



# Rivaroxaban Induced Hallucinations: A Case Report

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Hallucinations induced by rivaroxaban are not much described in literature. This case report describes the occurrence of a specific adverse event during rivaroxaban use in an elderly male who developed hallucinations few months after starting rivaroxaban. Other possible causes for these events were ruled out through comprehensive medical examination. Drug discontinuation led to resolution of adverse drug reaction. The mechanism involved in rivaroxaban-induced hallucinations is not known. The adverse event in our patient was possibly caused by rivaroxaban. Although there is still no strong evidence that can associate hallucinations to rivaroxaban use, and others unknown factors might be involved, this adverse event should be kept in mind when prescribing this drug to older patients.

**KEYWORDS:** Hallucinations, Adverse Event, Drug Reaction

## INTRODUCTION

Rivaroxaban inhibits activated coagulation factor Xa and belongs to the group of direct acting oral anticoagulants (DOACs). Together with vitamin K antagonists, DOACs are first choice drugs for the prevention of thromboembolic events in atrial fibrillation. The number of rivaroxaban users is increasing, and it has been added to WHO's Essential Medicines List.<sup>1</sup>

A hallucination, defined by the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders, is a sensory experience that does not correspond to what actually happens.<sup>2</sup> In a hallucination as perception, the stimulus from the outside world is missing. Hallucinations can affect all the senses namely visual, auditory, smell, taste and somatic and can be caused by the use of hallucinogenic drugs, alcohol, medication, sleep deprivation or delirium, among others. The occurrence of hallucinations without the use of drugs or medication or outside influences is a symptom that usually indicates a serious psychological or physical problem.<sup>2</sup>

To date, except for intracerebral hemorrhage, headache and dizziness, adverse effects on the central nervous system are not part of the adverse event profile of rivaroxaban and other DOACs. In this article, we describe hallucinations in rivaroxaban use based on a case study from our own practice. We suspect that the medicine has contributed to the symptoms. Already published literature does not say much about the

chance of occurrence or getting an adverse event or the frequency of occurrence.

## CASE REPORT

A 69-year-old man with a history of atrial fibrillation, heart failure, hypertension and well controlled sleep apnea was referred to us for an analysis of his cognitive decline. The patient was taking rivaroxaban, metoprolol, bumetanide, omeprazole, simvastatin, perindopril and digoxin at home. The patient was a past smoker, did not take alcohol and had no known allergies. Rivaroxaban has been in use for the indication of atrial fibrillation for six months.

The course of the disease was short, in which the symptoms had only existed for six months and in the last eight weeks there were additional visual hallucinations and suspicion. The differential diagnosis was delirium and subdural hematoma. No underlying somatic substrate for delirium was found during repeated physical examinations and additional lab tests and urinalysis. The MRI showed no fresh hemorrhage or ischemia. Memory and concentration disorders had been observed at some other clinic. There was a positive temporal relationship between starting rivaroxaban and these adverse events. Rivaroxaban was discontinued on an outpatient clinic basis in consultation with the cardiologist. The hallucinations disappeared approximately 48 hours after stopping. Olanzapine was started a few days before stopping rivaroxaban and discontinued approximately 10 days



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after starting due to the improved psychological picture. Few weeks later, the patient reported that he is doing a lot better, and hallucinations have disappeared after stopping rivaroxaban. He was referred to cardiologist for guidance regarding treatment of atrial fibrillation.

## DISCUSSION

The mechanism by which rivaroxaban causes hallucinations is unknown. Animal studies have shown that, despite their lipophilic nature, DOACs barely cross the blood-brain barrier.<sup>3,4</sup> This could be partly explained by the fact that DOACs are substrates for P-glycoprotein, an ATP-dependent membrane protein that pumps all foreign substances out of the cell, limiting cerebral tissue perfusion.<sup>5</sup> In order to determine whether hallucinations in our case are related to rivaroxaban use, the Naranjo score was determined.<sup>6</sup> This score ranges from  $\leq 0$  to  $> 9$  whereby the certainty of a link between the use of rivaroxaban and the occurrence of hallucinations increases with an increasing score. In our case, the Naranjo score in the scale falls between 1 and 4 indicating a possible link. A positive dechallenge after drug discontinuation also favorably supports our diagnosis. Not much data was found in literature that have recorded hallucinations in the case of rivaroxaban use or that warn for this. This is in contrast to adverse events on the central nervous system, such as headache and dizziness, which occur much more often and can possibly be detected more quickly in smaller populations. The exact mechanism of our patient's adverse reaction is unclear. However, as these superior and safer drugs become the standard of care for many large patient populations requiring chronic anticoagulation, post-marketing peer-reviewed reports of idiopathic adverse drug reactions

to these, such as that experienced by our patient, are critical.

## CONCLUSION

Despite the fact that the mechanism of hallucinations with rivaroxaban is unknown and that several trigger factors are possible including age, cognitive decline, drug interactions, major life events, it remains something to be taken into account in clinical practice, especially if it concerns elderly patients.

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