Towards the development of specific antidotes: Idarucizumab for reversal of dabigatran effects

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Despite the proven efficacy of novel oral anticoagulants, bleeding still remains a serious complication (1–3). In case of life-threatening conditions, immediate reversal of the anticoagulant effect is needed, regardless of the relatively short-half life of new direct anticoagulants. However, there is a lack of experience in managing patients treated with new direct oral anticoagulants who need to undergo emergency surgery. In this situation, a careful balance between the risk of bleeding and of thromboembolism is required (4). Even in non emergent surgery, the widespread practice of bridging anticoagulation may increase bleeding risks (3).

Reversal strategies for the new agents have not yet been established. According to vitamin K antagonist reversal and based on preclinical and animal studies, current guidelines recommend the administration of prothrombin complex concentrates (PCC) (5), which contain the vitamin K–dependent coagulation factors II, IX and X, without (3-factor PCC) or with sufficient amounts of factor VII (4-factor PCC). A supposed mechanism by which PCCs reverse dabigatran effects is an enhanced thrombin generation, produced from the prothrombin in PCCs. Consequently, dabigatran molecules are saturated with thrombin and the remaining unbound thrombin stimulates coagulation without dabigatran inhibition (5). Therefore, there is a rationale that PCCs might overcome the effects of thrombin and factor Xa inhibitors (6, 7).

However, no studies have been conducted in bleeding human patients, and therefore the effectiveness of this procedure and the appropriate doses need to be established. Furthermore, there is a considerable variation in the amounts of the different factors, and it is currently unknown which components of PCCs improve haemostasis after the administration of new oral agents. A considerable shortcoming of the use of high PCC doses is the increased risk of thromboembolic events, which may evolve from the over-correction of coagulation parameters and from an imbalance of pro- and anti-coagulant proteins (5, 6).

Other potential strategies for the reversal of new direct anticoagulants were also primarily established for the treatment of vitamin K–induced bleeding and include the use of fresh frozen plasma (8) with only limited available data or rationale for this approach to antagonise novel direct anticoagulants. Recombiant activated factor VII may be useful to reverse anticoagulation by the FXa inhibitors rivaroxaban and apixaban. In contrast, it was less effective in reversing the effect of dabigatran (6, 9–11), the only orally administered direct thrombin inhibitor.

Further recommended pathways for the management of new oral anticoagulant-induced bleeding include discontinuation of treatment, identification of the bleeding source, haemostatic control and blood volume replacement (6). Due to the relatively low plasma protein binding of dabigatran (~35 %) (12), haemodialysis and haemofiltration could be another option for life-threatening bleeding under dabigatran in haemodynamically stable patients (10, 13).

The fact that routine coagulation tests are poorly predictive for dabigatran plasma concentrations and do not correlate well with bleeding or reversal of anticoagulation in this setting (6, 10), is further complicating the situation.

This emphasises the potential advantages of more selective reversal agents.

Recently, a specific antidote to dabigatran was developed. Idarucizumab is a humanised monoclonal antibody fragment that specifically binds dabigatran and neutralises its anticoagulant activity in experimental models (5). In an ex vivo study, addition of idarucizumab restored dabigatran-prolonged coagulation parameters and thrombin levels to baseline values, which distinguished idarucizumab from substitution with PCCs, showing a greater impact on coagulation variables than PCCs without having pro-thrombotic effects (5).

More recently various companies have started working on more specific reversal agents. Glund et al. (14) have now studied the pharmacokinetics, safety and tolerability of ascending idarucizumab doses and its effect on coagulation parameters in healthy men. In this first-in-human study, idarucizumab was safe and well tolerated when given in single rising doses from 20 mg to 8 g over one hour or from 1 to 4 g over five minutes. Peak plasma concentrations of idarucizumab were achieved at the end of infusion, indicating prompt availability in plasma for dabigatran binding (14).

Of course, further investigations are required to confirm this approach of a specific antidote in bleeding patients, but the results indicate a progressive and innovative concept in reversing new oral anticoagulants. The application for drug approval is already submitted and an accelerated procedure is expected, as the U.S. Food and Drug Administration has appraised the idarucizumab as a “breakthrough therapy”.

However, there are also some potential drawbacks to discuss: specific and selective agents are not universal agents, with the

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limitation that hospitals have to ensure the availability of different reversal treatments depending on the oral anticoagulant used. Further, in case of emergency situations patients may not be able to articulate which drug they are taking, possibly making the development of a general reversal agent of interest (6). In that regard, the development of a universal antidote against FXa inhibitors is of interest (15).

Finally it should not be forgotten that vitamin K antagonists and heparin have been the gold standard for the treatment and prevention of thromboembolic disease for many decades in various conditions not yet covered in the label of novel oral anticoagulants. Their use is preferable to off-label use of the novel oral anticoagulants, not only because of proven efficacy but also the rapid availability of approved antidotes.

Conflicts of interest
None declared.

References