

Aripiprazole-Induced Rabbit Syndrome: How Safe is Its Use in Adolescence?

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Abstract

Aripiprazole (10 mg/day), when given to a 16 year old boy with solvent dependence, he developed rare movement disorder, 'rabbit syndrome'.

Keywords: Extrapyramidal syndrome; Antipsychotic agents; Volatile solvents; Adverse drug reaction

Introduction

'Rabbit syndrome' is an uncommon drug-induced extrapyramidal syndrome (EPS) characterised by rapid chewing movements similar to those made by rabbits, ordinarily faster and more regular than the orofacial tic of tardive dyskinesia; the tongue is spared [1].

Aripiprazole is a D2 dopamine receptor partial agonist, 5HT1A partial agonist, and 5HT2A antagonist. Theoretically, it is an atypical antipsychotic with reduced EPS and hyperprolactinaemia. Aripiprazole is effective in treating schizophrenia and mania; also approved for use in various child and adolescent groups, autism-related irritability in children [2].

The development of EPS and akathisia with aripiprazole was notable in most studies, though few studies showed development of tardive dyskinesia [3,4] and neuroleptic malignant syndrome [5]. Though few case reports of aripiprazole-induced rabbit syndrome are found, but very limited [6]. This case report of rabbit syndrome in 16 years old boy with 10 mg of aripiprazole raises questions about safety of aripiprazole in adolescents.

Case

A 16 years old boy presented with six months' history of taking solvent. Initially, it was once or twice weekly; then since last two months, it became regular. Most of the day, he would be confined to his room and take solvent. For last two months, his mother noticed changes in his behaviour. He communicated less with people, slept for long hours, used to get irritated easily, there were frequent anger outbursts, increased craving for the substance, verbally abusive at times, and increased demand for money. Due to this, he could not concentrate in his studies and his academic performance deteriorated. He was brought by his mother for de-addiction. Apart from solvent, there was no other substance intake and no past psychiatric illness. There was no psychiatric illness in the family. He was a student of class XI. Premorbidly, he was calm and quiet, social, responsible, excellent in sports, and good in studies. Mental state examination revealed ectomorphic built, irritable mood, philosophical ideas, no thought and perceptual disturbance, sustained attention, full orientation, intact comprehension, and level one insight. Detailed physical and neurological examinations were normal and laboratory investigations were inconclusive.

The patient was diagnosed as a case of "mental and behavioural disorders due to use of volatile solvents" as per the tenth revision of the International Statistical Classification of Diseases and Related Health

Problems (ICD-10) criteria [7]. He was admitted in the Department of Psychiatry of Gauhati Medical College Hospital, Guwahati and in the ward, he got aggressive, irritable, verbally and physically abusive towards mother. He was started on tab aripiprazole 10 mg once daily dosage. With this, his aggression and irritability decreased. But after seven days, he developed restlessness and rapid involuntary, rhythmic, chewing movements of the upper lip with no associated abnormal tongue movements. The patient did not develop any parkinsonian symptoms. He had no dental problem. The electroencephalography (EEG) was normal. His orofacial movement was diagnosed as rabbit syndrome. Aripiprazole was tapered and stopped. Tab lorazepam and trihexyphenidyl was started. The symptoms subsided completely with the combination treatment. The Naranjo adverse drug reaction (ADR) probability scale was given and a score of seven, indicating "probable" adverse drug reaction, was found.

The Naranjo ADR probability scale

The Naranjo criteria classify the probability that an adverse event is related to drug therapy based on a list of weighted questions, which examine factors such as the temporal association of drug administration and event occurrence, alternative causes for the event, drug levels, dose – response relationships, and previous patient experience with the medication. The ADR is assigned to a probability category from the total score as follows: *definite* if the overall score is nine or greater, *probable* for a score of five to eight, *possible* for one to four and *doubtful* if the score is zero. The Naranjo criteria do not take into account drug-drug interactions. Drugs are evaluated individually for causality, and points deducted if another factor may have resulted in the adverse event, thereby weakening the causal association [8] (Table 1).

Discussion

Rabbit syndrome is antipsychotic-induced EPS which may appear in absence of other extrapyramidal symptoms as found in this case [9,10].

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To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score	Yes	No	Do not know	Score
1. Are there previous <i>conclusive</i> reports on this reaction?	+1	0	0	+1
2. Did the adverse event occur after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a <i>specific</i> antagonist was administered?	+1	0	0	+1
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the blood detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in <i>any</i> previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
			Total	7

Table 1. The Naranjo adverse drug reaction probability scale.

With regard to aripiprazole dosing in children and adolescents, slow titration is needed to reduce side effects. The recommendation of the United States' prescribing information in children and adolescents is a starting daily dose of 2 mg titrated to 5 mg/day after two days and then to the target dose of 10 mg/day after two additional days [11]; rapid dose increment, without titration, may have resulted in rabbit syndrome in this case.

Aripiprazole is a D2 dopamine receptor partial agonist and earlier trials have shown extrapyramidal side effects of aripiprazole similar to those of placebo administration [12]. Some case reports also found aripiprazole-induced improvement in tardive dyskinesia [13]. Here, in this case, we found aripiprazole-induced rabbit syndrome and adding an anticholinergic led to discontinuation of symptoms.

In conclusion, aripiprazole, though a dopamine system stabilizer, can cause rabbit syndrome, even in low dosage in adolescents. Slow titration may help in prevention of EPS, and clinicians should be vigilant and cautious regarding emergence of side effects, regardless of which antipsychotic a patient is prescribed.

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