Case Report

Risperidone-induced mania: An emergent complication of treatment

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ABSTRACT

The occurrence of manic/hypomanic switch in patients being treated with risperidone has been reported by various authors, and they have described a variety of strategies for their management. In this report, we describe two cases of induction of elevated mood symptoms in patients treated with risperidone. We propose that the emergence of these symptoms may be a complication of treatment with this drug in susceptible individuals, of which the clinicians should be aware, mainly in those diagnosed with schizophrenia and bipolar disorder. We then discuss a few findings that might be useful in the management of such cases. We thereby also propose a mechanism for such an induction.

Key words: Mania, risperidone, side-effect

INTRODUCTION

The occurrence of manic/hypomanic switch in patients being treated with risperidone has been reported by various authors. A review of these cases, and those due to other atypical antipsychotics (APs) was done by Michalopoulou and Lykouras.[1] The authors described a total of 22 reported cases with risperidone induced elevated mood, and the findings brought out a few salient features of the reported cases.

- The most frequently used strategy to control manic/hypomanic symptoms induced by atypical APs was the discontinuation of the agent.
- Reduction of the dose of the atypical AP was the second most frequent strategy used.
- The manic/hypomanic symptoms induced by a certain atypical AP were successfully treated in several cases by another atypical AP.
- In three risperidone treated cases the hypomanic symptomatology of the patients was self-limited and resolved without alternation of risperidone dose or the addition of any other medication. The hypomanic symptomatology in these cases was thought to be a transient paradoxical behavioural response during the 1st days or weeks of treatment.
- The dose of risperidone was not altered and valproate was added to control the manic symptoms in two cases.
- When dose of the atypical AP that induced the manic/hypomanic symptoms was increased to control them, the management of the symptoms was unsuccessful
- In case of risperidone treated patients, time until remission of the manic/hypomanic symptoms ranged from 36 h to 2 months

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- The rapid remission of manic/hypomanic symptoms that was observed in three risperidone treated cases after discontinuation of the atypical AP suggested that these symptoms might be the direct effect of the compound.

We present here, two case reports of induction of elevated mood symptoms in patients treated with risperidone, and then discuss a few findings that might be useful in the management of such cases. Furthermore, we also propose a mechanism of such inductions.

CASE REPORTS

Case 1

Mr A.B., a 30-year-old married, Hindu, male, a farmer by profession from the rural part of Eastern India, with no significant family, past or personal history. He had a well-adjusted pre-morbid personality and gave an account of harmful use of tobacco. He presented to the Out Patient Department of the Institute with an illness of 1.5 years duration with insidious onset, a continuous course and deteriorating symptoms characterized by decreased social interaction, abusive and assaultive behavior, muttering and smiling to self, suspiciousness, wandering tendency, and decreased sleep. During the time of admission, the physical examination was unremarkable. On mental status examination, the patient had inadequate eye contact, withdrawn manner of relating, inappropriate smiling, and constantly muttering to self. The affect was constricted and poorly communicable. He harbored a delusion of persecution and experienced 3rd person auditory hallucinations of running commentary type, with derogatory content. His judgment was impaired, and had no insight into his illness. The patient was provisionally diagnosed according to International Classification of Diseases (ICD-10) to have undifferentiated schizophrenia. He was started on risperidone 3 mg, which was hiked to 6 mg in 3 days.

Five days following the initiation of risperidone, the patient developed euphoric affect, which was appropriate and communicable, inflated self-esteem and 2nd person auditory hallucinations with grandiose content. No other drug side-effects were noted. Score on Young's Mania Rating Scale (YMRS) was 21. In order to control the mood symptoms, carbamazepine 400 mg was added to the drug regime, which was gradually, hiked up to 800 mg. Four days after reaching the dose of 800 mg carbamazepine, the YMRS score came down to 15. Risperidone was then hiked to 8 mg.

On 8 mg risperidone and 800 mg carbamazepine, the thought and perception abnormalities improved, but the affect remained euphoric. The patient was discharged after 1 month of admission, on request from the guardian, on 800 mg of carbamazepine, 8 mg risperidone and 4 mg Trihexyphenidyl. At the time of discharge, the YMRS score was 13. On follow-up after 1 month, patient was asymptomatic with cheerful affect, no thought/perceptual abnormality and YMRS score of 7.

Case 2

Mr. K.A., a 55-year-old married, Muslim, male from urban part of Eastern India belonging to middle socio-economic class, with history of intake of tobacco, harmful use and nil contributory family history; presented with an illness of abrupt onset, continuous course and deteriorating progress of 6 days duration characterized by wandering tendency, crying spells, low mood, decreased interest, decreased sleep, fearfulness and increased talkativeness, following a stressor prior to the onset of the illness. The physical examination findings were unremarkable. On mental status examination, there was a fearful facial expression, fidgety behavior, increased speech productivity mostly concerned with the content of his fearfulness, a communicable dysphoric affect, and delusion of persecution and reference. The patient was diagnosed as a case of acute and transient psychotic disorder without symptoms of schizophrenia, according to the ICD-10. He was started on 900 mg of lithium carbonate (in view of mood instability) and risperidone 2 mg that was increased gradually to 4 mg (hiked 1 mg every 3 days). On 900 mg of lithium carbonate, serum lithium levels were 0.61 mEq/L.

Seven days after admission, the patient developed elated affect, overfamiliar attitude, inflated self-esteem; with a complete resolution of the delusions of persecution and reference. After 3 more days, in addition, there was an increase in his goal directed activities and an unfounded optimism. His insight deteriorated and the YMRS score was found to be 19. Two days following this, lithium carbonate was hiked to 1200 mg and risperidone was hiked to 6 mg. With this, the over familiarity and hyperactivity improved. Serum lithium level was 0.66 mEq/L on 1200 mg. Risperidone was further increased to 7 mg. YMRS score decreased to 13. The patient was discharged after 20 days on request by the guardian; on 1200 lithium carbonate and 7 mg risperidone. On follow-up after 1 month, serum lithium level was 0.76 mEq/L. The patient had a cheerful affect, with no active psychopathology. Insight was grade 4, and the YMRS score was 7.

DISCUSSION

Clozapine, the prototype of atypical APs, demonstrates a higher affinity for 5HT-2A receptors than for the D2 receptors. Risperidone, olanzapine, quetiapine and ziprasidone also share this property with clozapine and are therefore considered to be serotonin-dopamine antagonists (SDAs).[2] Adjunctive atypical AP therapy appears to benefit patients experiencing manic episodes in the course of bipolar and schizoaffective

disorder. Some studies suggest that mono-therapy may also be efficacious.[3] Their role in the maintenance phase of treatment of bipolar and schizoaffective disorder as an adjunct to mood stabilizers or as mono-therapy has also been explored.[4,5]

Further, there is accumulating evidence, though still limited, that patients with non-psychotic treatment resistant depression may benefit from the combination of atypical APs with (selective) serotonin reuptake inhibitors ([S] SRIs).[4,6] It has been suggested that the synergistic effects of atypical APs in combination with (S) SRIs on dopamine and norepinephrine release in the prefrontal cortex may contribute to their ability to augment the antidepressant effect in patients suffering from treatment resistant depression.[7]

It has been suggested that the mood altering effects of the atypical APs are dose dependent, with lower doses resulting in the enhancement of forebrain dopaminergic activity via mechanisms that will be discussed below.[8]

Possible mechanisms of mania induction by atypical APs

Combined 5HT-2A and D2 antagonism, especially the relative higher affinity for 5HT-2A than D2 receptors is characteristic of SDAs.[9] It has been suggested that the mood altering effects of risperidone result from its high 5HT-2A receptor affinity, as a function of the 5HT-2A/D2 occupancy ratio.[8] Indeed, low doses of risperidone are associated with relatively higher 5HT-2A occupancy that can result in enhancement of forebrain dopaminergic activity by disinhibition of the dopaminergic system, influencing the mood state. At higher doses, however, the saturation of the 5HT-2A receptors and the increasing D2 occupancy counteracts this action of the associated 5HT-2A activity.[10] It has also been suggested that the combined 5HT-2A and D2 receptor blockade of the SDAs increases dopamine release in the prefrontal cortex - at least partly - via 5HT-1A receptor activation, regardless of intrinsic 5HT-1A affinity.[11] The atypical APs appear to be involved in the induction of manic/hypomanic symptoms in susceptible individuals not only through a dose dependent discriminant activation of 5HT-2A and D2 receptors, but also through their 5HT-1A receptor activity. The occurrence of amisulpride-induced mania - a non-SDA atypical AP - may suggest that the enhancement of the frontal dopaminergic transmission and the subsequent mood alternation is not necessarily associated with combined 5HT-2A and D2 receptor antagonism. It is possible that other mechanisms, which are not necessarily dose related, are also involved in the induction of manic/hypomanic symptoms in susceptible individuals.

We believe that the emergence of these symptoms may be a complication of treatment with drugs in susceptible individuals. Clinicians should be aware of the possibility of mood switching effects of these medications in susceptible individuals.

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