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A Low Rivaroxaban Plasma Level May Indicate Anticoagulation Undertreatment

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ABSTRACT

Few reports have been published on the correlation between plasma concentrations of rivaroxaban and clinical outcome in patients who have experienced venous thromboembolism. This article describes the case of a 44-year-old woman who experienced deep vein thrombosis during anticoagulation therapy with rivaroxaban, with evidence of repeated low plasma levels of the drug. We postulate that the determination of plasma rivaroxaban anti-Xa activity can be useful in the evaluation of anticoagulation therapy in selected cases.

LEARNING POINTS

- Some patients with deep vein thrombosis do not respond to rivaroxaban therapy.
- Accurate determination of rivaroxaban plasma concentrations is important in clinical practice.
- The clinical value of rivaroxaban plasma concentrations might be limited by intra- and inter-individual variations.

KEYWORDS

Rivaroxaban, anti-Xa assays, recurrent venous thrombosis

INTRODUCTION

Rivaroxaban is a direct oral anticoagulant (DOAC) used in clinical practice for atrial fibrillation and thromboembolism. Due to the predictable pharmacokinetic and pharmacodynamic outcomes of DOACs, a fixed dose is administered without routine coagulation monitoring. However, data in the literature have shown variability in the anticoagulant effects of DOACs, raising concerns about their effectiveness and safety[1–3]. Consequently, the assessment of DOAC plasma concentration may be helpful in patients with comorbidities. Rivaroxaban plasma levels (RivLev), as for all DOACs with anti-Xa action, are assessed using the anti-factor Xa chromogenic assay. Drug levels are usually assayed twice: before (trough level) and 2 hours after drug administration (peak level).

The anti-factor Xa method measures drug concentration, not the intensity of drug anticoagulant activity: a higher than expected RivLev does not necessarily indicate an increased risk of bleeding complications. Currently, there is not enough experience or evidence to establish a correlation between low RivLev and the risk of thrombotic complications [4–6].

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CASE DESCRIPTION

A 44-year-old woman was hospitalised in October 2015 due to pulmonary thromboembolism and distal deep vein thrombosis (DVT) involving the right lower limb with lumen occlusions in the gastrocnemius vein. For about 3 years before hospitalization, the patient had been taking the oral contraceptive Yasminelle (0.02 mg ethinyl estradiol+3 mg drospirenone).

Following confirmation of pulmonary thromboembolism and DVT by tomography angiography and ultrasound examination, the patient was advised to stop taking the oral contraceptive and was prescribed fondaparinux 7.5 mg for 30 days followed by rivaroxaban 20 mg for 3 months. Screening for thrombophilia after the end of anticoagulant therapy showed only compound heterozygosity for the C677T and A1298C mutations of the MTHFR gene without evidence of hyperhomocysteinaemia. For 9 months after the first follow-up, plasma D-dimer concentrations were tested monthly, showing normal levels.

In October 2016 the patient experienced a new episode of DVT. Ultrasound examination showed a solid and immobile occlusion filling the lumen of the right gastrocnemius vein. After a short course of enoxaparin (6,000 IU anti-Xa activity), the patient was restarted on rivaroxaban. At 1, 2 and 3 months after the start of therapy, blood samples were tested for DOAC plasma concentration, haemoglobin, renal and liver function.

In February 2017, the trough plasma level of RivLev was 0.9 ng/ml and the peak level was 123.8 ng/ml. As the low trough level was within the current recommendations, the same therapy was maintained. However, after 3 months the patient again experienced a vein thrombosis in the left calf as confirmed by a repeat ultrasound which showed a persistent DVT involving the same right gastrocnemius vein.

Laboratory testing once again confirmed the low trough level of RivLev (6 ng/ml), which led to the decision to replace rivaroxaban therapy with apixaban therapy (5 mg twice a day).

Monitoring of apixaban plasma levels during the following months with anti-Xa assay showed trough and peak values within the therapeutic ranges: 74 ng/ml and 180 ng/ml, respectively, after 1 month and 30 ng/ml and 165 ng/ml after 3 months. After 10 months of follow-up, the patient had no clinical or laboratory signs of recurrent thromboembolism.

DISCUSSION

Rivaroxaban therapy is widely used and approved for the pharmacological treatment of DVT, but in our case did not show the expected results.

A thorough literature review revealed only few recent case reports on possible failure of rivaroxaban for the treatment of DVT[1,2]. Furthermore, recommendations on the ranges or cut-offs for effectiveness and efficacy have not yet been confirmed. In our case, measuring the variation in drug concentrations was useful for documenting the patient's underexposure to the drug and for deciding to change the type of DOAC[3–5]. However, it is not possible to determine if changing the drug when the first low RivLev value was measured could have prevented the third thrombotic episode in our patient. In the light of this experience, repeated evaluation of DOAC levels and their consistent analysis could be a promising strategy to determine appropriate treatment in some clinical conditions.

We conclude that information about RivLev can be used to determine treatment. Our strategy, which included routine therapeutic drug assessment with the goal of determining personalised patient DOAC treatment, may be useful also for dose adjustment in contrast to current clinical care standards which do not include such monitoring, New and more substantial studies on this topic are warranted.

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