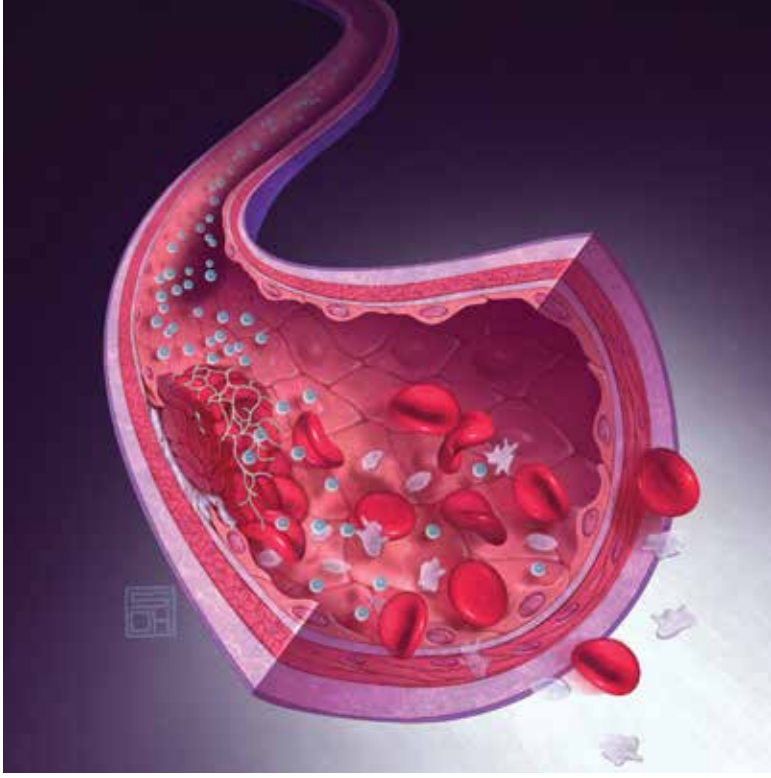
Idarucizumab

An anticoagulant reversal agent for dabigatran

ANTHONY F.T. BROWN MB ChB, FRCP, FRCSEd, FRCEM, FACEM
HARSHAL NANDURKAR MB BS, PhD, FRACP, FRCPA



Idarucizumab is a specific reversal agent for the novel oral anticoagulant (NOAC) dabigatran. Idarucizumab is indicated when rapid, complete and sustained reversal of dabigatran's anticoagulant effect is needed, such as when the patient requires emergency surgery or an urgent procedure, or has life-threatening or uncontrolled bleeding.

Novel oral anticoagulants (NOACs) currently available in Australia include the thrombin inhibitor dabigatran and the factor Xa inhibitors apixaban and rivaroxaban. These agents (also known as non-vitamin K antagonist oral anticoagulants) are approved for use in patients with nonvalvular atrial fibrillation (AF), and for the prevention and treatment of venous thromboembolism. Their advantages over warfarin include minimal drug or food interactions, and no requirement for regular laboratory monitoring, although the dose must be carefully considered in elderly people and those with renal impairment.[1]

MedicineToday 2016; 17(11): 63-65

Professor Brown is Professor of Emergency Medicine in the Discipline of Anaesthesiology and Critical Care, Faculty of Medicine MD Program, University of Queensland, Brisbane; and a Senior Staff Specialist in the Department of Emergency Medicine, Royal Brisbane and Women's Hospital, Brisbane, Qld. Professor Nandurkar is Professor of Haematology at Monash University, Melbourne; and Director of Clinical Haematology at Alfred Health, Melbourne, Vic.

However, a major concern with all NOAC use has been the lack of a specific reversal agent. Idarucizumab is the first such agent for any of the NOACs and is available now, targeted at dabigatran. Idarucizumab gained TGA approval in May 2016 for patients taking dabigatran who require emergency surgery or an urgent procedure, or have life-threatening or uncontrolled bleeding.

What is idarucizumab?

Idarucizumab is a humanised monoclonal antibody fragment developed as a specific reversal agent for dabigatran. It rapidly binds to both unbound and thrombin-bound dabigatran with 350-fold higher affinity than dabigatran for thrombin, reducing its anticoagulant effect to nil, with the effect lasting up to 12 hours. It is packaged as two 50 mL glass vials, each containing 2.5 g idarucizumab for intravenous (IV) use. These have a shelf life of 24 months when stored at 2 to 8°C.[2,3]

How is idarucizumab given?

The recommended dose of idarucizumab is 5 g IV, regardless of age, sex, body mass or renal status. This dose is given either as two consecutive infusions of 2.5 g, each one over 5 to 10 minutes, by hanging the 50 mL vial, or as a bolus by injecting both vials consecutively via a syringe.

Who is suitable to receive idarucizumab?

Patients suitable for idarucizumab are:

- patients taking dabigatran who require emergency surgery or an urgent medical procedure necessitating rapid reversal of its anticoagulant effect
- patients taking dabigatran with life-threatening or uncontrolled bleeding.

Other support measures, including surgical haemostasis and administration of blood and blood products, may well still be necessary according to the patient's clinical condition,

irrespective of the elimination of dabigatran's anticoagulant effect.

The potential need for idarucizumab has been estimated based on figures from the RE-LY study, which compared dabigatran with warfarin in people with atrial fibrillation. These figures suggest that approximately 0.98% of patients treated with dabigatran may need emergency surgery per year (RE-LY database, unpublished data) and 1.34% per year may experience life-threatening bleeding.[4] All will be eligible and may be suitable to receive idarucizumab.

However, it should be noted that most cases of bleeding in patients taking dabigatran are likely to be non-life threatening and readily managed by delaying or discontinuing the next dose of dabigatran, maintaining adequate diuresis and considering haemodialysis. In addition, many patients taking dabigatran who require non-emergency surgery can be managed by delaying surgery if possible for more than 12 to 24 hours after the last dabigatran dose or by providing general measures, including local haemostasis, blood and blood products.[5]

What about laboratory testing?

No laboratory tests are recommended to determine the anticoagulant effect of dabigatran in a life-threatening situation. In other situations, when time allows, a normal activated partial thromboplastin time (aPTT) and thrombin time (TT) indicate no dabigatran effect. Conversely, a prolonged aPTT or TT can act as a qualitative indicator of dabigatran's effect. The dilute thrombin time (dTT) or ecarin clotting time (ECT) are quantitative measures of dabigatran's anticoagulant effect, but neither test is currently readily available in many hospitals.[5,6]

How effective is idarucizumab?

Idarucizumab is safe, rapid and reliable in binding free and thrombin-bound dabigatran to completely reverse its anticoagulant activity within minutes, with the effect sustained for up to 12 hours. Idarucizumab has no procoagulant effects, requires no dose modifications, and has no reported contraindications or other drug interactions.

Dabigatran treatment can be restarted 24 hours after administration of idarucizumab, assuming any excessive bleeding tendency has been successfully mitigated. The ability to restart anticoagulation minimises the risk of a thromboembolic event, as patients taking dabigatran have underlying disease states predisposing to this.

How good is the evidence?

A randomised, placebo-controlled, double-blind, proof-of-concept phase I trial in 47 healthy volunteers aged 18 to 45 years found that idarucizumab 5 g IV was associated with immediate, complete (up to 99th percentile of levels measured) and sustained reversal of dabigatran-induced anticoagulation. Idarucizumab was well tolerated with no unexpected or clinically relevant safety concerns.[7]

The interim analysis of 90 people from an ongoing, single-arm, open-label, phase III, uncontrolled cohort study (RE-VERSE AD) in adults taking dabigatran who either had serious bleeding or required urgent surgery, found that 5 g idarucizumab IV reversed the anticoagulant effect of dabigatran, with a median maximal reversal at four hours of 100% (95% confidence interval, 100 to 100%).[8] This primary endpoint of anticoagulant reversal was used as a surrogate for efficacy, as net clinical benefit would still depend on the individual patient's underlying disease plus comorbidities, the reason for surgery and/or the site and severity of bleeding. These factors explain the apparently anomalous findings that the median investigator-reported time to cessation of bleeding was several hours and that 18 patients died – essentially illustrating that this was a sick group of patients with a broad range of inclusion criteria.[8] The study results were considered compelling enough to publish early, and were instrumental in idarucizumab's approval in the USA, Europe, New Zealand and now Australia.

Is there a factor Xa inhibitor reversal agent?

Idarucizumab is currently the only licensed reversal agent for any of the NOACs, but is used specifically for patients taking dabigatran and is not effective against the factor Xa inhibitors.

Andexanet alfa is a recombinant decoy factor Xa molecule developed as a reversal agent for factor Xa inhibitors such as apixaban and rivaroxaban. It could also potentially be used to reverse low molecular weight heparins and fondaparinux.[9] Healthy volunteer studies have shown andexanet alfa's success in terminating the anticoagulant effects of apixaban and rivaroxaban, but of note, different doses were needed and it had to be given as an IV infusion to sustain the effect. Recently, a preliminary analysis was reported of the phase IIIb-IV ANNEXA-4 study of andexanet alfa in patients taking a factor Xa inhibitor who had acute bleeding, but not specifically those about to undergo emergency surgery.[10] The results showed substantially reduced antifactor Xa activity by 4 to 4.5 hours, with good to excellent haemostasis in 79% of patients at 12 hours after an initial bolus and 2-hour infusion of andexanet alfa.[10]

The time line for regulatory approval of andexanet alfa in Australia and, if successful, the supply of commercial quantities is still to be determined. However, it is likely to be at least a couple of years from now.

How might idarucizumab influence practice?

As idarucizumab stock becomes available across Australia, it should be held in every public or private hospital that might care for a patient taking dabigatran. A reliable history of the time since the last dose and any renal impairment are invaluable in predicting

TABLE. PRACTICAL CONSIDERATIONS IN SELECTING A NOAC FOR PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION[13]*

Patient feature or consideration	Suggested NOAC
High risk of stroke, low bleeding risk	Dabigatran 150 mg twice daily
High bleeding risk	Apixaban or reduced-dose dabigatran
Renal impairment, history of gastrointestinal bleed or dyspepsia	Apixaban or rivaroxaban
Preference for a once-daily regimen	Rivaroxaban
Availability of specific reversal agent	Dabigatran

Abbreviation: NOAC = novel oral anticoagulant.
* Adapted from Maan et al. J Thorac Dis 2015; 7: 115-131.[13]

the likelihood of a significant level of dabigatran in the blood. Algorithms that include testing for dabigatran in plasma using qualitative TT or quantitative dTT assays should be incorporated into bleeding-management protocols in suitably equipped hospitals, to avoid the unnecessary use of idarucizumab when the dabigatran level in plasma may be negligible.

As proven in the REVERSE-AD study, the ease of use of idarucizumab means it could feasibly be stocked even in smaller hospitals staffed by GPs, who may be the first to see and treat patients taking dabigatran who present with a life-threatening bleed.

However, idarucizumab's biggest impact may be in influencing NOAC choice and patterns of use. After all three NOACs received PBS listing in 2013, analysis of an older veteran population showed that the overall rate of anticoagulation for patients with AF increased over the next year, and the rate of warfarin use declined.[11] Of around 5500 patients newly initiated on anticoagulation, 72% received a NOAC.[11] National PBS data show that warfarin prescriptions are still higher in total numbers, but are increasing at a slower rate than NOAC prescriptions. For example, NOAC prescriptions for stroke prevention in patients with AF increased tenfold from 2013 to 2014.[12]

The choice of which NOAC to commence should be individualised for every patient, with the current availability of three drugs increasing flexibility. Some practical considerations in selecting the most appropriate agent for an individual with nonvalvular AF are shown in the Table.[13]

The increasing use of NOAC agents appears justified by real-world, everyday-use patient data that demonstrate their efficacy in comparison with warfarin and their superiority in terms of reduced bleeding risk (particularly dabigatran and apixaban).[14]

Conclusion

Idarucizumab is a monoclonal antibody fragment that specifically reverses the anticoagulant effect of the NOAC dabigatran. The decision to use a NOAC rather than warfarin has been negatively influenced by the lack of a specific reversal agent, even though the risk of serious bleeding is generally less with the use of NOACs than with warfarin. The availability, efficacy and ease of delivery of idarucizumab should now reassure clinicians and patients about the use of dabigatran. MT

References

1. Brieger D, Curnow J. Anticoagulation: a GP primer on the new oral anticoagulants. Aust Fam Physician 2014; 43: 254-259.
2. Eikelboom JW, Quinlan DJ, van Ryn J, Weitz JI. Idarucizumab. The antidote for reversal of dabigatran. Circulation 2015; 132: 2412-2422.
3. Praxbind® idarucizumab, rch. Product information. Sydney: Boehringer-Ingelheim; 2016. Available online at: http://files.boehringer.com.au/files/PI/Praxbind PI.pdf (accessed October 2016).
4. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139-1151.
5. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace 2015; 17: 1467-1507.
6. Tran H, Joseph J, Young L, et al. New oral anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management. Intern Med J 2014; 44: 525-536.
7. Glund S, Stangier J, Schmohl M, et al. Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial. Lancet 2015; 386: 680-690.
8. Pollack CV, Reilly PA, Eikelboom JW, et al. Idarucizumab for dabigatran reversal. N Engl J Med 2015; 373: 511-520.
9. Connors JM. Antidote for factor Xa anticoagulants. N Engl J Med 2015; 373: 2471-2472.
10. Connolly SJ, Milling TJ, Eikelboom JW, et al. Andexanet alpha for acute major bleeding associated with factor Xa inhibitors. N Engl J Med 2016; 375: 1131-1141.
11. Pratt NL, Ramsay EN, Caughey GE. Uptake of novel oral anticoagulants in Australia. Med J Aust 2016; 204: 104-105.
12. Baker D, Wilsmore B, Narasimhan S. Adoption of direct oral anticoagulants for stroke prevention in atrial fibrillation. Intern Med J 2016; 46: 792-797.
13. Maan A, Heist EK, Ruskin JN, Mansour M. Practical issues in the management of novel oral anticoagulants – cardioversion and ablation. J Thorac Dis 2015; 7: 115-131.
14. Lin I, Masseria C, Mardekian J, et al. Real-world bleeding risk among non-valvular atrial fibrillation (NVAF) patients prescribed apixaban, dabigatran, rivaroxaban and warfarin: analysis of electronic health records. Eur Heart J 2015; 36(Abstr Suppl): 1084.

COMPETING INTERESTS: Professor Brown is Chair of the Idarucizumab Advisory Board, Boehringer-Ingelheim and has received honoraria and educational expenses from Boehringer-Ingelheim, Bayer and Shire. Professor Nandurkar is a Member of the Idarucizumab Advisory Board, Boehringer-Ingelheim. He has received research support from Pfizer and honoraria from Bayer.