Commentary

Specific reversal agents: Fast and fearless – A new era in anticoagulation care

Coumarins (including warfarin) have been the time-tested oral anticoagulants in clinical practice but came with a baggage of specific time for ingestion, need for monitoring/dose adjustment and food and drug interaction. While effective, it needed to maintain the international normalised ratio (INR) specifically between 2 and 3 for the duration of its need as per the clinical situation.[1,2]

The dawn of the 21st century witnessed a major revolution in the world of anticoagulation. Direct thrombin inhibitor dabigatran and Factor Xa inhibitors such as rivaroxaban, apixaban and edoxaban have emerged as extremely effective and safer alternatives to the vitamin K antagonist anticoagulants for stroke prevention in patients with atrial fibrillation (SPAF) and also for prevention and treatment of venous thromboembolism (VTE). These drugs inhibit specific enzymes in the coagulation cascade unlike warfarin that causes a deficiency. As per various trials, a predictable action of these drugs does not necessitate monitoring of therapy to maintain anticoagulation and have demonstrated a comparable or superior efficacy as well as safety, compared with warfarin for treatment and prevention of VTE and SPAF.[1,2]

However, the perceived fear of bleeding after initiation of these potent drugs and the lack of reversal agents have restricted widespread use of direct oral anticoagulants (DOACs). Unlike INR testing for warfarin, there is no specific single test that tells the efficacy of the DOACs. Specific coagulation assays and evaluation of the DOACs' peak and trough drug levels pose a costly barrier.[3,4]

Factor Xa inhibitors, namely, rivaroxaban and apixaban, can be tested using prothrombin time, which depicts relatively good sensitivity to these agents, but for standards for maximum sensitivity anti-Xa assay (not easy to set up for routine use) would be the gold standard.[5]

Dabigatran, the direct thrombin inhibitor, can be evaluated using activated partial thromboplastin time (aPTT), thrombin time (TT), diluted thrombin time, ecarin clotting time (ECT) and ecarin chromogenic assays apart from the various factor-based aPTT assays. However, TT demonstrates the maximum sensitivity followed by aPTT and PT. ECT can also be used, wherever available, to assess the levels of dabigatran.[5]

Hence, physicians found the INR testing as a useful 'comfort zone' tool to dose adjust warfarin so as to prevent either bleeding or clotting; in short, they felt 'things were under control'! This same feel good factor was missing with the DOACs which meant they could not predict a risk of bleed. This was abetted by the fact that there was no reversal agent for the DOACs unlike warfarin that had fresh frozen plasma (FFP), vitamin K, prothrombin complex concentrates (PCCs), or rFVIIa for reversal in case of a bleed.

In this issue of the Indian Journal of Anaesthesia, Shah *et al* have given the history of the DOACs with scientific information of their availability, clinical trials and safety issues of the reversal agents for these DOACs.[6]

With the approval of the reversal agents for DOACs, the anticoagulant management has become easier and accessible in cases of emergencies and for management mainly aimed at controlling the bleeding or complications during emergency procedures. PCCs or FFP and other general measures of bleeding management are not so effective for the DOACs as are these reversal agents.[7]

Warfarin reversal with plasma and vitamin K is rather slow process depending on the synthesis of clotting factors and may not help in cases of active bleeding. Idarucizumab, andexanet alfa and ciraparantag are the reversal agents for the newer oral anticoagulants, which have been studied and are under various stages of research and use in clinical practice.[8]

Ciraparantag is a molecule under early trials as a universal reversal agent for all the DOACs and heparins. It consists of two L-arginine chains with a piperazine containing linker chain, binding the anticoagulants by hydrogen bonds.[8]

Andexanet alfa has been recently US Food and Drug Administration (FDA)-approved as antidote for the reversal of rivaroxaban and apixaban. It acts as a decoy receptor, binding to rivaroxaban and apixaban, eventually freeing up the natural Factor Xa for haemostasis. It has side effects and has to be used with caution as it may rarely attract pneumonia, urinary tract infections, or an increased risk of prothrombotic effects.[8]

Idarucizumab is a fully humanised monoclonal antibody (MAB) fragment, which acts as a specific immediate, complete and sustained reversal of dabigatran with uncontrolled bleeding controlled in 2.5 h as well as in cases of conditions requiring emergency interventions (normal haemostasis in 1.6 h). The incidence of adverse effects, especially immunogenicity or prothrombotic complications, with this molecule was very low as the Fc fragment of the MAB has been removed. This was contrary to that observed with andexanet alfa and ciraparantag. It was approved by the US FDA in 2015 and is available in India since 2017.[9]

The approval of these reversal agents for DOACs has increased the confidence of the healthcare professionals with respect to their use for anticoagulation in VTE and SPAF. It indeed ushers in a new welcome era for safer and surer anticoagulation in our patients.

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