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Review

Detection of lupus anticoagulant in the era of direct oral anticoagulants

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ABSTRACT

Lupus anticoagulant (LAC) is an *in vitro* phenomenon determining a phospholipid-dependent elongation of clotting times. The presence of LAC associated with anticardiolipin (aCL) and anti-β2 glycoprotein I (anti-β2GPI) antibodies is strongly associated with thrombosis and pregnancy morbidity. Direct oral anticoagulants (DOACs) targeting thrombin and factor Xa are currently widely use to prevent and treat venous and arterial thromboembolism. Some concern has, however, been expressed about the possibility of false laboratory results during LAC assessment in patients taking these drugs. Several *in vitro* studies, spiking DOACs into normal plasma as well as *ex vivo* at peak levels in treated patients, led in false-positive LAC. The dilute Russell Viper Venom time is the assay that is most influenced by rivaroxaban, edoxaban, dabigatran and less by apixaban. Both screening and confirmatory tests have resulted equally prolonged for activated partial thromboplastin time and have not led to false-positive results, but this may depend on the type of reagent used for the test. Taipan/Ecarin snake venoms ratios, has been recommend by some investigators as they do not seem to be affected by rivaroxaban or edoxaban, but these tests are neither standardized nor generally available in clinical practice. In conclusion, for the time being it does not seem advisable to carry out LAC testing during anti-factor Xa and anti-factor IIa treatment because of the risk of false-positive results. Whenever needed in deciding the suspension of DOACs or in case of recurrent thrombosis, LAC determination should be carried out at trough better if DOAC concentration is known.

Contents

1. Introduction

Lupus anticoagulant (LAC) defines a heterogeneous group of immunoglobulins that inhibit phospholipid-dependent coagulation reactions *in vitro* in the absence of a specific coagulation factor deficiency. According to consensus classification criteria [1], persistent LAC, and/or

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medium-high levels of IgG/IgM anti-β2 glycoprotein I (anti-β2GPI), and/or IgG/IgM anticardiolipin (aCL) antibodies constitute the laboratory criteria for the diagnosis of antiphospholipid syndrome (APS). Clinical features of the syndrome are arterial and/or venous thrombosis and/or pregnancy morbidity. As clinical manifestations strongly correlate with the presence of LAC, it is considered the most important acquired risk factor for thrombosis and foetal loss [2]. Andreoli et al. [3], in fact, recently reported a higher rate of LAC in patients with stroke, myocardial infarction, deep venous thrombosis and both early and late pregnancy morbidity. LAC has also been found to be an independent risk factor for thrombosis in aPL carriers [4]. These findings have been confirmed by a recent meta-analysis showing that LAC is associated to a higher risk for thrombotic events with respect to aCL and anti-β2GPI antibodies [5]. Finally, LAC positivity has emerged in the majority of studies as the strongest predictor of pregnancy morbidity [6,7], and it is, in fact, significantly associated with poor infant outcome [8].

Direct oral anticoagulants (DOACs) targeting thrombin and factor Xa have recently begun to be utilized worldwide to prevent and treat venous thromboembolism, embolic stroke associated with non-valvular atrial fibrillation, and acute coronary syndromes [9–12]. Some concern has, however, been expressed about the possibility of false laboratory results during LAC assessment in patients taking these drugs. *In vitro* and *ex vivo* studies on the effect of DOACs on thrombophilia screening assays including those for LAC have led to controversial findings [13–22]. Given these considerations, this review aimed to summarize data published on recent findings on the risks of false test results on LAC testing in patients taking direct oral anticoagulants and to propose measures to avoid them.

2. Methods

A MEDLINE search was conducted following established reproducible methodology for data on lupus anticoagulant and new oral anticoagulant therapies. The search terms included lupus anticoagulant, new oral anticoagulants, rivaroxaban, dabigatran, apixaban, edoxaban. The computerized search was supplemented by a manual search of the reference lists of the articles that were retrieved.

3. Results

3.1. Lupus anticoagulant: pathophysiology and detection

LAC is an *in vitro* phenomenon determining a phospholipid (PL)-dependent elongation of clotting times. Its mechanism of action involves the binding of autoantibodies and their target protein to PLs thereby limiting the binding of prothrombinase complex; this in turn delays the conversion of prothrombin to thrombin (Fig. 1). Anti-β2GPI [23] and anti-prothrombin [24] antibodies have been identified as the most relevant mediators of LAC, although other inhibitors may also be involved [25].

The guidelines of the International Society of Thrombosis and Haemostasis (ISTH) [26] and those of the British Committee for Standards in Haematology [27] have recommended using two tests, each based on different principles, for LAC detection. The first is the dilute Russell Viper Venom time (dRVVT) and the second is a sensitive activated partial thromboplastin time (aPTT). The primary criteria for LAC detection [26,27] include the following: a) a prolonged PL-dependent clotting assay, b) failure of mixing studies to correct the abnormality, c) the shortening of coagulation time in the presence of high PL concentrations, and d) the absence of specific coagulation factor inhibitors.

A number of variables can affect assays used for LAC detection leading to false results. The effects of heparin and vitamin K antagonists (VKAs) on LAC detection have, in particular, been well documented. Given these findings, the ISTH guidelines for LAC detection [26] recommended caution when tests to assess LAC are carried out in patients on heparin or taking VKAs with international normalized ratio (INR) >3. To avoid misinterpretation, the guidelines recommend performing laboratory procedures after low molecular weight heparin (LMHW) has been discontinued for at least 12 h or, in the case of VKAs, two weeks after discontinuation or until an INR of 1.5 or less has been achieved. Alternatively, if the INR is between 1.5 and <3.0, a 1:1 proportion of patient-to-pooled normal plasma (PNP) could be used.

3.2. New anticoagulant drugs: pharmacological properties

The pharmacological characteristics of DOACs are outlined in Table 1. Unlike VKAs or heparins, DOACs directly inhibit a specific factor in the coagulation cascade. While DOACs ending with gatran (dabigatran etexilate) target thrombin, those ending with xaban (rivaroxaban, apixaban, edoxaban) target factor Xa (Fig. 2). Xabans are able to inhibit both free and prothrombinase-bound factor Xa as well as clot-associated factor Xa [28,29]. Onset of anticoagulation effects are expected to begin 2 h following the first dose, reaching a maximum concentration between 0.5 and 4 h [30]. Unlike what occurs when VKAs are used, DOACs anticoagulant effect drops rapidly after discontinuation. Dabigatran is eliminated primarily in an unchanged form in the urine [9]. Instead, one third of rivaroxaban is eliminated as unchanged drug in the urine and two-thirds of the drug undergoes metabolic degradation into inactive metabolites in the liver *via* cytochrome (CYP) 3A4 and CYP 2J2 and CYP-independent mechanisms. Fifty percent of the metabolites are excreted *via* kidney and the other half *via* the hepatobiliary route [10,30]. Two-thirds of apixaban is eliminated unchanged, 40% of which is excreted in the urine and 60% in the faeces and one-third is metabolized in the liver *via* CYP3A4 and CYP-independent mechanisms and excreted *via* the biliary/faecal route [11]. Finally, 40% of edoxaban is eliminated unchanged in the urine and 60% in the faeces [12]. Beyond their different mechanisms of action, it is important to remember the

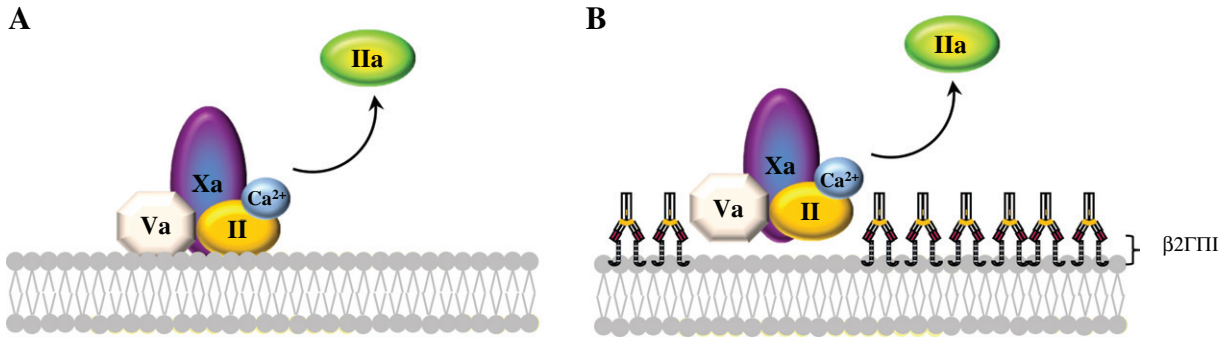

Fig. 1. Lupus anticoagulant (LAC) activity refers to the elongation of clotting times due to the binding of antiphospholipid antibodies to phospholipids which limits the phospholipid surface that is necessary for prothrombinase complex binding. The prothrombinase complex, which consists of coagulation factors Va and Xa and II with Ca^{2+} and phospholipids, is the product of both the intrinsic and extrinsic coagulation pathways. Its function is to convert prothrombin into thrombin. β2GPI I: β2 glycoprotein I.