Direct oral anticoagulant-induced hallucination: Review of the French Pharmacovigilance Database

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Introduction

Until now, central nervous system disorders, apart from intracerebral he-morrhage, headache and vertigo, are not part of the adverse effects profile of Direct Oral Anticoagulants (DOAs *i.e.* dabigatran, apixaban and rivaroxaban).

Aim

To describe hallucination reports with DOAs in the French Pharmacovigilance Database (FPVD).

Materials & Methods

All cases of hallucination recorded in the FPVD from 2008 to December 2017 in which a DOA was suspected were included.

The cases were selected using the MedDRA High-Level Term "Perception disturbance".

Results

During the study period, 8198 adverse drug reactions reports involving a DOA were registered in the FPVD. Among these cases, 9 were DOA-induced hallucination observations. DOA was the only drug suspected in all the cases. Characteristics of these cases are described in the table below.

Sex ratio was 1.25 and median age was 79 years. Median time from DOAs introduction to hallucination onset was 10 days (from 1 day to 3 months). No patient had a previous history of hallucination.

In seven cases, hallucinations disappeared after DOA withdrawal.

For one patient, hallucinations did not reappear despite reintroduction of the same DOA (dabigatran). Another concomitant cause of visual hallucination was suspected in one case (Charles Bonnet syndrome).

Table. Description of DOA-induced hallucination reports in the FPVD.

Gender	Age (years)	DOA	Indication	Dosage	Type of hallucination	Time of onset	Imputability[1]
F	81	Dabigatran	-	75mg bid	Visual	2 months	Doubtful
F	80	Dabigatran	AF	110mg qd	-	3 months	Doubtful
F	65	Dabigatran	THP	75mg bid	-	2 days	Doubtful
M	78	Rivaroxaban	AF	20mg qd	Visual	1 month	Plausible
F	85	Rivaroxaban	TVP	15mg bid	Visual, auditory	2 days	Likely
M	-	Rivaroxaban	-	-	-	-	Doubtful
M	70	Rivaroxaban	-	20mg qd	Visual	10 days	Doubtful
M	88	Rivaroxaban	AF	10mg qd	Visual, auditory	1 day	Doubtful
M	35	Rivaroxaban	TVP	15mg bid	-	43 days	Doubtful

AF = atrial fibrillation; DVT = deep vein thrombosis; F = female; M = male; THR = total hip replacement

Discussion

Hallucinations induced by DOAs are not mentioned in the summary of product characteristic of these drugs and have never been described in literature.

Despite their lipophilic nature, the passage of DOAs across the blood-brain barrier would be low according to animal studies (estimated at less than 7% for rivaroxaban)[2,3]. This could be partly explained by the fact that DOAs are substrates of the P-glycoprotein[4], an ATP-dependent protein which pumps many foreign substances out of cell, limiting tissular (notably cerebral) diffusion.

Although the mechanism involved in these DOA-induced hallucinations is not known, their occurrence in a patient treated with rivaroxaban is probably multifactorial (age, gender, genetic polymorphism, drug interaction) but should be kept in mind.

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