

Management of Bleeding Complications of Dabigatran

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Abstract

Dabigatran etexilate is a new oral non-peptidic direct thrombin inhibitor approved by the FDA and EMA for stroke prevention in patients with non-valvular atrial fibrillation. Unlike warfarin, there are no antidotes available for reversing its anticoagulant effect, a strategy for the optimal management of major bleeding has not yet been developed, and most recommendations are based on expert opinions and small trials. This review aims to summarize the published data and identify potential issues in the management of bleeding complications associated with this drug.

Keywords: Dabigatran; Bleeding; Anticoagulant reversal

Introduction

Dabigatran etexilate is an oral direct thrombin inhibitor initially approved by the European Medicines Agency (EMA) for primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip-replacement surgery [1] or total knee-replacement surgery [2]. Dabigatran was also approved for stroke prevention in patients with non-valvular Atrial Fibrillation (AF) by the United States Food and Drug Administration (FDA) and EMA, based on the results of the RE-LY trial, in which dabigatran at a dose of 150 mg, twice daily, was superior to warfarin at reducing the rate of stroke and systemic embolism among patients with non-valvular AF [3]. In this study, both drugs were associated with a similar risk of bleeding (for major bleeding, the rates were 3.3% and 3.6% per year among patients who received dabigatran and warfarin, respectively) [3], although the rate of spontaneous intracranial hemorrhages was significantly lower among patients who received dabigatran compared with those treated with warfarin (0.09% vs. 0.36% per year), there being no differences in the intracranial hemorrhage mortality rates [4]. However, major Gastrointestinal Bleedings (GIB) were more frequent in the dabigatran group (1.51% vs. 1.02% per year) [3], which was confirmed from a subsequently reported analysis (1.85% vs. 1.25% per year) [5]. In addition, a recent meta-analysis showed that the risk of GIB associated with dabigatran use was 1.58 (95% CI, 1.29-1.93), higher than for warfarin [6]. In addition, the risk of hemorrhage could be between 3- and 15-fold higher since the current evidence is based on selected patients and so does not accurately reflect the circumstances of patients in clinical practice [6-8]. In fact, a subgroup analysis from the RE-LY trial, showed that patients over 75 years of age had a significantly higher rate of major bleeding than younger patients; this higher rate was evident for extracranial bleeding (2.80% vs. 2.19% per year for GIB), but not for intracranial bleeding [5]. Therefore, bleeding associated with dabigatran needs to be correctly managed, since increasing numbers of patients are receiving this new drug.

Unlike warfarin, there are no antidotes currently available for reversing the anticoagulant effect of dabigatran, an optimal strategy for managing severe bleeding has not yet been developed, and most recommendations are based on expert opinions and small trials. This review aims to summarize the information and identify potential issues and strategies for the management of bleeding complications associated with this novel drug.

Treatment Options

Conservative management

Observation and general supportive measures, such as

mechanical compression, could be enough for the management of minor bleeding [9]. Because of the short half-life of dabigatran, for less significant bleeds we recommend to delay or discontinue the drug and wait for the anticoagulant effects to wear off in few hours. Additionally, for mucosal bleeding (epistaxis, gingivorrhagia) which tend to be very uncomfortable for the patient, tranexamic acid could be especially useful [9].

However, for major bleeding episodes or if the patient continues bleeding, haemostatic agents should be administered.

Fresh-frozen plasma

Fresh-Frozen Plasma (FFP) is human donor plasma, either recovered from a single whole-blood donation or obtained by plasmapheresis, frozen within 8 hrs of collection and then stored, typically at -30°C [10]. FFP contains all the soluble coagulation factors and has been given to stop bleeding in several situations, such as congenital or acquired deficiencies of one or more coagulation factors, reversal of the warfarin effect or disseminated intravascular coagulation [11].

FFP has been evaluated in a murine model of intracranial hemorrhage associated with dabigatran. Dabigatran at a dose of 9.0 or 4.5 mg/kg was administered to mice for 1 h before inducing intracranial hemorrhage. The use of FFP prevented hematoma growth after dabigatran at 4.5 mg/kg, but did not when a 9.0 mg/kg dose was administered; mortality was not affected at either dose [12]. As there are no data about the use of FFP in the setting of human bleeding related to dabigatran [13,14] we would not recommend its use outside of clinical trials.

Prothrombin complex concentrates

Prothrombin Complex Concentrates (PCCs) are concentrated virus-reduced pooled plasma products that contain a combination of either three or four nonactivated factors (II, IX, and X, or II, VII, IX, and X). The FDA also approved factor eight inhibitor bypassing activity,

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which is an activated PCC (aPCC) that contains equal units of non-activated factors II, IX, and X and activated factor VII [13].

Experimentally induced bleeding in rats showed that aPCC at 50 or 100 IU/kg significantly reduced bleeding after a high dose of dabigatran (1 μ mol/kg in bolus followed by 0.5 μ mol/kg/h i.v. for 25 min), although the activated partial thromboplastin time (aPTT) was not shortened [15]. aPCC was also tested in a rabbit trauma bleeding model used to reverse dabigatran after overdosing (0.4 mg/kg i.v.). In this study, although aPCC had no effect on plasma levels of dabigatran, it reversed dabigatran-induced bleeding in a dose-dependent manner: aPCC at 20 IU/kg had no influence on the volume of blood loss or the time to hemostasis, while doses of 35 IU/kg and 50 IU/kg reduced both [16]. Therefore, the authors concluded that aPCC could be used in cases of severe bleeding complications.

Another murine oral anticoagulant-associated intracranial hemorrhage model demonstrated that excess hematoma expansion caused by dabigatran could be effectively prevented by administering four-factor PCC in a dose-dependent manner (PCC at 100 IU/kg reversed the effect of dabigatran on tail vein bleeding time more effectively than at a dose of 50 or 25 IU/kg); and administration of PCC at 100 IU/kg and 50 IU/kg PCCs prevented excess hematoma growth. It is of particular note that PCC administration significantly reduced 24 h mortality to the level of non-anticoagulated control mice [12].

However, animal models are not truly representative of major hemorrhagic events in humans. In a double-blind, placebo-controlled study, 12 healthy male volunteers received dabigatran 150 mg, twice daily, for 2.5 days, followed by administration of PCC at 50 IU/kg. The treatment had no influence on the anticoagulant effect of dabigatran, as indicated by persistent increases in the aPTT, ecarin clotting time and thrombin time [17].

In an *ex vivo* study of ten healthy volunteers who received 150 mg of dabigatran in one oral dose, four-factor PCC and aPCC were tested *in vitro* using thrombin-generation tests at different dosages to reverse the anticoagulant activity of dabigatran. Both agents increased the endogenous thrombin potential in a dose-dependent manner, but higher doses over-corrected it. However, only aPCC corrected the lag-time of thrombin generation and time to peak concentration of thrombin, and the minimal efficient dose of aPCC was not clearly determined [18]. The authors noted several limitations of their study: first of all, the dose of dabigatran was not comparable with that used in clinical practice; and secondly, overdose conditions or bleeding models were not tested.

Recently, an ongoing clinical trial reported early results from an *ex vivo* study using blood samples from six healthy subjects treated with 150 mg/12 h of dabigatran. PCC at 50 IU/kg or aPCCs at 75 IU/kg were tested *in vitro*. However, only aPCC reversed the effects of dabigatran on aPTT and the alterations in fibrin formation [19].

In summary, these conclusions are based on the extrapolation from results obtained *in vitro* to the *in vivo* setting, and further studies are needed since the experience of the use of PCCs in patients receiving dabigatran is very limited.

Recombinant factor VIIa

Recombinant factor VIIa (rFVIIa) is a non-plasma-derived activated factor VII approved by the FDA for management of bleeding in hemophilia patients with inhibitors of factors VIII and IX.

Experimentally induced bleeding in rats demonstrated that rFVIIa at a dose of 0.1 or 0.5 mg/kg significantly reduced bleeding after a high

dose of dabigatran, and the prolonged aPTT was dose-dependently reversed [15]. However, in another murine model of intracranial hemorrhage, the administration of rFVIIa at 8.0 mg/kg was ineffective in reducing hematoma growth after injection of 4.5 or 9 mg/kg dabigatran [12].

Thrombin-generation tests have been used to test rFVIIa *in vitro* at several doses in an *ex vivo* study of ten healthy volunteers who received 150 mg of dabigatran in a single dose. The administration of rFVIIa at 3 μ g/ml, which was the highest dose tested, reduced the lag-time of thrombin generation to almost that at baseline. This raises the problem of safety, although in this study rFVIIa did not increase the amount of thrombin generated [18].

An ongoing clinical trial reported early results from an *ex vivo* study using blood samples from six healthy subjects treated with 150 mg/12 h of dabigatran. In this study, rFVIIa at 270 μ g/kg was tested *in vitro* and found not to reverse the effects of dabigatran on aPTT, thrombin generation, viscoelastic properties of the clot or alterations in fibrin formation [19].

Recently, several case reports have provided support for the use of rFVIIa to manage bleeding in patients treated with dabigatran. The first reported case, to our knowledge, was of a 79-year-old patient, weighing 80 kg, who had developed life-threatening postcardiac surgery bleeding. The administration of three doses of rFVIIa at 2.4 mg did not control the bleeding; however, after two additionally higher doses of 7.2 mg of rFVIIa, bleeding was reduced from >1500 ml/h to ~800 ml/h [20]. Notably, administration of rFVIIa was followed by hemodialysis, which makes it difficult to determine the real efficacy of rFVIIa. Another case of a 76-year-old patient with a spontaneous intracranial hemorrhage showed that a single dose of rFVIIa at 90 μ g/kg normalized the aPTT, reduced the lag-time, increased the endogenous thrombin potential as determined by the thrombin generation test, and reduced the R-value as established by thromboelastography about 45 min after the administration of rFVIIa. However, the effect of rFVIIa was only partial and temporary, suggesting that multiple doses may be required [21].

Activated charcoal

Activated charcoal is a processed form of carbon with a very fine network of pores and a large internal surface area available for binding to oral drugs, reducing their absorption from the gastrointestinal tract [9]. Given this property, the use of activated charcoal to reduce absorption following a potential overdose of dabigatran has been evaluated *in vitro* [14], demonstrating that it could be successfully adsorbed by activated charcoal [22]. Moreover, a second *in vitro* study showed that dabigatran could also be removed from whole bovine blood by adsorption across an activated charcoal column [23].

Recently, a porcine model (*in vitro* and *in vivo*) showed that dabigatran can be successfully removed from the circulation after activated charcoal perfusion (75-80% of circulating dabigatran was reduced after 1 h, and levels were undetectable after 2 h). However, the active charcoal filter had a maximum binding capacity of 30 mg drug and there was no further clearance upon saturation [24].

Although these results are promising, we think that further data about the use of activated charcoal is needed before it is recommended for use in patients.

Hemodialysis

Dabigatran has a low protein binding capacity (~35%), so it can be removed from the circulation by hemodialysis [9]. In fact, it has been shown that the plasma concentration of dabigatran is reduced by 50-

60% within 4 h of hemodialysis, and could be an effective option in case of dabigatran overdose [25].

A recent *in vitro* and *in vivo* porcine model showed that dabigatran could be successfully removed by hemodialysis depending on dialysate flow rates, reaching a plateau at 300 ml/min. With this dialysate flow rate dabigatran levels were undetectable after 2 h [24].

Two recent case reports have also suggested that hemodialysis can effectively reduce dabigatran levels and help manage intracranial hemorrhage in patients treated with dabigatran [20,26]. However, the use of high-dose rFVIIa [20] and aPCC [26] before hemodialysis makes it difficult to assess the real efficacy of hemodialysis. Notably, the patient in the latter study had normal kidney function, so his native kidney excretion could help reduce dabigatran levels.

Specific antidote

Monoclonal antibodies have been successfully used to neutralize several drugs. Based on this, a humanized monoclonal antibody fragment (termed aDabi-Fab) from a hapten-immunogen derived from dabigatran has recently been generated. Initially, the specific-dabigatran antibody was shown to rapidly reverse the anticoagulant activity of dabigatran in a concentration-dependent manner. This was tested *in vitro* in a modified thrombin time assay [27], and *in vivo* in rat [27] and monkey [28] models. These results could be explained by the choice of higher affinity clones for humanized aDabi-Fab development, which resulted in greater binding [27]. These results were subsequently demonstrated in a monkey model. It is of note that, although aDabi-Fab mimicked thrombin, the affinity for dabigatran was ~350 times stronger than it was for thrombin (including its known substrates) [27]. Furthermore, in the absence of dabigatran, aDabi-Fab showed no influence in platelet aggregation studies or functional clotting assays. Therefore, aDabi-Fab did not result in any prothrombotic activity [27,29].

This is a new and promising drug; however, further studies of anticoagulant reversal in animal models of bleeding and clinical trials are still needed.

Conclusions

Dabigatran etexilate is a new oral direct thrombin inhibitor approved for stroke prevention in patients with non-valvular AF by the FDA and EMA. However, the risk of hemorrhage could be 3- to 15-fold higher than reported, since the current evidence is based on selected patients and so does not accurately reflect the circumstances of patients in clinical practice. Therefore, a strategy for the correct management of bleeding associated with dabigatran is needed, since increasing numbers of patients are receiving this drug.

A strategy for the optimal management of severe bleeding in this context has yet to be developed. Instead, most recommendations are based on expert opinions and small trials. One of the recommendations for minor bleeding is to discontinue dabigatran and wait for the anticoagulant effects to wear off. However, for major bleeding episodes, or if bleeding continues, haemostatic agents should be administered. There are no data from humans to support the effectiveness of the use of FFP in the setting of dabigatran-related bleeding. There has been little experience of the use of PCCs and further studies of this aspect are needed. In contrast to PCC, there are no *in vivo* studies with rFVIIa and its use in dabigatran overdose has not been explored. In addition, there are no hemorrhagic models, so the use of this agent is based on clinical data. Moreover, clinical case reports showed that the effect of rFVIIa on dabigatran-associated bleeding was unclear, and only

partial and temporary. On the other hand, hemodialysis has proved to be an effective option for dabigatran overdose, resulting in the restoration of blood coagulation, and recent case reports also suggest that hemodialysis can successfully reduce dabigatran levels and help manage intracranial dabigatran-associated bleeding. Finally, a specific antidote (aDabi-Fab) has recently been developed. aDabi-Fab rapidly reverses the anticoagulant activity of dabigatran *in vitro* and *in vivo* in animal models. This specific antidote (aDabi-Fab) could be a useful drug; however, additional studies of anticoagulant reversal in animal models of bleeding and subsequent clinical trials are needed.

References

1. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, et al. (2007) Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 5: 2178-2185.
2. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, et al. (2007) Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 370: 949-956.
3. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, et al. (2009) Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 361: 1139-1151.
4. Hart RG, Diener HC, Yang S, Connolly SJ, Wallentin L, et al. (2012) Intracranial hemorrhage in atrial fibrillation patients during anticoagulation with warfarin or dabigatran: the RE-LY trial. *Stroke* 43: 1511-1517.
5. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, et al. (2011) Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 123: 2363-2372.
6. Holster IL, Valkhoff VE, Kuipers EJ, Tjwa ET (2013) New Oral Anticoagulants Increase Risk for Gastrointestinal Bleeding - A Systematic Review and Meta-Analysis. *Gastroenterology* 145:105-112.
7. Southworth MR, Reichman ME, Unger EF (2013) Dabigatran and postmarketing reports of bleeding. *N Engl J Med* 368: 1272-1274.
8. Levi M, Hovingh GK, Cannegieter SC, Vermeulen M, Büller HR, et al. (2008) Bleeding in patients receiving vitamin K antagonists who would have been excluded from trials on which the indication for anticoagulation was based. *Blood* 111: 4471-4476.
9. Alikhan R, Rayment R, Keeling D, Baglin T, Benson G, et al. (2013) The acute management of haemorrhage, surgery and overdose in patients receiving dabigatran. *Emerg Med J*.
10. Stanworth SJ (2007) The evidence-based use of FFP and cryoprecipitate for abnormalities of coagulation tests and clinical coagulopathy. *Hematology Am Soc Hematol Educ Program*.
11. Stanworth SJ, Hyde CJ, Murphy MF (2007) Evidence for indications of fresh frozen plasma. *Transfus Clin Biol* 14: 551-556.
12. Zhou W, Schwarting S, Illanes S, Liesz A, Middelhoff M, et al. (2011) Hemostatic therapy in experimental intracerebral hemorrhage associated with the direct thrombin inhibitor dabigatran. *Stroke* 42: 3594-3599.
13. Akwa F, Spyropoulos AC (2013) Treatment of bleeding complications when using oral anticoagulants for prevention of strokes. *Curr Treat Options Cardiovasc Med* 15: 288-298.
14. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, et al. (2010) Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost* 103: 1116-1127.
15. van Ryn J, Ruehl D, Priepe H, Huel N, Wienen W (2008) Reversibility of the anticoagulant effect of high doses of the direct thrombin inhibitor dabigatran, by recombinant factor VIIa or activated prothrombin complex concentrate. *Haematologica* 93(s1): 148.
16. van Ryn J, Dörr B, Kaspereit F, Krege W, Zeitler S, et al. (2010) Beriplex P/N reverses bleeding in an acute renal injury model after dabigatran overdose of rabbits. *Pathophysiology of Haemostasis and Thrombosis* 37(s1): A94.

17. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, et al. (2011) Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 124: 1573-1579.
18. Marlu R, Hodaj E, Paris A, Albaladejo P, Cracowski JL, et al. (2012) Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: a randomised crossover ex vivo study in healthy volunteers. *Thromb Haemostasis* 108: 217-224.
19. Galan AM, Arellano-Rodrigo E, Sanz VV, Molina P, Reverter JC, et al. (2012) Reversal of the Antithrombotic Action of Rivaroxaban and Dabigatran: A Clinical Study in Healthy Volunteers. *ASH Annual Meeting Abstracts* 120: 2261.
20. Warkentin TE, Margetts P, Connolly SJ, Lamy A, Ricci C, et al. (2012) Recombinant factor VIIa (rFVIIa) and hemodialysis to manage massive dabigatran-associated postcardiac surgery bleeding. *Blood* 119: 2172-2174.
21. Aron JL, Gosselin R, Moll S, Arkin CF, Mantha S (2013) Effects of recombinant factor VIIa on thrombin generation and thromboelastography in a patient with dabigatran-associated intracranial hemorrhage. *J Thromb Thrombolysis*.
22. van Ryn J, Sieger P, Kink-Eiband M, Gansser D, Clemens A (2009) Adsorption of Dabigatran Etexilate in Water or Dabigatran in Pooled Human Plasma by Activated Charcoal in Vitro. *ASH Annual Meeting Abstracts* 114: 1065.
23. Van Ryn J, Neubauer M, Flieg R, Krause B, Storr M, et al. (2010) Successful removal of dabigatran in flowing blood with an activated charcoal hemoperfusion column in an in vitro test system. *Haematologica* 95(s2): 293.
24. Lange J, Thiel C, Thiel K, Klingert W, Klingert K, et al. (2012) Acceleration of Dabigatran Elimination by Activated Charcoal Perfusion and Hemodialysis in a Pig Model. *ASH Annual Meeting Abstracts* 120: 2272.
25. Stangier J, Rathgen K, Stähle H, Mazur D (2010) Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet* 49: 259-268.
26. Chang DN, Dager WE, Chin AI (2013) Removal of dabigatran by hemodialysis. *Am J Kidney Dis* 61: 487-489.
27. Schiele F, van Ryn J, Canada K, Newsome C, Sepulveda E, et al. (2013) A specific antidote for dabigatran: functional and structural characterization. *Blood* 121: 3554-3562.
28. Toth J, Gan G, van Ryn J, Dursema H, Isler J, et al. (2012) Reversal of Dabigatran's Anticoagulant Activity in the Monkey by a Specific Antidote and Pharmacokinetic and Pharmacodynamic Modeling. *ASH Annual Meeting Abstracts* 120: 22.
29. Millar CM, Lane DA (2013) Blocking direct inhibitor bleeding. *Blood* 121: 3543-3544.