Severe dizziness following rivaroxaban introduction in a parkinsonian patient: Drug-drug interaction?

Introduction

Rivaroxaban is a direct factor Xa inhibitor that reduces the rate of ischemic stroke in patients with atrial fibrillation and is an effective therapy for the treatment of deep-vein thrombosis and pulmonary embolism [1-3]. It requires no specific monitoring and seems to provoke less intracranial and fatal bleedings than warfarin. The most frequent adverse effects (AEs) are, with the exception of bleeding complications: nasopharyngitis, peripheral edema, diarrhea, headaches, and elevated transaminases. Dizziness is also reported as an adverse effect of rivaroxaban. We report the case of a patient who developed severe imbalance following treatment with rivaroxaban.

Case report

A 55-year-old man was referred for sudden onset of dizziness. His past medical history included idiopathic Parkinson’s disease diagnosed 3 years earlier and active tobacco smoking. He was only affected by a left arm tremor without akinesia and/or rigidity. He was treated with trihexyphenidyl and rasagiline since 2 years. He was totally completely autonomous for daily life activities. He had no signs of autonomic dysfunction. One month before admission, the patient had spontaneously presented left gastrocnemius and popliteal veins thrombosis, confirmed by ultrasonography. Rivaroxaban was then introduced (15 mg twice a day). As he had felt mild imbalance after introduction of this treatment, he spontaneously stopped it. Three weeks later, repeated ultrasonography had shown extension of the thrombosis to the left superficial femoral vein. Rivaroxaban was then reintroduced. One week after reintroduction, the patient was admitted for severe dizziness and inability to walk. General examination at entrance was normal. The patient was unable to stand, without neither cerebellar nor vestibular signs. He had no orthostatic hypotension. Brain MRI, doppler ultrasonography of the supra-aortic trunks, continuous ECG monitoring, fasting plasma glucose (=6.0 mmol/L; N < 7) and LDL cholesterol (2.99 mmol/L) were strictly normal. Rivaroxaban was stopped and replaced with warfarin. Gait disorder totally disappeared within 72 hours. The French pharmaceutical regulatory agency was notified. One month later, venous ultrasonography showed marked decrease of venous thrombosis and he had no recurrence of dizziness.

Discussion

Rivaroxaban is a recent anticoagulant that showed non-inferior efficacy to standard therapy for initial and long term treatment of pulmonary embolism and symptomatic venous thromboembolism, and the prevention of stroke or systemic embolism in patients with atrial fibrillation [1-3]. Results differ depending on studies, but it seems that rivaroxaban causes less major bleedings compared to warfarin, especially for intracranial bleedings [1]. Major and non-major clinically relevant bleedings occurs in 8 to 14.5% in patients with rivaroxaban [1,4]. AEs are reported from 23 to 82% in patients with rivaroxaban depending on studies. It includes nasopharyngitis (6 to 32% of patients), diarrhea (5 to 9%), liver enzyme elevation (0.5 to 2%), peripheral edema (6%), back pain (5 to 8%) [1,4]. Dizziness is only reported in one study with a frequency of 6.09% in patients with rivaroxaban versus 6.30% in patients with warfarin [1]. It does not specify the severity and the impact of dizziness, and if the treatment had to be stopped because of this symptom. In comparison, only one case of dizziness is reported with apixaban, another factor Xa inhibitor, and the final diagnosis was a hemopericardium in a patient with renal insufficiency [5]. In our case, we consider that this AE was severe because the patient had to be hospitalized.

The pathophysiological mechanism of dizziness with rivaroxaban remains unclear. Brain penetration of rivaroxaban is fairly low and therefore, dizziness probably cannot be explained by a direct cerebral toxicity [6]. Metabolism and excretion of rivaroxaban involve cytochrome P450 3A4 (CYP3A4) and 2J2 (CYP2J2), CYP-independent mechanisms, and P-glycoprotein (P-gp) and breast cancer resistance protein (Bcrp) (ABCG2). Renal dysfunction and CYP3A4, P-gp and Bcrp (ABCG2) inhibitors (mainly comprising azole-antimycotics, apart from fluconazole, and HIV protease inhibitors) can interfere with rivaroxaban metabolism and lead to increased plasmatic concentrations. In our case, the patient had normal renal function and rasagiline and trihexyphenidyl are not known to inhibit CYP3A4, P-gp, and Bcrp (ABCG2). However, we can hypothesize in our case that an interaction with usual treatments (rasagiline and trihexyphenidyl) or intolerance to an excipient of rivaroxaban could explain dizziness. Further observations and pharmacological studies are needed to better understand drug-drug interactions with rivaroxaban.

Conclusion

Our observation emphasizes that, although often well tolerated and effective, rivaroxaban may cause severe dizziness. Dizziness
is reported with rivaroxaban and we wonder if drug-drug inter-
action is an explanation for this phenomenon. Physicians must
be aware of this AE and pay particular attention to drug-drug
interaction when rivaroxaban is prescribed.

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