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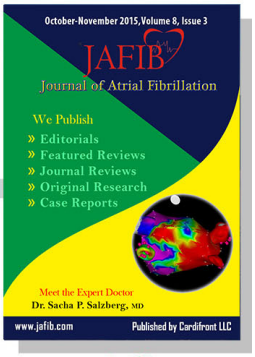

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Coagulation Testing For New Oral Anticoagulants

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Abstract

Atrial fibrillation is the most common and important cardiac rhythm disorder, which increases the risk of stroke and mortality.New oral anticoagulants are an alternative for vitamin K antagonists to prevent stroke in patients with non-valvular atrial fibrillation.New oral anticoagulants do not require routine monitoring of coagulation. However, the quantitative assessment of the anticoagulant effect drug levels may be needed in emergency situations, such as a serious bleeding or need for urgent surgery, or in patient with renal or hepatic insufficiency. In the paper we focus on the coagulation testing for new oral anticoagulants.

Introduction

Atrial fibrillation (AF) is the most common cardiac rhythm disorder. The estimated prevalence of AF ranges from 0.4% to 2% in the general population and increases by age. AF is associated with a five-fold risk of stroke and a three-fold incidence of congestive heart failure, and higher mortality.[1,2,3,4]

New oral anticoagulants (NOACs) are an alternative for vitamin K antagonists (VKAs) to prevent stroke in patients with non-valvular AF.

The NOACs for stroke prevention in AF fall into two classes: the oral direct thrombin inhibitors (dabigatran) and oral direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban). In contrast to VKAs, which block the formation of multiple active vitamin K-dependent coagulation factors (factors II, VII, IX, and X), these drugs block the activity of one single step in coagulation.[4]

The NOACs so far tested in clinical trials have all shown non-inferiority compared with VKAs, with better safety, consistently limiting the number of intracranial hemoraji. On this basis, ESC guideline recommends them as broadly preferable to VKA in the vast majority of patients with non-valvular AF.[4]

NOACs do not require routine monitoring of coagulation. However, the quantitative assessment of the anticoagulant effect drug levels may be needed in emergency situations, such as a serious bleeding and thrombotic events, need for urgent surgery, or in special clinical situations such as patients who present with renal or hepatic insufficiency, suspected overdosing because of drugs interactions.

The maximum effect of the NOACs on the clotting test will occur at its maximal plasma concentration, which is approximately 2-3 h after intake of drugs. A coagulation assay obtained on a blood sample taken 2-3 h after the ingestion of the drugs.[5]

The activated partial thromboplastin time (aPTT) may provide a qualitative assessment of the presence of dabigatran and the pro- thrombin time (PT) for rivaroxaban (and likely other factor Xa inhibitors), but these respective tests are not sensitive for the quantitative assessment of the NOAC. Quantitative tests for direct thrombin inhibitors (DTIs) and FXa inhibitors do exist, but they may not be routinely available in most hospitals. Point of care tests should not be used to assess the international normalized ratio (INR) in patients on NOACs An overview of the inter- pretation of all the coagulation tests for different NOACs can be found in Table 1.

Direct Thrombin Inhibitors (Dabigatran)

For dabigatran, the ecarin clotting time (ECT) and thrombin clotting time are useful tests, and directly reflect thrombin inhibition; however, an activated partial thromboplastin time (aPTT) can also be used (especially in an emergency setting).[6] The aPTT may provide a qualitative assessment of dabigatran (direct thrombin inhibitor) level and activity. The relation between dabigatran and the aPTT is curvilinear. Nevertheless, the sensitivity of the different aPTT reagents varies greatly. In patients receiving chronic therapy with dabigatran 150 mg twice daily (bid), the median peak aPTT was approximately two-fold that of control. Twelve hours after the last dose, the median aPTT was 1.5-fold that of control.

Therefore, if the aPTT level exceeds two times the upper limit of

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Table 1: Coagulation assays for NOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Plasma peak/trough level (after ingestion)	2h/12-24h	2-4h/16-24h	1-4h/12-24h	1-2h/12-24h
PT	Cannot be used Advantage: linearity of dose-response curve, availabilty. Disadvantage: standardization and responsiveness to drug concentration problem	Prolonged Advantage: linearity of dose-response curve, availabilty and responsiveness to drug concentration Disadvantage: standardization ?	Cannot be used	prolonged
INR	Cannot be used	Cannot be used	Cannot be used	Cannot be used
aPTT	At trough:>2xULNSuggest bleeding risk Advantage: responsiveness to drug concentration, availabilty. Disadvantage: standardization and linearity of dose-response curve problem	Cannot be used Advantage: linearity of dose-response curve, availabilty and responsiveness to drug concentration Disadvantage: standardization problem	Cannot be used	Prolonged but bleeding risk?
dTT	At trough:>200 ng/ml or >65s Suggest bleeding risk Advantage: linearity of dose-response curve, availabilty and responsiveness to drug concentration Disadvantage: standardization ?	Cannot be used	Cannot be used	Cannot be used
ECT	At trough:>3xULN Suggest bleeding risk Advantage:responsiveness to drug concentration, linearity of dose-response curve	Not affected	Not affected	Not affected
Anti-FXa assay	Not applicable	Quantitative; threshold values for bleeding? Advantage: linearity of dose-response curve, responsiveness to drug concentration Disadvantage: standardization, availabity	Quantitative; threshold values for bleeding?	Quantitative; threshold values for bleeding?

PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ULN, upper limit of normal.

normal, this may be associated with a higher risk of bleeding, and may warrant caution especially in patients with bleeding risk factors.

Dabigatran has little effect on the PT and INR at clinically relevant plasma concentrations. Prolongation of the PT is related linearly and dose-dependently to the plasma dabigatran concentration, but the responsiveness is low. The INR is therefore unsuitable for the quantitative assessment of the anticoagulant activity of DTIs.[7]

ECT prolongations above the basal value are related linearly and dose-dependently to the dabigatran concentration; responsiveness is also adequate. The ECT assay provides a direct measure of the activity of DTIs. ≥3 times elevated ECT at trough is associated with a higher risk of bleeding in patients taking dabigatran.[8]

Thrombin time results depend on the coagulometer and the thrombin lot used. Unlike diluted thrombin time (dTT) test can more accurately predict the coagulation state. A dTT has been developed, with appropriate calibrators for interpretation in the context of dabigatran use (Hemoclotw). The dTT is suitable for the quantitative assessment of dabigatran concentrations. A normal dTT measurement indicates no clinically relevant anticoagulant effect of dabigatran. When dabigatran is used with twice daily dosing, a dTT measured at trough (≥12 h after the previous dose) with the Hemoclotw of >200 ng/ml dabigatran plasma concentration (dTT approximately >65 s), is associated with an increased risk of bleeding.[13] still that there are no data on a cut-off dTT below which elective or urgent surgery is 'safe', and therefore its use in this respect cannot be recommended at this time.[5]

Factor XA Inhibitors (Rivaroxaban, Apixaban, Edoxaban)

Factor Xa-inhibitors prolongs the prothrombin time (PT) and aPTT varying degree and this might be used as a rough estimate of an anticoagulation effect. But the aPTT cannot be used for evaluation of FXa inhibitory effect because of the weak corelation and variability of assays.

The prolongation of the PT is related linearly and dose-dependently to the Factor Xa-inhibitor concentration, and the responsiveness is adequate. Nevertheless the effect on the PT depends both on the assay and on the FXa inhibitor. For rivaroxaban, the PT may provide some quantitative information, but the sensitivity of the different PT reagents varies greatly.

The INR is unreliable for the evaluation of FXa inhibitory activity. A better estimate for an anticoagulant effect for the oral Factor Xa inhibitors is an anti-Xa assay.[4,5,9]

Anti-FXa 'chromogenic assays' have been developed to assess plasma concentrations of the FXa-inhibitors and are commercially available. However, there are currently no data that associate a coagulation parameter or a drug level at trough or at peak with bleeding risk or risk for thrombo-embolism.

Impact Of NOACs On Coagulation System Assessment

The NOACs interfere with routine coagulation tests, thrombophilia tests or the measurement of coagulation factors. Abnormal coagulation tests should be interpreted with caution if the time window between blood sampling and NOAC intake is unknown. Therefore, a time window of at least 24 h is recommended between the last intake of a NOAC and blood sampling to assess coagulation parameters and this time window may be even longer for lupus anticoagulant measurements (≥48 h).[10]

Because NOACs may have an additional impact on the INR (especially the FXa inhibitors), influencing the measurement while on combined treatment during the overlap phase, it is important that the INR be measured just before the next intake of the NOAC during concomitant administration, and be retested 24 h after the last dose of the NOAC (during sole VKA therapy).

References

1. Rodney HF. Atrial Fibrillation. N Engl J Med 2001;344:1067-78.
2. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation executive summary:a report of the American College of Cardiology/American Heart Association Task Force on practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing

Committee to Revise the 2001 Guidelines fort he management of Patients With Atrial Fibrillation) J Am Coll Cardiol 2006;48:854-906.

3. Go AS, Hylek EM, Philips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults:national implications for rhytm management and stroke prevention:the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study.JAMA 2001;285:2370-5.
4. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH et al. Focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Europace 2012;14:1385–413.
5. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, et al.European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2013;15(5):625-51.
6. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, Clemens A. Dabigatran etexilate-a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity.Thromb Haemost 2010;103:1116-1127.
7. Huisman MV, Lip GY, Diener HC, Brueckmann M, van Ryn J, Clemens A. Dabigatran etexilate for stroke prevention in patients with atrial fibrillation: resolving uncertainties in routine practice. Thromb Haemost 2012;107:838-847.
8. Lindhoff-Last E, Samama MM, Ortel TL, Weitz JI, Spiro TE. Assays for measuring rivaroxaban: their suitability and limitations. Ther Drug Monit 2010;32:673-9.
9. Tripodi A. Measuring the anticoagulant effect of direct factor Xa inhibitors. Is the anti-Xa assay preferable to the prothrombin time test? Thromb Haemost 2011;105:735-736.
10. Douxfils J, Mullier F, Robert S, Chatelain C, Chatelain B, Dogne JM. Impact of dabigatran on a large panel of routine or specific coagulation assays. Laboratory recommendations for monitoring of dabigatran etexilate. Thromb and haemost 2012;107:985-97.