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Letter to the Editor

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Rivaroxaban non-responders: do plasma measurements have a place?

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To the Editor,

Direct oral anticoagulants (DOACs) are used increasingly for treatment and prophylaxis of thrombosis [1]. The benefits are a more uniform dosing, improved safety and efficacy and no need for routine laboratory monitoring, while a major drawback is the lack of experience with these drugs in a number of more specific situations, e.g. overdose or acute surgery [2]. In many of these situations, measurement of the DOAC plasma concentration seems favorable [3, 4], but DOAC monitoring is generally discouraged by the industry and not yet regarded as a well-known possibility by clinicians. We here report on a case of apparent rivaroxaban non-response that emphasizes some of the aspects we still need to address for these drugs.

A 43-year-old Moroccan woman with known Takayasu arteritis and phospholipid antibody syndrome was admitted with left side hemiparesis and rotatory vertigo. Due to multiple previous occasions of cerebral stroke, the patient was on anticoagulant treatment: vitamin K antagonist treatment had resulted in uncontrollable international normalized ratio (INR) values, and while receiving dabigatran, a direct thrombin inhibitor, the patient had experienced bleeding episodes. She was therefore treated with rivaroxaban, a direct factor Xa inhibitor, 20 mg oral once daily. Concomitant treatment was levetiracetam, 1500 mg twice daily, due to epilepsy.

The patient was referred for acute thrombolysis, but before this could be initiated, the status of the DOAC treatment was necessary: as the measurement of plasma rivaroxaban has been found valuable due to a dose-dependent relationship between anti-factor Xa activity and the plasma rivaroxaban concentration [5], plasma rivaroxaban was measured using an anti-FXa chromogenic assay with reagents from Stago Diagnostica (Asnières-sur-Seine, France) on STA-R Evolution analyzer (Diamond Diagnostics, Holliston, MA, USA). The result was <20 μg/L (i.e. below the functional sensitivity limit of the assay), which was repeated with the same result, and thereafter, thrombolytic therapy was instituted, with good clinical results.

To elucidate why the patient had unmeasurably low plasma rivaroxaban values despite an ongoing treatment, the measurement was repeated the following day prior to medication and 2 and 4 h after rivaroxaban intake, respectively: when comparing with expected values in the literature [6], results strongly indicated decreased systemic availability of the drug: <20 μg/L (prior to medication), <20 μg/L (2 h after medication) and 65 μg/L (4 h after medication). To assure that the plasma measurements were correct and not due to interference of phospholipid antibodies (which, however, not should have influenced on the assay according to the analysis performance characteristics), plasma with known phospholipid antibodies were spiked with different levels of rivaroxaban, showing a high recovery rate without indications of assay interference.

We therefore considered pharmacokinetic explanations for these observations, e.g. decreased absorption or increased elimination: rivaroxaban metabolism is primarily catalyzed by CYP3A4, with minor contributions from CYP2J2 and CYP-independent mechanisms [4]. Based on in vitro investigations, rivaroxaban is a substrate of the efflux transporter proteins P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Active substances that inhibit CYP3A4 or P-gp are expected to increase rivaroxaban plasma concentrations, while induction is expected to
reduce systemic exposure [7, 8]. P-gp is the product of the multidrug resistance gene (*mdr1*), which is polymorphically expressed. The C3435T polymorphism in exon 26 correlates with expression of P-gp in the intestine, and people homozygous for the T allele have substantially lower intestinal P-gp expression than those homozygous for the C allele. Since levels of P-gp in the intestine determine the extent of drug absorption, genotype-related differences in bioavailability of drugs are seen [9]. A study compared allele frequencies of the C3435T polymorphism in random samples of Ghanaians, African-Americans, Caucasian and Japanese subjects: 142 (83%) of 172 Ghanaians and 25 (61%) of 41 African Americans were homozygous for the C allele, whereas only 139 (26%) of 537 Caucasian and 7 (34%) of 50 Japanese had this genotype. The frequency of the C allele (C/T or C/C genotype) was 90% (311/344 alleles) in Ghanaians compared with 50% (534/1074 alleles) in Caucasians [9]. A similar study recorded a genotype frequency of the homozygous CC genotype ranging from 52% to 70% in four African groups and from 15% to 38% in Caucasian and Asian subjects. The high frequency of the C allele in the African groups implies that populations of African ancestry will have higher P-gp protein levels and drug efflux [10]. A study of 14 healthy volunteers showed that for digoxin, a prototype P-gp substrate, Cmax was 38% higher in the volunteers with the homozygous T/T genotype in exon 26 as compared to the volunteers with the C/C genotype [11]. However, other papers describe an association in the opposite direction or fail to find an association at all. The lack of a clear conclusion probably reflects limitations of the studies [12].

In our patient, the concomitant use of levetiracetam may have reduced systemic exposure by induction of either P-gp or CYP3A4 [4]. However, levetiracetam appears to be only a mild inducer of CYP2B6 and CYP3A4, and according to the summary of product characteristics, a clinically significant interaction is considered unlikely [13]. Animal studies have shown that levetiracetam induces P-gp, but no human data have been reported [8, 14]. Of note, isolated case reports have shown that other antiepileptic agents inducing CYP3A4 and P-gp have caused decreased rivaroxaban and dabigatran plasma concentrations [8].

Altogether, this patient of North African origin presented with unmeasureably low levels of plasma rivaroxaban. We believe this could be the result of a genomic ethnicity-related high-level of intestinal P-gp expression combined with an induction of P-gp through levetiracetam. This emphasizes that attention must be payed to ethnicity and concomitant medication in cases with discrepancy between anticoagulant dose and exposure. Despite the general impression that DOACs can be used in a more uniform manner than VKA (i.e. fixed doses and no plasma monitoring), attention must be drawn to different settings where this is not necessarily true. In case of on-treatment thromboses, other mechanisms must therefore always be considered, and in such a setting, we find that plasma monitoring of the DOAC used has an important place.

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