Importance of clot permeability and clot degradability for determination of rivaroxaban efficacy

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In an article published in the *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Frączek et al1 showed that recurrence of thromboembolism in patients undergoing rivaroxaban treatment occurs in those for whom clot structure is tight, which leads to defective thrombolysis. This could be due either to an anomaly of rivaroxaban metabolism or to a common fibrinogen genetic variant increasing the risk of thrombosis, which could be detected in an in vitro assay by measuring clot permeability (Ks) and degradability formed by adding rivaroxaban to plasma before clotting.

The first case demonstrating that thrombosis may be due to an abnormal clot structure, characterized by a very tight clot resulting in decreased Ks and defective fibrinolysis, was reported as Dusart syndrome.2,3 Many other cases have since been described, and it is now well established that such dense fibrin structures induce venous thromboembolism (VTE). By 1994, Blomback et al4 had demonstrated in vitro that the concentration of thrombin present during coagulation profoundly influences fibrin clot structure.4

We now know that clots formed in the presence of low thrombin concentrations are composed of thick fibrin fibers highly susceptible to fibrinolysis, while clots formed in the presence of high thrombin concentrations are composed of thin fibers and are resistant to fibrinolysis.5 Consequently, it was important to analyze the effect of anticoagulant drugs in clot structure modifications, and we tested the effect of rivaroxaban on fibrin clot structure in vitro.

Whole blood Ks and degradability were much lower compared with those of plasma clots because of occlusion of fibrin pores by red blood cells and consistently greater thrombin generation in whole blood as compared with plasma due to the presence of platelets and red blood cells in whole blood. Rivaroxaban reduced thrombin generation and, when added to plasma or whole blood before clotting, it led to the formation of a looser clot that is more degradable by fibrinolytic enzymes. The permeability and degradability of whole-blood clots formed in patients on rivaroxaban were similar to those of plasma clots. We concluded that this reduced resistance to fibrinolysis of whole-blood clots formed in patients on rivaroxaban could have implications for the development of antithrombotic agents.6

Obviously, in vivo studies are required to analyze the efficacy of rivaroxaban (or other direct oral anticoagulants [DOACs]) in thromboembolic syndromes. In the first studies, rivaroxaban efficacy and risk of bleeding were determined in patients with VTE. Analyses were performed using data provided by trial publications in which a relative risk was determined for each outcome.7,8 The results indicated that DOACs and vitamin K antagonists have similar efficacy in the treatment of acute symptomatic VTE, and that treatment with a DOAC reduces the risks of major bleeding.

In another study, clinical trial data supported the use of DOACs as an effective and safe alternative to vitamin K antagonist therapy in both atrial fibrillation and VTE contexts.9 However, the authors emphasized that most studies, including their own study, have limitations since study patients have different risk profiles and baseline characteristics.

In order to distinguish patients with VTE for whom rivaroxaban was not effective, Frączek et al1 have reported an interesting study with a follow-up of 32 months in a cohort of 132 patients with VTE treated with rivaroxaban for more than 8 weeks. The patients were classified into 2 groups according to rivaroxaban dose: high rivaroxaban...
The remaining one-third of the dose is eliminated as an unchanged drug in the urine via active renal secretion involving transporters P-glycoprotein and breast cancer resistance protein (BCRP [ABCG2]).

Consequently, drugs that induce cell efflux transporter P-glycoprotein or drugs that are strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenobarbital, and phenytoin induce a decrease in the plasma rivaroxaban concentration, thus attenuating its pharmacodynamic effects. Therefore, these drugs increase the risk of thromboembolic events. Conversely, drugs that inhibit P-glycoprotein and/or CYP3A4 may increase DOAC concentrations, thereby enhancing the risk of bleeding. The plasma concentration of rivaroxaban is also substantially increased in renal impairment, liver injury, and in patients older than 75 years.

However, not all ABC gene variants cause defects in rivaroxaban elimination. For example, the ABCB1 genotype did not affect rivaroxaban pharmacokinetics (the ratio of rivaroxaban plasma concentrations in mutant-allele carriers versus wild-type volunteers was 1.2). Considering the nature of fibrinogen, its structure may be influenced by common fibrinogen genetic variants, arising from single nucleotide polymorphisms. Two haplotypes were found to increase the risk of thrombosis: haplotype FGG-H2, expressing a C-to-T variant at position 10 034 in the fibrinogen γ chain (single nucleotide polymorphisms 10034C>T [rs2066865]), influences thrombosis risk by promoting synthesis of the γ chain over that of the γ' chain. Reduced fibrinogen γ' levels and elevated fibrinogen levels were found to be independent risk factors for venous thrombosis, suggesting that the risk of VTE depends on both quantitative (high fibrinogen levels) and qualitative (reduced γ' fibrinogen) abnormalities. About 6% of individuals carry this variant responsible for an approximate 2-fold increase in thrombotic risk.

Haplotype (α-fibrinogen Thr312Ala polymorphism) occurs within the αc domain of fibrinogen, known to be important for lateral aggregation and factor XIII–induced crosslinking of fibrin fibers. Ala312 influences clot structure and properties by increasing factor XIII cross-linking, leading to formation of stiffer clots with thicker fibrin fibers. These findings may provide a mechanism by which Ala312 fibrinogen could predispose to clot embolization. The genotype distribution of patients with pulmonary embolism (TT = 49%, TA = 36%, AA = 15%) differed from that of healthy controls (TT = 60%, TA = 34%, AA = 6%) (P = 0.02). These results supported the hypothesis that Ala312 fibrinogen alters FXIII-dependent cross-linking, making a formed fibrin clot more susceptible to embolization.

Frączek et al showed that recurrence of thromboembolism in patients undergoing rivaroxaban treatment occurs in those for whom clot structure is tight (low Kc), and thrombolysis is therefore defective. Consequently, based on their results, it appears that this could be due to the haplotype of fibrinogen leading to the formation of a tight clot.
thus it might be useful to test the response of each patient to rivaroxaban in vitro beforehand, by adding rivaroxaban to plasma (or whole blood) before clotting and then evaluating its effect on clot permeability and degradability, that is, in advance of patient treatment. In addition, concomitant therapies likely to interfere with rivaroxaban metabolism should be avoided in order to lower the risk of recurrence of thrombosis or bleeding.

ARTICLE INFORMATION

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