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Rabbit syndrome after short term treatment with antipsychotics: Case series

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Abstract
Rabbit syndrome (RS) is a rare form of extrapyramidal side effect associated with the use of antipsychotics. It usually appears after a long period of antipsychotic treatment. We present three cases of RS that occurred within two weeks of starting treatment with antipsychotics. We emphasize on reporting such rare cases to the native Pharmacovigilance programme in order to establish their prevalence rate in the patient population of any country.

Keywords: Extrapyramidal side effect, two weeks, Pharmacovigilance

Introduction
Rabbit syndrome (RS) is an antipsychotic induced dyskinesia of the mouth, characterized by fine, rapid, involuntary perioral motion that resembles the chewing motion of a rabbit [1]. The oral movements occur in a vertical direction and can be differentiated from tardive dyskinesia by the lack of involvement of tongue and by the rhythmic pattern [2]. RS affects mostly middle aged and elderly patients, with women being at higher risk [3]. The reported prevalence of RS ranges from 2.3-4.4% of patients treated with typical antipsychotics [4]. To the best of our knowledge, no prevalence studies have been published to date showing the association of RS with atypical antipsychotics. There are only isolated reports of RS due to atypical antipsychotics, most of which are due to Risperidone, making it the most common atypical antipsychotic associated with RS [4]. RS usually appears after a long period (in most cases months or years) of antipsychotic treatment [5] after extensive search on Pub Med and Google Scholar, we did not find any report of RS occurring within a short period of starting antipsychotics. We report here three cases of RS in young males from our inpatient wards that occurred within two weeks of treatment with typical antipsychotic (Haloperidol) in one patient and atypical antipsychotic (Risperidone) in the other two patients.

Case report 1
A 27 year old male, known alcoholic for the past ten years, was admitted in the surgery ward for treatment of acute pancreatitis. On the third day of admission, he became stressed, talked excessively and started having visual hallucinations. On the next day, he became disoriented, openly psychotic with visual and auditory hallucinations for which a psychiatric consultation was done. He was diagnosed to have alcohol withdrawal psychosis and was prescribed Haloperidol 5mg IM q.i.d to contain psychosis. He also received a single dose of Thiamine 100mg IV, Lorazepam 4mg IV q.i.d and Pantoprazole 40mg IV OD. 3 days later he developed perioral tremors which worsened over the next 2 days. The symptom was consistent with Haloperidol induced RS. The dose of Haloperidol was reduced to 5mg IM OD. He was also prescribed Promethazine 25mg IM OD. The abnormal movements completely disappeared over the next 48hours. His psychosis also remained controlled with the reduced dose of Haloperidol.

Case report 2
A 36 year old male, diagnosed with Paranoid Schizophrenia was started on Risperidone 2 mg b.i.d. After 1 week, the dose of Risperidone was increased to 4 mg b.i.d because of inadequate response to treatment. When dose was increased, symptoms began to improve but 8 days after the increase in dose, he developed perioral tremors coupled with rigidity of upper limbs. Considering a diagnosis of Risperidone induced RS, the treating psychiatrist substituted Risperidone with Olanzapine 2.5 mg b.i.d along with Trihexyphenidyl 2mg b.i.d. The abnormal movements decreased in few hours and completely disappeared after 3 days. Olanzapine dose was subsequently increased to 5 mg b.i.d without the recurrence of RS.

Case report 3
A 29 year old male diagnosed with bipolar disorder and maintained with 75 mg of Venlafaxine was brought to our institute with complaints of manic symptoms. He was started on Risperidone 20mg/day and his Venlafaxine dose was reduced. He was seen for follow up after 2 weeks. During the follow up visit, he complained of abnormal perioral movements along with muscle rigidity over the last 4 days. The symptoms were consistent with Risperidone induced RS. The treating psychiatrist decreased the dose of Risperidone to 1.5 mg b.i.d, with addition of Olanzapine 5mg OD and Benztropine 1mg b.i.d. His symptoms improved over the next 3 days. Risperidone was stopped and Olanzapine dose was increased to 5mg b.i.d without the re-emergence of RS.
We assessed the causality for all 3 cases as “Certain” because these events could not be explained by any other drug received by the patients, dechallenge was positive and the reactions were pharmacologically definitive.

Discussion

All three cases occurred in young males receiving antipsychotics. All the patients developed RS within two weeks of starting an antipsychotic. The exact mechanism of RS is not known. It has been suggested that RS occurs due to a hypercholinergic state created due to blockade of dopaminergic neurons in extrapyramidal system [6]. Typical antipsychotics, especially the high potency ones like Haloperidol, having predominant dopamine blockade are thus associated with RS. This also explains the inclusion of anticholinergic drugs to treat RS. The lower prevalence of RS with atypical antipsychotics may be the result of their more favourable serotonin to dopamine receptor affinity ratios [7]. The high incidence of RS with Risperidone however may be due to its lower anticholinergic activity compared to other atypical antipsychotics [8]. Also, at higher doses (>6mg/day) of Risperidone, dopamine antagonism predominates over serotonin antagonism, leading to an increased rate of RS with higher doses of Risperidone [9]. The occurrence of RS in two of our patients can thus be attributed to the high doses of Risperidone they received.

The reason for the occurrence of RS within a short period of starting antipsychotics is not known. The role of patient specific genetic polymorphisms in CYP2D6 enzymes leading to poor metabolism of the antipsychotics could offer a possible explanation for the acute development of RS in all our patients [10, 11].

RS was treated successfully in all the patients by reducing the dose of offending antipsychotic, addition of an anticholinergic drug or by switching to an atypical antipsychotic with stronger anticholinergic activity, such as Olanzapine. The anticholinergic drugs chosen were Promethazine, Trihexiphenidyl and Benztropine respectively in the three cases. Promethazine was chosen in the first case to provide additional sedation. All the three patients recovered completely with the treatment.

Conclusion

RS can occur with short term exposure to typical antipsychotics such as Haloperidol as well as atypical ones like Risperidone. Hence, clinicians must be cautious against the possibility of RS even after short duration of treatment with antipsychotics. We have reported our cases to Pharmacovigilance Programme of India. Detecting and reporting rare cases can serve as useful tool in quantification of adverse drug reaction among patient population of individual's country thereby redefining the prevalence rate of such adverse effects which often go unnoticed.

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