Antidotes for direct oral anticoagulants

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Direct oral anticoagulants (DOACs) are now recognized as a major step forward for our patients [1]. In orthopaedic surgery (total hip and total knee replacement only) they are replacing the classical low molecular weight heparin prophylaxis. They are also progressively taking over the Vitamin K antagonists (VKA) in atrial fibrillation patients and in patients treated for a venous thromboembolism event. However, several issues may deserve our attention. Reports on the pharmacokinetics and pharmacodynamics for these agents show a major intra- and inter-individual variability and a high number of drug-drug interactions. In addition, alteration of renal function interferes with most of DOACs. As a result, an unexpected high number of major bleeding events have been reported, especially with dabigatran, focusing the attention on these new anticoagulant agents [2]. Furthermore, as new biological tests become more readily available for monitoring that include the diluted thrombin time for dabigatran (Hemoclot®) and specific anti-Xa assays for rivaroxaban, apixaban, and edoxaban, ranges for optimal anticoagulation and potential thresholds for increased bleeding risks are not well defined [3].

Prothrombin Complex Concentrates (PCC) and activated Prothrombin Complex Concentrates (FEIBA®) have been tested with various doses and conflicting results in different animal models [4] [5] and healthy volunteers [6], and they are now used by clinicians in bleeding patients on a non-evidence-based basis, and with a variable efficacy. However, several series, especially in neurology/neurosurgery patients show a better outcome in patients treated with PCC [7]. In the GIHP-NACO registry, PCC and aPCC have been shown to partially or totally control bleeding in bleeding patients treated with DOACs.

Specific antidotes are also being developed. Three of them have already performed phase II and/or phase III studies :

- Idarucizumab (Praxbind®) is a fully humanized antibody fragment (Fab) which binds to the thrombin binding site of dabigatran hence inactivating the molecule [8]. In healthy young and older volunteers, idarucizumab was associated with immediate, complete, and sustained reversal of dabigatran-induced anticoagulation [9]. It was well tolerated with no unexpected or clinically relevant safety concerns. A phase III study is ongoing (REVERSE-AD), including bleeding patients who have serious bleeding or require an urgent procedure. Preliminary results have been disclosed for the first 90 patients, showing a complete reversal of the anticoagulant effect of dabigatran within minutes…and 20% mortality (mainly unrelated to the antibody) [10]. Even if the European (EMA) and US (FDA) regulators have granted a temporary approval for this compound, we need further studies and a much larger number of patients to be fully reassured Nevertheless, this antibody may save lives.

- Andexanet alpha is a recombinant modified human factor Xa protein that binds factor Xa inhibitors [11]. This specific reversal agent is designed to neutralize the anticoagulant effects of both direct and indirect factor Xa inhibitors.
Its half-life is short (less than 90 minutes) and the bolus has to be combined with a continuous IV infusion. Up to know, no data are available after a 6hrs administration. However Andexanet appears to be very effective in healthy volunteers [12] and the development plan is ongoing with phase III studies with apixaban or rivaroxaban treated patients. Yet no

approval has been given (expected mid-2017?) but the future of this agent appears very promising.

At the same time, other similar agents are being developed by several research groups.

- PER977 is a small, synthetic, water-soluble, cationic molecule that is designed to bind « specifically » to unfractionated heparin, low-molecular-weight heparin, to the new oral factor Xa inhibitors, and to the oral thrombin inhibitor, dabigatran [13]. Few data are available for the moment.

As DOACs are very effective and increasingly popular, more and more patients are shifting from VKA treatments to DOACs. As a result, the number of DOACs treated patients undergoing an emergency procedure, a trauma or an overdose is increasing steadily and the need for long lasting, safe, user-friendly and cheap antidotes will increase.

CONCLUSION

No doubt that we stand at the beginning of new complicated but exciting developments, either for severely bleeding patients and for DOACs. However, we have to acknowledge that we need some more evidenced-based data to be fully reassured.

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