Idarucizumab

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Approved indication: dabigatran reversal

Praxbind (Boehringer Ingelheim)
vials containing 2.5 g/50 mL
Australian Medicines Handbook section 7.4

A limiting factor in the use of the newer oral anticoagulants is that, unlike warfarin, there have been no antidotes. Reversal of anticoagulation may be required if the patient develops severe bleeding or requires emergency surgery. Idarucizumab has been developed to reverse the effect of dabigatran, a direct thrombin inhibitor.

The development of idarucizumab involved genetically engineering a humanised monoclonal antibody fragment. The affinity of this antibody for dabigatran is greater than the affinity of dabigatran for thrombin.

To test the concept that idarucizumab would reverse the effect of dabigatran a trial was carried out in 47 healthy men. They were given dabigatran for a few days then, within two hours of the last dose, they were infused with idarucizumab or a placebo. Idarucizumab immediately bound to dabigatran so unbound dabigatran concentrations fell quickly. After idarucizumab doses of 2 g or more, they remained close to the lower limit of quantification during 72 hours of observation.[1] There was a rapid improvement in clotting studies such as thrombin time and activated partial thromboplastin time.

Idarucizumab is rapidly cleared. It is probably catabolised with 32% of the dose being excreted in the urine within six hours of infusion. There may be a transient proteinuria. Clearance is reduced in patients with renal impairment, but no dose adjustment is currently recommended by the manufacturer.

A prospective cohort study is investigating patients taking dabigatran who present with life-threatening bleeding or require surgery that cannot be delayed. The dose of idarucizumab used in this trial is two infusions of 2.5 g given no more than 15 minutes apart. Interim results on 51 patients with bleeding and 39 surgical patients have been published.[2] Most of these patients had atrial fibrillation and had been using dabigatran for stroke prevention. They had a median age of 76.5 years.

Compared to clotting tests taken before the first infusion, there was a complete reversal of the anticoagulant effect in almost all patients before the second infusion was given. The concentrations of unbound dabigatran had fallen to levels that would have little effect on coagulation. At 24 hours after the second infusion, the thrombin time was within the upper limit of the normal range in 90% of the patients with bleeding and 81% of the surgical patients. Normal haemostasis was reported in 33 of the 36 patients (92%) who had urgent surgery.[2]

The interim analysis reported nine deaths in each group of patients. Most of these were related to the presenting problem, particularly bleeding. Reversing the anticoagulant effect was associated with thrombosis in five patients.[2] While it is difficult to attribute adverse effects to idarucizumab, problems such as fever, rash and pruritus may be signs of hypersensitivity.

The idarucizumab solution contains a large amount of sorbitol and sodium. Patients with hereditary fructose intolerance are potentially at risk of adverse reactions from the sorbitol.

In some patients the anticoagulant effects of dabigatran may re-emerge up to 24 hours after an infusion of idarucizumab. Repeating the treatment may need to be considered. If the anticoagulant effect has been completely reversed, the patient will be at risk of thrombosis. A decision has to be made when to resume anticoagulant therapy. If dabigatran is still indicated, it can be resumed 24 hours after idarucizumab.

Although idarucizumab effectively reverses the anticoagulant effect of dabigatran, patients still require other supportive treatments. In the interim analysis the mortality rate was 20% and, without a control group, it is difficult to know if this was a significant improvement on supportive care. Interestingly, 24% of the patients presented with thrombin times that were within the normal range at baseline, so they would not have derived much benefit from idarucizumab. As these patients were excluded from the analysis, the assessment of effectiveness was limited.[2] More data will be required to define the role of idarucizumab especially in patient populations, such as those with renal impairment. As the drug is specific for dabigatran it should not be used to reverse the effects of other anticoagulants.

T T manufacturer provided additional useful information

REFERENCES

1. Glund S, Stangier J, Schmohl M, Gansser D, Norris S, van Ryn J, 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;386:680-90. http://dx.doi.org/10.1016/S0140-6736(15)60732-2
2. Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for dabigatran reversal. N Engl J Med 2015;373:511-20. http://dx.doi.org/10.1056/NEJMoa1502000

The Transparency score (T) is explained in 'New drugs: transparency', Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov) and the website of the European Medicines Agency (www.ema.europa.eu).