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REVIEW

Measurement and reversal of the direct oral anticoagulants

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ABSTRACT

Direct oral anticoagulants (DOACs) offer noninferior efficacy and improved safety compared to vitamin K antagonists (VKAs) for the prevention and treatment of venous thromboembolism and for the prevention of stroke and systemic embolism in nonvalvular atrial fibrillation. Unlike VKAs, DOACs do not require routine laboratory monitoring of anticoagulant effect and dose adjustment. In certain situations, however, laboratory assessment of anticoagulant effect may be desirable. Here we review the utility of currently available assays for assessment of DOAC effect and recommend an optimal assessment strategy for each drug, including calibrated dilute thrombin time or ecarin-based assays for dabigatran and calibrated anti-Xa activity assays for the factor Xa inhibitors. We also discuss reversal strategies, both specific and nonspecific, for each drug, including the preferential use of idarucizumab for the reversal of dabigatran and two agents, andexanet and ciraparantag, currently under development for the reversal of rivaroxaban, apixaban, and edoxaban.

1. Introduction

Since 2010, four direct oral anticoagulants (DOACs) have become available in North America, Europe, and elsewhere. Dabigatran, a direct thrombin inhibitor, and rivaroxaban, apixaban and edoxaban, direct factor Xa inhibitors, are approved in various jurisdictions for the treatment and secondary prevention of venous thromboembolism (VTE), the prevention of stroke and systemic embolism in nonvalvular atrial fibrillation (AF), and the prevention of VTE after major orthopedic surgery. DOACs offer noninferior efficacy and a number of advantages over vitamin K antagonists (VKAs), including decreased bleeding [1], lack of requirement for routine laboratory monitoring of anticoagulant effect and dose adjustment based on laboratory measurement, simplified perioperative management, and fewer drug and dietary interactions. On the basis of these advantages, both the American College of Chest Physicians (ACCP) [2] and the Anticoagulation Forum [3] released updated guidelines in 2016 recommending DOACs over VKAs for patients with noncancer associated VTE.

The DOACs are not without limitations, however, including difficulty measuring and interpreting anticoagulant effect and, for the anti-Xa agents, lack of a clear reversal strategy. In this article, we review current data regarding the laboratory measurement of anticoagulant effect and reversal strategies for these agents.

2. General principles of measurement

Liquid chromatography/tandem mass spectrometry (LC–MS/MS) is the reference standard method for DOAC measurement [4]. LC–MS/MS has been used to define expected steady-state plasma DOAC levels in pharmacokinetic studies (Table 1) [5–8]. These studies show that DOAC levels vary widely from peak to trough. For twice daily drugs such as dabigatran and apixaban, there is approximately a 2-fold difference between the median peak and trough concentrations. For once daily drugs such as rivaroxaban and edoxaban, the difference is 8 to 10-fold. While comparisons of median peak and trough values provide a sense of the expected variation in drug levels within an individual patient, percentile ranges shed light on the striking interindividual variation in DOAC levels. For instance, peak dabigatran levels vary by a factor of ~7 from the 5th to the 95th percentile. Trough rivaroxaban levels vary 14.5-fold over this range (Table 1).

Although limited data linking DOAC levels with clinical outcomes have been published [9,10], therapeutic ranges over which clinical outcomes are optimized have not been defined for these agents. In lieu of therapeutic ranges, we use the concept of "on-therapy range" [11]. We define the on-therapy range for a given DOAC at a given dose as the interval delineated by the 5th percentile trough and the 95th percentile peak plasma level. Care must be taken with timing of these measurements, particularly as trough levels may be misleading if drawn well after the time of the next expected dose. By definition, the large majority of patients in steady state will have levels in the on-therapy range at any time during treatment. Very low drug levels below the 5th percentile

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Table 1
Steady-state peak and trough levels of approved DOACs.

Drug	Dose	Time to peak	Median peak (5th to 95th percentile)	Median trough (5th to 95th percentile)	References
Dabigatran	150 mg BID	1–2 h	184 ng/mL (64–443)	90 ng/mL (31–225)	4, 16
Rivaroxaban	20 mg daily	2–4 h	270 ng/mL (189–419)	26 ng/mL (6–87)	6, 34
Apixaban	5 mg BID	3–4 h	171 ng/mL (91–321)	103 ng/mL (41–230)	5, 36
Edoxaban	60 mg daily	1–2 h	170 ng/mL (120–250)[a]	22 ng/mL (10-40)[a]	7, 11

[a] Interquartile range.

trough may be regarded as below the on-therapy range and very high levels above the 95th percentile peak as above the on-therapy range.

2.1. Indications for DOAC measurement

The laboratory measurement of the anticoagulant effect of DOACs is not routinely recommended but may be helpful in certain circumstances. In the emergent setting, such as trauma, urgent/emergent surgery, and recent stroke within the thrombolytic therapy window, rapid assessment of anticoagulant effect has the potential to guide clinical management. In other circumstances, such as the frail elderly, patients with extremes of body weight, impaired or hyper-renal function, overdose, gastrointestinal malabsorptive disorders, and suspected drug interactions, assessment of plasma levels may be desirable to detect potentially below on-therapy or above on-therapy levels [12].

2.2. Characteristics of an ideal assay

To measure DOAC levels accurately, an assay result (or a mathematical adjustment of the assay result) must show a high degree of linearity with drug concentration, as measured by LC–MS/MS and have minimal inter- and intra-assay variability. Because there are situations when it may be desirable to measure below on-therapy, on-therapy, or above on-therapy levels, an ideal assay should show linearity across a broad range of drug concentrations. The assay should be sufficiently sensitive to the lowest clinically relevant concentrations of drug. It should also be highly specific for the drug of interest such that it is not influenced by other anticoagulants or by biological variables known to affect coagulation assays such as lupus anticoagulants and clotting factor deficiencies. Finally, because there may be an emergent indication for measurement, an assay should be available 24 h a day, 7 days a week, with a short turnaround time.

Unfortunately, no currently available assay meets these idealized criteria. As discussed in detail below, widely available assays such as the prothrombin time (PT) and activated partial thromboplastin time (APTT) do not show sufficient sensitivity and linearity. Specialized assays have enhanced operating characteristics but are not widely available [13].

3. General principles of reversal

Indications for DOAC reversal include serious bleeding and need for an emergent, unplanned procedure. Appropriate use of any reversal strategy requires careful consideration of risks (including thrombosis) and benefits and should take into consideration the necessity of reversal and time since last dose, as well as drug-specific half-life. For bleeding patients, supportive care measures including local control, hemodynamic support, transfusions and early involvement of interventionalists should be utilized and may be all that is needed to control most bleeds. The use of reversal agents should be reserved for cases of serious or life-threatening hemorrhage in which supportive measures are inadequate and for emergent procedures that cannot be delayed.

Strategies for DOAC reversal include drug removal, bypass agents (which activate coagulation downstream of or through pathways unaffected by the drug in question), and specific reversal agents that sequester and neutralize the anticoagulant. Examples of these strategies are shown in Table 2. Removal strategies have important limitations. Because DOACs are absorbed rapidly from the gastrointestinal tract, activated charcoal is generally only useful for impeding absorption when administered within 1–2 h of ingestion. Hemodialysis removes approximately half of circulating dabigatran over 1.5–5 h [14], but placement of a dialysis catheter may be problematic in an anticoagulated patient, and a rebound increase in plasma dabigatran levels may be observed as redistribution from the extravascular space occurs. The factor Xa inhibitors are not efficiently removed by hemodialysis because they are more heavily protein bound.

The mechanism by which bypass agents may promote hemostasis in DOAC-treated patients is unclear since DOACs inhibit coagulation downstream from the points at which some or all bypass agents activate coagulation. For example, dabigatran inhibits thrombin, which is downstream from factor VIIa, the active ingredient in recombinant factor VIIa. Evidence on bypass agents for DOAC reversal is conflicting and is limited to in vitro analyses, animal bleeding models, and healthy volunteer studies [15]. The use of bypass agents for the reversal of DOACs in bleeding patients has not been systematically investigated. Specific sequestration agents are either recently approved (e.g. idarucizumab) or in clinical development (e.g. andexanet alfa, ciraparantag). As detailed below, these agents correct coagulation parameters in DOAC-treated patients within minutes of infusion. More data are required to define their safety and efficacy.

4. Dabigatran

Dabigatran is a direct thrombin inhibitor. The half-life of dabigatran in individuals with normal renal function is approximately 12–14 h with 80% renal elimination. The standard dose of dabigatran for both AF and VTE in patients with normal renal function is 150 mg BID. In some jurisdictions, a dose reduction to 110 mg BID is recommended in patients judged to be at increased risk for bleeding, including those ≥75 years of age. In the US, a dose of 75 mg BID is recommended in AF patients with a creatine clearance (CrCl) of 15 to 30 mL/min [16]. The on-therapy range in AF patients taking dabigatran 150 mg twice daily for at least one week is 31–443 ng/mL (Table 1) [5,17].

4.1. Measurement of anticoagulant effect

4.1.1. Thrombin time

The thrombin time (TT) is exquisitely sensitive to dabigatran. Depending on which reagent is used, dabigatran concentrations as low as 25 ng/mL (below the on-therapy range) may result in an unmeasurable

Table 2
DOAC reversal strategies.

Strategy	Example
Removal	Activated charcoal Hemodialysis (dabigatran only)
Bypassing	Prothrombin complex concentrate Activated prothrombin complex concentrate Recombinant factor VIIa
Sequestration	Idarucizumab (dabigatran only) Andexanet alfa (factor Xa inhibitors) Ciraparantag