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LECTURE

Reversal of anticoagulation in intracranial haemorrhage

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Abstract

Oral anticoagulants are increasingly used for long-term primary and secondary prevention of stroke, systemic embolism and venous thromboembolism. Intracranial haemorrhage (ICH) is the most severe complication of anticoagulation, with high mortality rates (>30%). Oral anticoagulants are associated with 10% to 15% of all ICH. Vitamin K antagonists (VKAs) present the higher rates of ICH (12 to 20%); non-vitamin K oral anticoagulants (NOACs) present a reduction of 50% in ICH rates, when compared with VKAs. The approved NOACs are dabigatran, a direct reversible thrombin inhibitor, and apixaban, edoxaban and rivaroxaban, direct reversible factor Xa inhibitors.

In most cases, haematoma expansion is responsible for the high mortality rates associated with ICH, which normally occurs within the first hours after symptoms onset, regardless of whether the patient is under VKA or NOAC. Therefore, reversal of anticoagulation must be performed as soon as possible, as it may limit haematoma expansion and improve outcomes.

Anticoagulation activity must be assessed before reversal, but different tests are used according to the anticoagulant agent the patient is taking.

VKAs are monitored by international normalized ratio (INR), a widely available test. Routine coagulation tests are less useful for measuring anticoagulation activity of NOACs. However, activated partial thromboplastin time (aPTT) is more sensitive to dabigatran and prothrombin time is more sensitive to rivaroxaban and edoxaban. If available, quantitative tests can be performed to determine NOACs concentration: reversal is required if concentrations are >30ng/ml. It is important to emphasize that reversal should not be delayed due to the lack of these tests.

There are two main treatments that must be given to a patient with VKA-associated ICH. Vitamin K, which normalizes INR by providing substrate necessary to the synthesis of clotting factors, must be given intravenously in high doses (5-10mg); however, it takes at least 12 hours to be effective. Prothrombin complex concentrates (PCC) contain the clotting factors II, VII, IX and X, as well as proteins C and S, and correct INR within minutes. They are rapidly administered in small volumes and do not need crossmatching.

Several specific reversal agents have been developed.

Idarucizumab is the specific reversal agent for dabigatran. It is a Fab fragment of a humanized monoclonal antibody. In REVERSE-AD trial, a dose of 5 g of idarucizumab was given intravenously (5-10 min) to patients with severe bleeding or needing emergent invasive procedures. Idarucizumab reversed dabigatran anticoagulant activity in 88-98% of patients, with an immediate, sustained and complete effect. The mortality rate was 13.6% in the bleeding group, including 98 patients with ICH. In this subgroup, mortality rate was 16.4%. By comparison, mortality rates in patients with

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ICH included in RE-LY study (a trial to evaluate the efficacy and safety of dabigatran compared with warfarin among patients with atrial fibrillation) were ≥35%. Idarucizumab is approved and available worldwide since November 2015.

Andexanet alfa is a recombinant human factor Xa that binds and inhibits FXa inhibitors, reversing their anticoagulant activity. It has been evaluated in patients with severe bleeding. Patients receive an intravenous bolus followed by a 2 h infusion. Anticoagulant activity was reduced in >89% patients, but there is a rebound increase after the infusion is stopped. Andexanet alfa has been approved in the USA in May 2018, but it is still waiting approval in Europe.

Meanwhile, PCC has been the reversal agent used for FXa inhibitors. Activated PCC (aPCC) has also been used for this purpose if PCC fails to reverse anticoagulation; however, it is more expensive than PCC and the risk of thrombotic complications is higher. PCC and aPCC can also be used to reverse dabigatran anticoagulation activity whenever idarucizumab is not available.

Ciraparantag is a synthetic small molecule that binds to heparin, low-molecular-weight-heparin and DOACs, but phase III studies are still lacking.

The efficacy of tranexamic acid (TXA) in ICH is also being assessed in TICH-2 trial (Tranexamic acid for hyperacute primary intracerebral haemorrhage: an international randomised placebo-controlled, phase 3 superiority trial). However, patients under anticoagulation were excluded from this trial. Nevertheless, the results of this trial can help to determine if TXA will be an adjuvant therapy in anticoagulation-associated ICH.