

Practical considerations on anticoagulation reversal: spotlight on the reversal of dabigatran

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Abstract: Idarucizumab (Praxbind) is a humanized antibody fragment, that reversibly and with high affinity binds dabigatran (Pradaxa). Anticoagulation reversal is achieved immediately, and with no procoagulant effect. It is administered intravenously and clearance is renal. The main clinical application of idarucizumab is to antagonize bleeding related to dabigatran, especially if it occurs at critical sites, such as nervous system (central or peripheral), intraocular, pericardial, retroperitoneal or pulmonary. Other indications are: i) dabigatran-induced anticoagulation reversal in the need for emergency surgery or procedures at high risk of bleeding; and ii) second-line treatment in bleedings that persist despite local hemostasis procedures. In this narrative review, we comprehensively address clinical indications for idarucizumab, summing up evidence derived from a systematic literature review, but also from case reports.

Keywords: dabigatran, idarucizumab, bleeding, surgery

Introduction

In the last ten years, there has been a revolution in the treatment of patients who need oral anticoagulants. The advent of non-vitamin K antagonist oral anticoagulants (NOACs) in the clinical practice has provided a treatment more effective and safer than warfarin for primary and secondary prevention of stroke and thromboembolic events in non-valvular atrial fibrillation (AF), as well as for the treatment and prevention of recurrences in patients with venous thromboembolic events (VTE).¹

NOACs radically changed the clinical routine for both clinicians and patients, with no need for continuous monitoring of coagulation tests, fewer drug-drug interactions, dose adjustment necessary only in few circumstances, and no interactions with food.

Among NOACs, dabigatran etexilate (Pradaxa) is a reversible, competitive, direct thrombin inhibitor. It has two main indications: i) stroke prevention in patients with non-valvular atrial fibrillation (NVAF); and ii) prevention and treatment of the venous thromboembolism. It is administered orally and binds and inhibits free and clot-bound thrombin. About three-quarters of a dabigatran dose is excreted with urine, and the elimination half-life is about 15 h if renal function is normal.² Although data from clinical trials and "real life" suggest that the risk of bleeding at critical sites with dabigatran is lower than that of warfarin, it still remains the most feared complication of dabigatran. When such unfortunate circumstances occur, lab tests have been implemented to define coagulation levels or the plasmatic drug concentration, and help clinicians in timing and management choices. Two tests are to date available for NOACs: i) a qualitative test (activated

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partial thromboplastin time (aPTT)), which can quickly be performed in all laboratories and give indications on the patient's coagulation status; and ii) quantitative tests (diluted thrombin time (dTT), and Ecarin clotting time (ECT)) that are used to measure drug plasma concentration by measuring the antithrombin effect; however, these are not readily available to most clinicians. Nevertheless, data on the timing of the last dose are still critical in limited resources settings, and to put laboratory findings into context.

aPTT does not have a linear response to the dabigatran dose or intensity of its anticoagulation effect, but a normal aPTT will exclude an anticoagulated state while an elevated aPTT will provide qualitative information about the increased risk of bleeding.

The dTT with hemoclot method and ECT correlate linearly with dabigatran, up to concentrations of 500 ng/mL.³

Dabigatran is the only new oral non-vitamin K anticoagulant that has had an available antidote (idarucizumab) since October 2015. Idarucizumab is a humanized antibody fragment, approved in Europe and the USA with the name Praxbind® (Boehringer, Ingelheim, Germany), that reverses the anticoagulant effects of dabigatran.³ It binds dabigatran with high affinity, about 350 times more than thrombin,⁴ and adheres with a ratio of 1:1 to dabigatran and its active metabolites, preventing thrombin inhibition.⁵ Furthermore, idarucizumab has no anticoagulant or pro-coagulant activity, and has no interaction with platelets.^{5,6}

The prospective cohort study RE-VERSE AD (reversal effects of idarucizumab on active dabigatran) showed that two sequential intravenous infusions of 2.5 g each (a total of 5 g) are able to completely reverse the anticoagulant effect of dabigatran within minutes in 88–98% of patients who had elevated dTT and ECT at baseline.^{6,7} Effectiveness in reversal was also demonstrated by regression within normal limits of such quantitative parameters in a few minutes after infusion, performed within 8 h of admission.^{3,4,7,8} Its distribution volume at steady state depends on the blood volume, and it was cleared from plasma with a half-life of about 45 min, mainly eliminated unchanged in the urine.⁸ Proteinuria is a common, transient condition after idarucizumab administration, and its blood levels rise in patients with renal insufficiency. Idarucizumab is not affected by renal or hepatic dysfunction, but possible adverse events are headache, migraine,

constipation, and erythema at the injection site.^{9,10} After reversal, the effect of dabigatran is restored after 24 h.⁸

When we should use idarucizumab? – data from real life

Since the half-life of dabigatran is quite short (about 15 h), most bleeding events are managed by supportive methods alone. Nevertheless, there are some situations where it is crucial to use the antidote because every other measure had failed, as indicated by the European Society in a position paper.¹¹ A similar approach has been suggested in an Expert Consensus of the American College of Cardiology, in which the use of reversal agents was recommended when a hemorrhage occurs at a critical site or is life-threatening.¹²

If the dabigatran concentration is unknown, normal aPTT indicates that the drug levels are likely low enough to allow invasive procedures without additional risk due to the treatment. When drug levels in plasma are low, dabigatran does not play a major role in bleeding, so the administration of the antidote could be unnecessary and should be avoided. On the other hand, when higher drug levels are observed (a threshold value of 50 ng/mL has been proposed), the administration of the antidote is justified.¹³ Due to the mechanism of action of dabigatran, usual strategies that reduce the antithrombotic effect, such as concentrating pro-thrombin factors, are less effective; in fact, the thrombin inhibition is not antagonized in this way. Furthermore, hemodialysis, although possible, is time-consuming due to the large volume of distribution of dabigatran, and carries risks for complications.

Currently, idarucizumab is reserved to reversing the dabigatran-associated probable bleeding from critical closed-space sites such as central nervous system, intraocular, retroperitoneal, pericardial, pulmonary or compartment syndrome. Another crucial indication is in patients in whom the bleeding persists, despite a local hemostasis procedure being performed, or the dabigatran anticoagulant activity being reversed in emergency surgery or invasive procedures at high risk of bleeding. Recently, the administration of idarucizumab in patients taking dabigatran candidate of thrombolysis for ischemic stroke is spreading.¹⁴

Currently, intravenous thrombolysis with recombinant tissue-type plasminogen activator (rt-PA) is indicated in the treatment of ischemic stroke patients within 4.5 h of symptom onset. Anticoagulation is considered an absolute contraindication to intravenous thrombolytic therapy in ischemic stroke. The recommendation in the AHA Guidelines for the Early

Management of Patients With Acute Ischemic Stroke is that fibrinolytic therapy should not be administered to patients who take novel oral anticoagulants (NOACs) unless sensitive laboratory tests are normal or the patient has not received a drug dose for >48 h.¹⁵ Recent case reports, and data from registry and systematic reviews on this topic, show that clinicians could use idarucizumab before intravenous thrombolysis (IVT) when the last dabigatran assumption is within 24 h.¹⁶ This procedure seems to be safe, with side effects related to the stroke and patients characteristics rather than to the reversal of anticoagulation with idarucizumab.¹⁶ This topic needs further investigation, such as the aggregation of data from larger registries or clinical trials. This could provide more evidence on the use of IVT, especially in patients who have no indication for mechanical thrombectomy or favor bridging therapy.

Due to the advantages of an immediate-acting antidote, dabigatran has also been considered a first line anticoagulant among patients waiting for heart transplantation,¹⁷ though further studies are required on this topic.

As evidenced by the study recently published on Europace, idarucizumab usage could be inappropriate, and this is likely the result of the acute critical care setting in which a prompt decision is required.¹⁸ Clinicians should know, as far as possible, the last dabigatran intake and assess the urgency of the intervention as well as the bleeding severity when deciding upon administration and it would be better if the decision to administer idarucizumab was made by a multidisciplinary team.

Conclusion

Idarucizumab is an antidote and has no reversal function, therefore, it inhibits the activity of dabigatran but does not stop the bleeding.

Idarucizumab is indicated in:

- bleeding in critical close-spaced sites
- persistent major bleeding despite local hemostatic measures
- acute ischemic stroke before fibrinolytic therapy (more evidence is needed in order to standardize the procedure)
- emergency surgery
- invasive and high-risk bleeding procedures

Disclosure

Prof. Dr Giuseppe Ambrosio reports personal fees from Angelini, Boehringer, Behring, and Menarini, outside the

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