Direct oral anticoagulants and APTT, PT results: The risk of normal results in patients on therapy

Dorothy M. Adcock, MD

July 2018—With the introduction of direct oral anticoagulants (DOAC) there is a paradigm shift in the use and understanding of screening coagulation tests to determine a patient's bleeding risk. In patients on DOAC therapy, clinicians cannot rely on normal activated partial thromboplastin time (APTT) and prothrombin time (PT) results to reflect the patient's level of anticoagulation. Historically, these tests have been used to determine whether it is safe to allow emergency treatment, such as the use of thrombolytic therapy or the performance of an invasive procedure, in anticoagulant-treated patients. DOAC-treated patients, however, can be therapeutically anticoagulated yet have normal APTT and PT results. Laboratory scientists should actively engage in educational activities and provide consultation to bring this potential patient safety issue to the attention of our clinical colleagues.

Since initial Food and Drug Administration approval in 2010, DOAC use for the treatment of conditions that require long-term anticoagulation (for example, atrial fibrillation, pulmonary embolism) has been increasing. Advantages over oral vitamin K antagonists such as warfarin are substantial, including a lower incidence of intracranial bleeding, no dietary restrictions, and fixed-dose administration, without the need for routine (episodic) laboratory monitoring. Indeed, in 2016 the American College of Chest Physicians recommended the use of DOACs over vitamin K antagonists for the treatment of non-cancer-related venous thrombosis.

In general, there is a poor correlation between plasma concentrations of DOACs and prolongation of the APTT and PT. Drug effect on clotting time depends considerably on the specific DOAC administered and the particular APTT and/or PT reagent used. Early guidelines on DOAC therapy suggested that normal APTT and PT results would indicate that DOAC concentrations were sufficiently low to allow emergency treatment. The major shortcoming of these early recommendations is that they were primarily based on the use of contrived samples (DOAC-spiked normal plasma) or the use of commercial calibrators to assess APTT and PT reagent responsiveness (sensitivity).

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Contrived DOAC samples do not demonstrate the same correlation with DOAC concentrations as samples from patients on DOAC therapy and cannot be used to accurately predict reagent responsiveness to DOACs. Similarly, the use of DOAC calibrators to determine reagent responsiveness may significantly overestimate APTT and PT responsiveness to DOACs and thus provide an unrealistic and unsafe assumption that normal screening tests suggest the absence of therapeutic levels of DOACs. Data from more recent publications have assuredly refuted both of these early recommendations and have substantiated that normal APTT and PT results, even when using DOAC-responsive reagents, are not able to safely identify DOAC concentrations below the suggested safe-for-treatment threshold (30–50 ng/mL), especially in apixaban-treated patients. Of note, the most recently approved DOAC, betrixaban, has very little published information about the response of coagulation screening tests.

Laboratories should consider alternative strategies for assessing DOAC presence using methods that provide higher sensitivity and safe lower limits of detection. The thrombin time is highly sensitive to dabigatran, and a normal thrombin time virtually excludes dabigatran presence. The chromogenic anti-Xa method used for heparin testing can be calibrated with the specific DOAC to be measured in order to determine a quantitative drug level or can be used as a screening test to exclude the presence of anti-Xa DOACs.

The mechanism of anticoagulant effect of DOACs is fundamentally different from that of vitamin K antagonists and is more similar to heparin-like anticoagulants. VKA anticoagulants work by diminishing the levels of functional vitamin K-dependent factors: II, VII, IX, X, protein C, and protein S. Heparin-like anticoagulants (for example, unfractionated, low-molecular-weight, pentasaccharide) accelerate the action of circulating antithrombin to inhibit serine proteases (activated factors, for example, such as IXa, Xa, and thrombin). Depending on the drug, DOACs act through direct inhibition of either thrombin or activated factor X (FXa). Inhibition of either target ultimately functions to limit thrombin generation. The endpoint of the APTT and PT reactions, fibrin formation, requires only about three to five percent of the total thrombin generated, and thus neither the APTT nor the PT are an accurate measure of overall thrombin generation. A plausible explanation why DOACs can function clinically as an anticoagulant yet may have minimal to no effect on the APTT and PT may reflect the limited measure of total thrombin generation of these screening assays. In a similar fashion, low-molecular-weight heparin and fondaparinux, when administered in typical therapeutic doses, have little to no impact on the APTT and PT.

As VKAs diminish the synthesis of vitamin K-dependent coagulation factors II, VII, IX, and X, this leads to reduced activity that limits fibrin generation, causing prolongation of the PT. Prolongation of the PT in seconds correlates with the level of VKA anticoagulation. The PT result is reported with the international normalized ratio, a value calculated from the PT that is based on the international sensitivity index, a determination of the vitamin K-dependent factor responsiveness of a PT reagent. The INR allows clinicians to determine a patient's level of warfarin anticoagulation regardless of which PT reagent was used. The INR is specific for warfarin anticoagulation and is not valid as a means to measure the level of DOAC anticoagulation. Patients therapeutic on apixaban, for example, may have a normal INR.

The take-home message is that the APTT and PT/INR do not serve as global measures of the level of anticoagulation for all anticoagulant therapies. A normal APTT and/or PT/INR cannot ensure that a patient on a DOAC has a normal functioning hemostatic system. Patients with therapeutic plasma DOAC concentrations may have a normal APTT and/or PT depending on the DOAC administered and the reagent used. Laboratory scientists should proactively and endlessly educate our clinical associates, stressing that for patients who are or may be on treatment with DOACs, the APTT and PT can no longer be used as a general gauge of a patient's level of anticoagulation and associated bleeding risk. This potential patient safety issue is of particular concern in a patient who requires emergent therapy and whose medication history is unknown. Instead, the laboratory must provide an alternative recommendation for clinicians who seek our counsel on these anticoagulated patients. The laboratory should have a strategy in place to assure clinicians that significant levels of DOACs are not present in those patients who require an intervention, in order to reduce an otherwise potentially significant bleeding risk.

Dr. Adcock is chief medical officer of LabCorp Diagnostics, Burlington, NC.