication of anticoagulant activity, it is not suitable for the precise quantification of anticoagulant effect especially at high plasma concentrations of dabigatran [21].

b. The PT assay targets the extrinsic pathway of the coagulation cascade. Dabigatran has little effect on the PT at clinical plasma concentrations [29, 30]. The INR is therefore insensitive as a primary measure of dabigatran activity [31].
c. The TT assay directly assesses the activity of thrombin and therefore provides a direct measure of the activity of dabigatran. TT tests are available in routine clinical practice. The TT is particularly sensitive to the effects of dabigatran and displays a linear dose–response even at supra-therapeutic concentrations. Thus, the TT assay is the most useful and sensitive method for determining the anticoagulation effect of dabigatran.
d. The ECT uses ecarin, which is a snake venom that specifically activates prothrombin resulting in the generation of meizothrombin, an unstable precursor of thrombin. Dabigatran inhibits the thrombin-like activity of meizothrombin. Hence, ECT provides a direct measure of the activity of dabigatran [31]. ECT is not available in routine clinical setting and hence cannot be recommended for emergency monitoring of the anticoagulant effects of dabigatran.
e. Activated clotting time (ACT) is a quantitative assay that is based on a similar test principle as aPTT, except that clotting is initiated in whole blood samples. No systematic investigation into the use of ACT has been performed in patients and the rather flat dose–response curve limits the usefulness of this assay.

From the above-mentioned information, aPTT, TT and ECT assay are sensitive tests to monitor the anticoagulant effects of dabigatran. In emergency situations, the aPTT and TT are the most accessible qualitative methods for monitoring the anticoagulant effects of dabigatran. TT is more sensitive than aPTT for precise quantification of anticoagulation effect especially at higher doses. Table 1 describes the characteristics of different coagulation makers and their potential use in patients on dabigatran.

Management of Dabigatran-Treated Patients with New Ischemic Stroke

Incidence of Ischemic Stroke

The incidence of ischemic stroke on dabigatran was evaluated in RE-LY [19] over 2 years in median duration. The rate of non-hemorrhagic (i.e., ischemic or unspecified) stroke was significantly lower with 150 mg of dabigatran (0.92%) than with either 110 mg of dabigatran [1.34%; RR 0.76, 95% CI (0.60–0.98), $P = 0.03$] or warfarin [1.20%, RR 0.69, 95% CI (0.54–0.88), $P = 0.002$]. Both dabigatran 110 mg twice daily and dabigatran 150 twice daily groups had relatively lower event rates for transient ischemic attack (0.62 and 0.72%, respectively) than warfarin (0.84%) [32]. Ischemic stroke–related deaths were seen in 4, 5, and 7 patients among every 1,000 patients treated with dabigatran 150 mg, dabigatran 110 mg and warfarin [32].

Management of Ischemic Stroke in Patients on Dabigatran

Management of ischemic stroke in patients on dabigatran is a challenging issue particularly among patients who are candidates for intravenous (IV) recombinant tissue plasminogen activator (rt-PA) or endovascular treatment. Unlike vitamin K antagonists, dabigatran's therapeutic effect cannot be reliably measured using the INR. Therefore, the current recommendation to avoid rt-PA among patients with INR of 1.7 or greater is not useful. Though other tests such as the TT, aPTT and ECT have been correlated with dabigatran serum concentration, no guidelines exist on how to monitor its effect accurately [27].

No clinical study on IV rt-PA administration in the patients on dabigatran has been reported. There is only one case study by Ann De Smedt et al. [33], reporting a case of a patient who received IV rt-PA just below 4.5 h after onset of symptoms and 7 h after last intake of dabigatran. There were no complications. Reevaluation at 24 h after symptom onset showed improvement in the neurological deficits. The details on coagulation assays of this patient are follows: PT 87% (normal: >70%), INR 1.2 (normal: 0.8–1.3) and aPTT 34.8 (normal: 22.2–34.4 s). The value of TT and ECT were not presented.

The Interventional Management Stroke (IMS) III trial [34] proposed that administration of rt-PA or endovascular intervention could be considered 48 h after the last intake of DTI or within 48 h of last intake with normal aPTT (in same way as heparin). However, without accurate test to monitor its effect, dabigatran-treated patients presenting with ischemic stroke should be carefully scrutinized for eligibility for IV rtPA. Further studies in this area are strongly encouraged.

Laboratory Research

Ammollo et al. [35] studied the effect of dabigatran on clot lysis in the presence of rt-PA using in vitro models. The resistance of tissue factor-induced plasma clots to fibrinolysis by exogenous rt-PA was reduced by dabigatran in a

Table 1 Characteristics of different coagulation markers

	PT	aPTT	TT	ECT
Mechanism of makers	Extrinsic pathway	Intrinsic pathway	Activity of thrombin	Activity of thrombin
Response at recommended therapeutic concentration of dabigatran	Less linear	Linear	Linear	Linear
Response at high concentration of dabigatran	Less linear	Plateau effect	Linear	Linear
Commercially available	Y	Y	Y	N

PT prothrombin time, *aPTT* activated partial thromboplastin time, *TT* thrombin time, *ECT* ecarin clotting time, *Y* Yes, *N* No

concentration-dependent manner, with > or = 50% reduction of lysis time at clinically relevant concentrations.

Clinical Studies in Acute Ischemic Stroke

In a clinical study, treatment with the direct thrombin inhibitor argatroban in conjunction with rt-PA in acute ischemic stroke with middle cerebral artery occlusions led to a considerable increase in recanalization rate compared to rt-PA alone, with a moderately increased rate of symptomatic intracranial hemorrhage (ICH) (2/15, 13%) [36]. In this study, after standardized rt-PA treatment, a 100-μg/kg bolus of argatroban followed by infusion of 1 μg/kg per min for 48 h was adjusted to a target partial thromboplastin time of 1.75 times that of the control group. The mean ± SD time from symptom onset to argatroban bolus was 172 ± 53 min. Of the included 15 patients, recanalization was complete in 6 patients and partial in 4 detected by trascranial Doppler ultrasound. Similar results can be anticipated with low-dose dabigatran in conjunction with rt-PA. Low-dose rt-PA in the presence of prior dabigatran may enhance the clot lysis; however, the rate of ICH in such scenarios remains unclear [37].

Future studies should focus on the effect of low-dose dabigatran on rt-PA safety and efficacy and the establishment of reliable clotting assay for clinical decision making. In the mean time, careful clinical consideration is required before administering IV or intra-arterial thrombolytic therapy in this patient population.

Re-Initiating Dabigatran Treatment in Patients with Prior TIA or Stroke

Diener et al. [38] performed a subgroup analysis of RE-LY trial to assess the effects of initiation of dabigatran in patients with previous stroke or TIA. There was no increase in adverse events including ICH (using warfarin as reference) with either of the two doses of dabigatran between patients with and without previous stroke or transient ischemic attack. However, the RE-LY trial excluded all patients with TIA or ischemic stroke occurrence within the past 2 weeks before enrollment. Therefore, this substudy could not provide information on the efficacy of dabigatran in the early phase after TIA or stroke. Authors concluded that it is safe to use dabigatran in patients with prior TIA or stroke; however, further data are required regarding initiating dabigatran within the first 2 weeks following ischemic events.

Intracranial Hemorrhage

Incidence of Intracranial Hemorrhage

The incidence of hemorrhagic stroke in patients on dabigatran was evaluated in RE-LY trial [19]. The incidence of ICH was 12 per 10,000 and 10 per 10,000 patients treated on 110 and 150 mg of dabigatran, respectively. The rates ware lower than the rate observed with warfarin treatment, 38 per 10,000 treated patients per year. Hence, dabigatran has almost one-third reduction in the rate of ICH. Theoretically, warfarin acts at multiple levels of coagulation cascade by inhibiting factors II, VII, IX and X and proteins C and S. However, dabigatran etexilate is a selective inhibitor of thrombin, which may explain its excellent antithrombotic efficacy while preserving some other hemostatic mechanisms in the coagulation system and thus potentially extenuating the risk of bleeding.

Management of Intracranial Hemorrhage in Patients on Dabigatran

Most patients will require supportive treatment to control bleeding [29]. Though the anticoagulant effects of heparin and warfarin can be reversed with protamine sulfate and prothrombin supplementation, respectively, there is no antidote to dabigatran etexilate or dabigatran. In the event of ICH, dabigatran should be stopped immediately and symptomatic treatment should be initiated. Further managements should be individualized according to the severity of the hemorrhage (see Table 2). As dabigatran is primarily excreted in the urine, adequate diuresis is needed to flush it out of the system. Transfusion with fresh frozen plasma, red blood cells and platelet concentrates may be

Table 2 Management of dabigatran in case of intracranial bleeding

First step	Stop dabigatran, symptomatic treatment including BP control and diuresis
Second step	Measurement of TT, aPTT and ECT, consideration of transfusion with FFP, rFVIIa and PCCs
Third step (severe life-threatening situation)	Hemodialysis

BP blood pressure, *TT* thrombin time, *aPTT* activated partial thromboplastin time, *ECT* ecarin clotting time, *FFP* fresh frozen plasma, *rFVIIa* recombinant activated factor VII, *PCC* prothrombin complex concentrate

necessary especially in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used. Measurement of TT, aPTT and ECT may help guide the therapy. Also, specific reversal agents like recombinant activated factor VII (rFVIIa) and prothrombin complex concentrates (PCCs) may be considered. rFVIIa is an approved potent procoagulant and general hemostatic agent that has effect at sites of bleeding by directly activating thrombin on the surface of platelets in the absence of tissue factor [39]. Consequently, it has been suggested that this agent may have procoagulant effects on a variety of anticoagulants, including dabigatran. It has been reported that "off-label" use was successful in patients with refractory life-threatening hemorrhage [40]. PCCs contain all the vitamin K-dependent coagulation factors and have therefore been useful for the rapid reversal of coagulopathy by replacing vitamin K-dependent clotting factors and restoring normal hemostasis in the over-anticoagulation condition induced by vitamin K antagonist (VKA) [41]. Following its successful use in patients with hemophilia A, activated PCCs (APCC) have also found a role as a general hemostatic agent outside of the setting of VKA reversal in patients with serious bleeding events. APCC have been reported to have thrombogenic potential; therefore, as in all emergency situations, a risk–benefit evaluation regarding use of this treatment is required. There are no published clinical data on the use of rFVIIa or PCC in patients on dabigatran or other newer oral anticoagulants [42]. However, careful consideration can be made in life-threatening situations. Careful consideration for surgery is required in life-threatening situations. If all the above measures fail to control bleeding and more rapid reversal of the anticoagulant effects is required, the use of hemodialysis is an option. Due to its relatively low plasma protein binding, dabigatran can be dialyzed with the removal of about 60% of drug over 2–4 h [43].

Surgical Procedure

In clinical stroke setting, a need of invasive procedures such as central venous line puncture, placement of a spinal catheter, or other surgeries is frequently encountered in patients on anticoagulation treatment. Patients with therapeutic levels of dabigatran etexilate who undergo invasive procedures are at increased risk for bleeding. Since patients with renal disorder may introduce elevated concentrations of dabigatran, it may be beneficial to check the CCr several days before elective surgery. Therefore, surgical interventions may require the temporary discontinuation of dabigatran etexilate depending on the degree of renal impairment and risk of bleeding [29]. Dabigatran should be discontinued 24 h before invasive procedure in patients with normal renal function (CCr $>$ 50 ml/min) and a standard bleeding risk. Dabigatran should be discontinued 2–4 days before invasive procedure in patients with normal renal function and a high bleeding risk where complete hemostasis may be required (i.e., patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port). Dabigatran should be discontinued at least 2 days before invasive procedure in patients with impaired renal function (CCr $<$ 50 ml/min) and a standard bleeding risk. In patients with impaired renal function and at higher risk of bleeding, dabigatran should be stopped 4 days before procedure.

If surgical procedure cannot be delayed, there is a definite increase in risk of bleeding. This risk of bleeding should be weighted against the urgency of intervention. Bleeding risk can be assessed by the aPTT, TT and ECT as described in the monitoring section of this article. For patients with higher risk of bleeding, coagulation makers should be assessed 6–12 h before surgery and a normal result should be obtained to perform an invasive procedure. Persistent abnormality of the coagulation makers in the absence of heparin, or other DTIs (e.g., lepirudin and bivalirudin) represent strong evidence of elevated levels of dabigatran. Invasive procedures should be delayed in patients at high risk of bleeding with an abnormal coagulation tests. Since patients with renal impairment may exhibit prolonged elevation in concentrations of dabigatran, serum creatinine may be checked when the patient has persistent abnormal coagulation values [29].

Dabigatran may need to be permanently discontinued in patients with severe renal impairment (CCr $<$ 30 ml/min) unless their renal function improves [29]. In addition, patients with severe renal impairment should have a delay in surgery; if possible, hemodialysis should be considered prior to surgery as their risk of bleeding will be increased.

In the post-procedural period, dabigatran treatment can be restarted as soon as clinically indicated. If oral

medication is not feasible, parenteral heparinization should be considered.

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