Measuring and Reversing the Effect of Non-Vitamin K Antagonist Oral Anticoagulants (NOACs)

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Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and the direct thrombin inhibitor (dabigatran) are the new players in the field of oral anticoagulants. This new class of non-vitamin K antagonist oral anticoagulants (NOACs) has been extensively studied in various settings, including venous thromboembolism (deep vein thrombosis and pulmonary embolism), atrial fibrillation and even secondary prevention after acute coronary syndrome.\(^1\) They offer many advantages over vitamin K antagonists (eg, warfarin, acenocoumarol and tiocoumarol), with a significant decreased risk for all-cause of stroke, systemic embolism, all-cause mortality\(^2\) and a better safety profile with significantly less major bleeding, especially intracranial bleeding.\(^3\)

Reversal Strategies

NOACs were developed for their stable pharmacological proprieties and their wide therapeutic window without the need for routine laboratory monitoring and antidotes for reversal strategies. However, there is a still residual risk of major or fatal bleeding in randomized trials,\(^4\) a risk that is likely to be more important in all comers, especially elderly patients with low body weight or renal insufficiency, in whom dose adjustment based on dedicated drug monitoring tests would be possibly useful.

The specific need for drug monitoring/reversal in emergency situations such as ongoing major bleeding or urgent surgery in patients on NOACs has led to a prolific literature looking at different possibilities of adapting available techniques or reagents to these new drugs. Indeed, in comparison with the classic warfarin for which INR monitoring is available anywhere and at anytime and restoration of an effective hemostasis can be obtained and titrated with oral vitamin K or prothrombin complex concentrates (PCCs), there is no reliable strategy for emergency situations in patients on NOACs. For emergency surgery on a patient at risk of bleeding, it has been proposed to dose the plasmatic concentration of each drug and postpone surgery if possible by monitoring the evolution of the drug concentration.\(^5\) If the dosage of the drug is not available, some preliminary works showed that available laboratory measurement could be performed and are summarized next.

Available Laboratory Tests

Thrombin-clotting time (TT) or the dilute TT assay determined by the Hemoclot thrombin inhibitor assay (HYPHEN BioMed, Neuville-sur-Oise, France), and ecarin clotting time are sensitive tests for a qualitative evaluation of the anticoagulant effects of dabigatran. Activated partial thromboplastin time (aPTT) can provide a useful qualitative assessment of the anticoagulant activity, because dabigatran has prolonged the aPTT in a concentration-dependent manner in both ex-vivo and in-vitro studies.\(^6\) However, it has been shown to be less sensitive at supratherapeutic levels of dabigatran\(^7\) and dependent on the reagents used,\(^8\) suggesting that each laboratory should perform dose-response studies to determine the sensitivity of their local aPTT method for dabigatran. Prothrombin time (PT/INR) was found to be less sensitive than other assays and cannot be recommended. We lack data for activated clotting time.

For rivaroxaban, the PT/INR was prolonged under treatment in a concentration-dependent linear fashion; however, the intermediate on-treatment concentration of rivaroxaban has shown a modest effect on PT. Similar to PT/INR, aPTT was prolonged in a concentration-dependent fashion but was non-linear, with studies reporting conflicting data regarding the concentration ranges.\(^9\) Anti-Xa using specific calibrators showed a good correlation for a wide range of drug concentrations, with even a modified anti-Xa test using diluted sample useful for low concentration.\(^10\)

For apixaban, the PT/INR was inadequately sensitive to apixaban according to studies using varieties of reagents. There are few data on aPTT and this test cannot be recommended. The best test seems to be, as for rivaroxaban, a modified anti-Xa with appropriate calibration.

For edoxaban, thrombin generation (TG) evaluation by the calibrated automated thrombogram method and anti-Xa activity demonstrated the more consistent concentration-dependent effects,\(^11\) whereas clotting assays coagulation parameters (PT/INR and aPTT) were again dependent on the reagent.

Reversal Strategies

Although there is not yet an available specific antidote to antagonize NOACs, because of their short duration of effect, drug discontinuation is usually sufficient to reverse any excessive anticoagulant activity. Renal or hepatic function impairment has to be taken into account when considering the discontinuation time. In case of potential overdose, physicians are left with non-specific ways of limiting absorption (early administration of activated charcoal and subsequent charcoal
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After a 20 mg/day dose, ie, 230 ng/ml alterations on hemostasis using different tests with steady (TG and thromboelastometry TEM) and circulating (perfusion study with whole blood in damaged rabbit aortas at a shear rate of 600 S⁻¹) human blood. Then, they investigated the ability of 3 available coagulation factor concentrates (PCCs, activated PCCs and rFVIIa) to reverse the antihemostatic actions of rivaroxaban in these 3 tests. This is the first evaluation using an in-vitro circulating test with perfusion of whole blood over a damaged vascular surface. The results are not sufficient to recommend the use of one coagulation factor concentrate over another, but they do bring new valuable knowledge to this fast-evolving topic. More is to come in the field and specific reversal agents are currently under development (idarucizumab for dabigatran, and exanetalfa for Xa inhibitors, and PER977 for both Xa- and thrombin inhibitors), which may facilitate clinical management of severe bleeding and emergency surgery.

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Figure. Decision-making tree for emergencies or surgery in patients being treated with non-vitamin K antagonist oral anticoagulants (NOACs).

References