DOACs: Consideraciones prácticas y avances en su reversión

DOACs: Practical considerations and advances on their reversal.

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Since 2010, 4 direct oral anticoagulants (DOACs) have become available for clinical use in many jurisdictions: a direct thrombin inhibitor (dabigatran) and 3 factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). Used primarily to prevent stroke in patients with atrial fibrillation (AF) or to prevent/treat venous thromboembolism (VTE), this class of medications has a number of characteristics that distinguish it from warfarin and other vitamin K antagonists (VKA). While many clinicians and patients are intrigued by medications that require neither routine anticoagulation monitoring nor ongoing dose adjustment, the uptake of DOACs in clinical practice has been somewhat slower than expected. Some of the reasons to choose a VKA over a DOAC are legitimate; for example, in some (though not all) cases, a DOAC will cost more than warfarin, even after considering the charges associated with international normalized ratio (INR) measurement and interpretation. Similarly, VKA would be a better choice for patients with a mechanical prosthetic heart valve, patients who weigh more than 120 kg, or patients taking a medication known to have a potentially clinically significant interaction with DOACs.

These exceptions notwithstanding, the DOACs should be strongly considered by all patients for whom they have a clinical indication because they reduce intracranial and fatal bleeding without compromising efficacy[1]. It is irrational to prescribe warfarin over a DOAC based on a fear of bleeding or because of a concern about "lack of reversibility". Despite the lack of a specific antidote or evidence-based reversal strategy, DOAC-treated patients who experienced major bleeding while enrolled in

phase III randomized trials were less likely to die from their hemorrhage than warfarin-treated patients who had a major bleed[2]. Moreover, specific reversal agents are now available. Idarucizumab, a humanized antibody fragment approved in the United States in November 2015, binds avidly to the active site of dabigatran. When given as a 5 gm bolus intravenously, idarucizumab achieves a reversal of thrombin inhibition that is immediate, complete and sustained in most patients[3]. Andexanet alpha, a protein structurally similar to human FXa, can eliminate anti-Xa activity from the plasma of volunteers taking rivaroxaban or apixaban[4]; at the time of this writing, the US Food and Drug Administration is scheduled to review early clinical trial data for andexanet alpha and respond to a request for expedited approval in the second half of 2016. Ciraparantag is a small molecule; early studies indicate it may reverse the effects of several anticoagulants but additional data are needed[5].

While the availability of specific reversal agents will provide comfort to patients and to clinicians who treat catastrophic bleeding with some frequency, there will be many episodes of DOAC-associated major hemorrhage for which general supportive care (e.g. red cell transfusion, search for bleeding source) without specific reversal will be appropriate. When deciding whether to use a reversal agent such as idarucizumab (in addition to supportive care), it may be helpful for a clinician to estimate the amount of DOAC effect in the plasma. If a patient has normal renal function and more than 12 hours have passed since the last dose was taken, less than 50% of the DOAC's peak effect will be present; by 24 hours after the last DOAC dose, very little anticoagulant effect will remain in most cases. If an objective assessment of DOAC effect is needed, there are some laboratory assays that may help. For example, depending on the reagent-instrument combination used, a normal partial thromboplastin time may indicate that no clinically relevant dabigatran effect is present. Similarly, a normal prothrombin time can be (but is not always) helpful in excluding the presence of rivaroxaban effect. Because not all reagents are sufficiently sensitive to prolong the clotting time at clinically important concentrations, clinicians should check with their local laboratory before creating clinical decision algorithms[6]. The most accurate measures of anticoagulant effect are the dilute thrombin time (for dabigatran) and anti-Xa activity (for FXa inhibitors); however, many hospitals do not provide these assays with a rapid turnaround time.

Declaración de conflictos de interés:
El autor declara haber recibido honorarios de consultoría y/o investigación de: Daiichi Sankyo, Boehringer Ingelheim, Janssen, Pfizer y Bristol Meyers Squibb.

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