ABSTRACT

There are several reports available on neuroleptic malignant syndrome (NMS) associated with risperidone but when a more stringent criterion is applied there are only a few. Report on challenge and rechallenge with various atypical antipsychotic drugs in re-emergence of post NMS psychosis is scanty. Our aim of presenting this is to highlight the differential response of various atypical antipsychotic drugs in the treatment of post NMS psychosis. This paper reports a young male with mild mental retardation who developed NMS on a low dose of risperidone. Earlier he was on haloperidol 10 mg, which was stopped 10 days prior to initiation of risperidone therapy. Symptoms of NMS resolved within 36 hours with bromocriptine; but the patient relapsed to psychosis. Re-challenge with risperidone 1mg resulted in a dystonic reaction, with clozapine 12.5 mg he developed marked sedation, hypotension and urinary incontinence. Ultimately post NMS psychosis responded well to olanzapine 10mg and there was no recurrence of NMS. Olanzapine may be the better choice for the treatment of post NMS psychosis.

Key words: NMS, risperidone, challenge and atypical neuroleptics.

A review article by Hasan and Buckley in 1988 identified 13 case of risperidone-induced NMS with variable diagnostic certainty. When the more stringent criteria of Caroff and Mann (1993) was applied, only five out of the thirteen cases were identified as being true NMS. Same article has drawn the tentative conclusion that NMS can occur with risperidone monotherapy but a proportion of these cases appear to have implicated risperidone inappropriately. A review on risperidone induced NMS observed that age and duration of exposure to risperidone did not seem to be of significance (Metenssian 1996). We found approximately 22 cases of risperidone-induced NMS after reviewing the literature in detail. Only single case report is available from India (Venkatasubramanian et al. 2000). In most of these cases strategic plan for post NMS phase has been not discussed. This case report highlights NMS induced by risperidone, which was resolved within 36 hours with bromocriptine and also highlights the differential response of various atypical neuroleptics.

CASE REPORT

Mr. S, a 22-year-old male with mild mental retardation presented to us with symptoms of disinhibited behavior abusiveness running away from home, second person auditory hallucinations, delusions of persecution, delusions of reference and disturbed biological functioning of one and a half months duration. He was treated with haloperidol 15 mg/day and Trihexyphenidyl 4mg/
day. He developed extrapyramidal symptoms (EPS) in the form of rigidity, bradykinesia and salivation, hence haloperidol was discontinued and his EPS was treated successfully with trihexyphenidyl 6mg/day. Within 10 days of stopping haloperidol and during recovery phase of EPS (mild) patient's psychosis worsened for which he was started on Risperidone 2mg. Six days later he was admitted to this hospital with symptoms of fever, unable to pass urine, not taking orally and stiffness of body of 2 days duration. On examination, he was found to be febrile with generalized rigidity and he also had retention of urine. His temperature varied from 100 F - 102 F and pulse rate was 100-120 beats/minute. Blood pressure was labile and he exhibited symptoms of altered sensorium. Laboratory tests done on first day of admission revealed serum creatine phosphokinase (CPK) level of 370 IU/L, albuminuria and a liver function tests showed deranged liver enzymes. A diagnosis of schizophreniform disorder with neuroleptic malignant syndrome was made. Risperidone was stopped immediately and patient was managed symptomatically with hydrotherapy and antipyretics. Bromocriptine 2.5 mg in three divided doses was started. Serum CPK repeated on the next day was found to be further elevated to 1558 IU/L. There was no improvement in fever, rigidity and altered sensorium. Bromocriptine was increased to a dose of 12.5 mg/day. On the third day of admission, he became afibrile and was oriented to time, place and person. He showed marked improvement in rigidity, serum CPK decreased to 58 IU/L and autonomic instability also settled. These fall in serum CPK was continued and subsequent CPK was 36 IU/L and 30 IU/L. Bromocriptine was tapered and stopped over two weeks. Cranial CT done during the course of his stay in the hospital revealed nonspecific calcified granulomas in the right parieto-occipital region and in the left parietal region. Within two weeks after complete recovery from NMS patient started exhibiting psychotic behavior similar to the previous one. Initially he was treated with 6 electro-convulsive therapies (ECT) for post NMS psychosis over a period of three weeks, but showed no significant improvement. In fact, he developed post-ECT memory disturbances. We have taken a separate informed consent from patient’s father for challenging and re-challenging with atypical antipsychotic drugs. With a single dose of clozapine 12.5 mg, he was sedated for 18 hours and had hypotension and urinary incontinence. Rechallenge was done with risperidone 1mg but on the second day he developed dystonic reaction of the neck muscles. Ultimately he responded very well to gradual administration of olanzapine 15 mg without developing any side effects. Serum CPK levels were done each time before increasing the dose of olanzapine and levels were within normal limits. At the time of discharge, serum CPK was 22 IU/L.

DISCUSSION

Our patient fulfilled the major and minor criteria as given by Levenson (1985), Caroff and Mann (1993) and also as per DSM-IV (1994). Risperidone a benzisoxazole derivative has high serotonin 5HT2 receptor blockade and dose related D2 receptor blockade. It is believed that this ratio would cause low frequency of EPS at lower doses (Jeste et al., 1999) and thus prevent the occurrence of NMS.

According to the most stringent criteria of Caroff and Mann (1993), a patient develops NMS within a week of oral use of neuroleptics and within 2-4 weeks of depot neuroleptic use. Our patient developed NMS within 4 days of risperidone therapy thus suggesting a temporal correlation between NMS and risperidone use. Though the rapid fall in serum CPK correlated with clinical improvement earlier clinical presentation was not correlated well with CPK level, where CPK was only 370 despite of having full-blown NMS. This showed that CPK is a non-specific finding as seen in other study (O'Dwyer & Sheppard 1993). Our patient was mentally retarded and concomitant diagnoses of mental retardation was also found in other case reports with atypical and typical antipsychotic induced NMS (Hasan and Buckley...
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Cranial CT scan finding could again have been a non-specific finding in our case.

Literature regarding management of post NMS psychosis is scanty reported particularly on atypical neuroleptic induced NMS and subsequent psychosis probably because of rarity of condition. Studies have examined the issue of re-challenge with only typical neuroleptics in post NMS cases and demonstrated safety of re-challenge (Rosenbush et al 1989 & Chopra & Raghuram 2001). Recent review showed that 19 out of 45 reports of rechallenge with an atypical antipsychotic after NMS with a typical antipsychotic had recurrence of NMS. Another of 45 rechallenges with a typical antipsychotic after NMS on a typical antipsychotic 17 had recurrences (Caroff et al 2000). This finding may be biased probably due to the lack of reporting of successful rechallenge with a new drug. Administration of high potency neuroleptic at a rapid loading appears to be crucial for recurrence of NMS on rechallenge (Chopra & Raghuram 2001).

Avoidance of neuroleptic drug for at least 2 weeks after complete recovery from NMS and gradual titration of low dose and low potency neuroleptic trial of newer anti psychotic such as clozapine may be useful to prevent recurrence of NMS (Bajjock et al 1997). In the review by Hassan and Buckley (1998) patients with typical antipsychotic induced NMS were given clozapine which they were able to tolerate without a recurrence of NMS. Three out of four patients with clozapine induced NMS were rechallenged with clozapine and one with risperidone without recurrence of NMS and subsequent problems. Both patients with risperidone induced NMS developed some symptoms of NMS when rechallenged. In contrast to these findings our case was dose-sensitive to clozapine and rechallenge with risperidone caused dystonia, which were the reasons to withdraw both neuroleptics. It is difficult to explain why this case showed good response to olanzapine. A possible explanation may be the olanzapine's receptor binding profile seems to occupy an intermediate position between clozapine and risperidone. It has greater affinity for 5HT2a and D2 receptors than clozapine but lower affinities than risperidone (Moore et al., 1992). We have reviewed the recent case reports on olanzapine induced NMS. In two cases, NMS probably has been promoted by the past history of conventional neuroleptic induced NMS (Gheorghiu et al., 1999 & Burkhard et al.) Another case already had medical history of glaucoma, possible parkinsons disease and confusion. He was on olanzapine, nefazadone and received low dose of haloperidol 2 days prior to the onset of NMS (Hansen and Alderman 2000).

One case of olanzapine induced NMS was already on benzotropin mesylate and ranitidine (Stanfield & Privette 2000). This showed that some of the cases were not true cases of NMS. Olanzapine is superior to risperidone in ameliorating both positive and negative symptoms in schizophrenia and other psychotic disorders (Tran et al., 1997). Clozapine causes agranulocytosis in about 1% of cases (Alvir et al., 1993) while none of the patients exhibited hematotoxicity among 2500 patients treated with olanzapine (Beasley et al 1997). In view of the available side effect profile of atypical antipsychotic drugs in post NMS phase, this case report showed that olanzapine may be the better choice for the treatment of post NMS psychosis.

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