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The new way of Dabigatran reversal – Idarucizumab

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Abstract

Since last few years a popularity of new oral anticoagulants significantly raised. There are following main direct oral anticoagulants (DOAC) used in therapy: Dabigatran, Rywaroxaban, Apixaban, Endoxaban. Dabigatran (Pradaxa) is the first oral direct thrombin inhibitor approved by FDA in stroke prevention in atrial fibrillation (AF). Anticoagulant effect occurs through direct thrombin binding. Unlike the vitamin K antagonists such as warfarin or acenokumarol, therapy with dabigatran has faster onset and offset action, doesn't require routine monitoring has much less interactions. The main problem of treatment with dabigatran was difficulty in reversal of anticoagulant effect and overdose. Since three years the new antidote for dabigatran is available – Idarucizumab (Praxbind). Main indications for such use are dabigatran overdose, need of fast effect reversal before any interventions and life threatening bleeding. Despite other ways of anticoagulant effect reversal such as transfusion of plasma coagulation factors Idarucizumab is still highly recommended for direct use.

Aim of this study is to review the new way of dabigatran reversal - Idarucizumab .

Key worlds Dabigatran, DOAC, Idarucizumab, Praxbind

Introduction

Dabigatran is a a drug which acts as a direct thrombin inhibitor [1], [Figure 1]. Unlike any other NOACs this one is highly specific to II human coagulation factor. Inhibition of thrombin may cause thrombin time (TT) and activated partial thromboplastin time (APTT) prolongation, causing increased bleeding risk PETRO study [2].

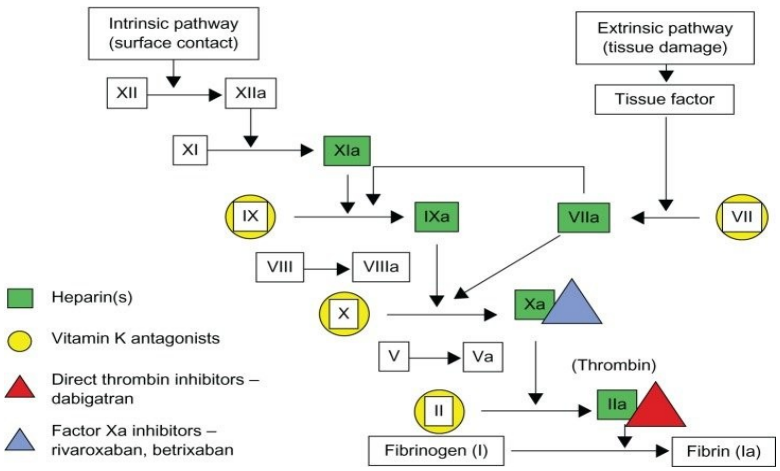

Figure 1 Mechanisms of anticoagulation drugs

Therapy with dabigatran is considered to be much more effective, at a dose 150mg twice daily than warfarin in stroke prevention, RE-LY study. [3.] Despite many benefits from therapy with dabigatran such as fast dose effect, less interactions and no need for regular blood controls there is lack of an effective reversal therapy, high price of the drug and dependence of proper renal function. [4] Prior to the idarucizumab treatment, local bleeding control, blood transfusions, plasma, vitamin K, platelets and cryoprecipitate were given. Major treatment strategy for Pradaxa reversal was hemodialysis[5,6]. Therapy with prothrombin complex plasma factors may not be effective in dabigatran effect reversal [7.] In October 2015, one month later in Europe, the FDA approved idarucizumab (Praxbind) as the first specific reversal agent for dabigatran. Drug was indicated for patients with life-threatening bleeding, and in cases where rapid reversal effect is needed for urgent interventions and become standard for such care if it is available [8,9].

Main body

Idarucizumab is a humanized monoclonal antibody, highly specific reversal agent for dabigatran. Drug binds with almost 350 times higher than thrombin affinity to dabigatran in blood, irreversibly [10,11] [Figure 2].

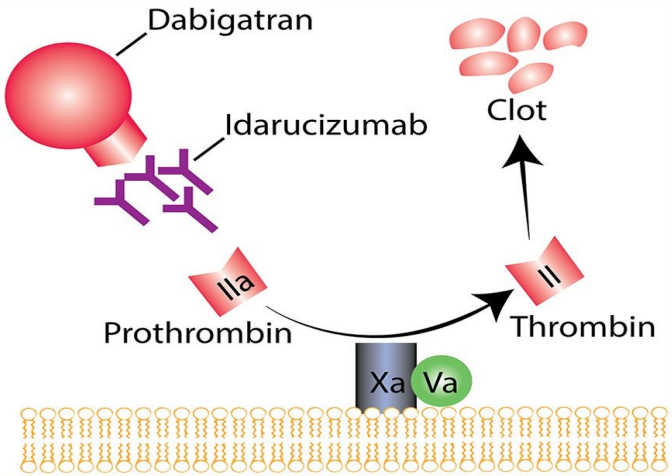

Figure 2 Mechanism of acting for Idarucizumab

Praxbind is primarily eliminated renally and so drug exposure is increased in patients with renal dysfunction. In clinical trials dabigatran reversal effect was proven due to a shortening of APTT, PT and activating clotting time (ACT)[12,13]. The biggest study of dabigatran reversal drug THE RE-VERSE AD, has proven both safety and efficacy of idarucizumab as two consecutive rapid 2.5 g intravenous boluses, for patients dabigatran treated with life threatening bleeding (group A) and nonbleeding who required immediate invasive procedures (group B) with total number of 503 patients. In both groups excellent results in anticoagulation reversal were achieved with median time of bleeding time 2,5 hours (group A) and 1,6 hour median time for beginning of surgical procedure. [14,15]. During the study single dose of idarucizumab without previous dabigatran therapy didn't cause any coagulation effect. [16]

On the other hand thrombotic events occured in 2,4% (4,8 % in A group and 6,8% in B group), of treated patients during 90 days of follow up time. Among 5,6% acute immunization caused severe

symptoms, such as rush, vomiting and loss of consciousness or even anaphylaxis. Also cases of delirium or septic shock were observed, [14].

Conclusion

Anticoagulation treatment with DOAC is considered to be the most effective and safest way. There are many benefits with this therapy such as no need for regular INR monitoring, less food and drug interactions. On the other hand cons like high cost therapy, lack of renal failure and significant valve failure occur. Therapy with DOAC may also be safer because of the presence of direct dabigatran antagonist – Idarucizumab. According to the latest EBM antibody is proven safe for use, having strong indications for rapid dabigatran reversal in severe bleeding and before surgical procedures. Biggest research THE RE-VERSE AD shown that Idarucizumab was effective in almost 98% of use, with only few percentage of thrombotic events. Such high percentage of success in therapy made Praxbind safe and effective drug. Praxbind is recommended by ESC (European Society of Cardiology) in life threatening bleeding among patients treated with dabigatran with AF. Future years may also bring us new antidotes for other DOACs acting for tenth plasma factor, such as Andexanet alpha or aripazin.

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