

REEMERGENCE OF POSITIVE SYMPTOMS OF SCHIZOPHRENIA DURING THE COURSE OF TREATMENT WITH RISPERIDONE

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ABSTRACT

Thirty patients suffering from schizophrenia (diagnosed as per DSM-IV criteria), for more than 2 years and having predominant negative symptoms were started on risperidone (2-10 mg/day) and were followed up over a period of 16 weeks. The improvement was assessed using PANSS (Positive and Negative Syndrome Scale).

During this 16 weeks follow up, it was interestingly noted that though there was a significant improvement in negative symptoms in all the patients, in 7 patients there was a reemergence of positive symptoms. Four patients had increase in rating on suspiciousness and hostility and two patients reported auditory hallucinations. One patient developed delusions and conceptual disorganization along with suspiciousness and hostility.

Key words : Risperidone, positive symptoms, schizophrenia.

In patients suffering from schizophrenia, the positive symptoms appear more closely related to a hyperdopaminergic state at the mesolimbic pathway (Davis et al., 1991) whereas the negative symptoms may be associated with hypodopaminergic mesocortical pathway (McGlashan & Fenton, 1992; Kibel et al., 1993; Peralta & Cuesta, 1996).

Blockade of D₂ receptors by the conventional antipsychotics at the mesolimbic system seems to effectively control the positive symptoms. The blockade of 5HT₂ receptors, by a typical antipsychotic like clozapine and risperidone seems to potentiate dopamine release in the prefrontal cortex and enhance the dopaminergic neurotransmission at the basal ganglia, thereby alleviating negative symptoms of schizophrenia and minimizing the extrapyramidal symptoms respectively (Kapur & Remington, 1996; Love, 1996).

Research data indicate that Risperidone with significant antagonist activity at the 5HT₂ and the D₂ receptors may be more effective than currently available dopamine antagonists at treating both the positive and the negative symptoms of schizophrenia (Carman et al., 1995).

Number of open and comparative clinical trials have explored the efficacy and safety of risperidone. These studies have established its efficacy in positive as well as negative symptoms of schizophrenia and its safety in terms of low incidence of extrapyramidal reactions (Claus et al., 1992; Chouinard et al., 1993; Ceskov & Svestka, 1993; Marder & Meibach, 1994; Peuskens, 1995; Agarwal et al., 1998; Bondolfi et al., 1998).

Inspired by this research data, we tried risperidone in patients suffering from schizophrenia who had predominant negative

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symptoms and who had shown unsatisfactory response to the conventional antipsychotics as far as the negative symptoms were concerned.

MATERIAL & METHOD

Thirty consecutive patients who satisfied following inclusion and exclusion criteria were selected for the study.

Inclusion criteria: Patients satisfying the DSM-IV criteria for schizophrenia (APA, 1994); having total duration of illness at least of 2 years; having prior treatment with conventional antipsychotics (haloperidol, chlorpromazine, or trifluoperazine) and ECTs in adequate dose for at least two years; poor response to conventional antipsychotics as far as the negative symptoms were concerned; predominant negative symptoms at the time of inclusion in the study as assessed by negative syndrome subscale of PANSS (Positive and Negative Syndrome Scale) (Kay et al., 1987).

Exclusion Criteria: Patients with onset of illness after the age of 45 years & comorbidity of substance use disorder.

After the informed consent from the patients or their relatives, tablet risperidone was started with an initial dose of 1 mg twice daily. The dose was increased gradually every week by 2 mg/day till maximum of 10 mg/day, based on the clinical improvement, tolerance to side effect and improvement on negative syndrome subscale of PANSS. The conventional antipsychotics were

gradually discontinued over a period of 1 week after starting the patients on risperidone.

All the patients were regularly assessed clinically as well as on PANSS score; initially every week for 4 weeks followed by every 2 weeks for remaining 3 months.

The collected data was tabulated and analysed statistically using paired t-test.

RESULT AND DISCUSSION

In the study population of 30 patients, there were 15 males and 15 females in the age range of 15 to 40 years (mean \pm SD 28.67 years \pm 8.34).

During this 16 weeks follow up, it was interestingly noted that though there was a significant improvement in negative symptoms in all the patients, in 7 patients there was a reemergence of positive symptoms.

In the 23 patients there was significant improvement in all the subscales of PANSS. A substantial more improvement in these patients can be noted in the negative symptoms from the shift in the positive direction in the composite index (the mean of difference between positive and negative scores) (Table).

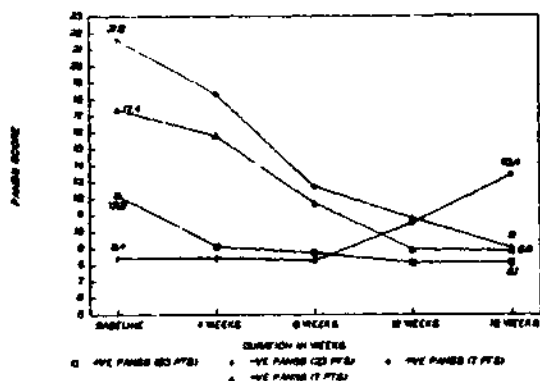
In contrast to these 23 patients, there was significant increase in the mean positive subscale score on PANSS for 7 patients in whom reemergence of positive symptoms was observed (Figure).

The improvement in negative symptoms in these 7 patients was negated by reemergence

TABLE
PANSS SCORES BEFORE AND AFTER THE TREATMENT

PANSS Subscales	N=23		N=7	
	Before treatment Mean (SD)	After treatment Mean (SD)	Before treatment Mean (SD)	After treatment Mean (SD)
Positive PANSS	12.26 (6.13)	8.13 (2.24)	8.43 (2.15)	13.43 (2.37)
		t=4.26, p<0.001		t=3.59, p<0.02
Negative PANSS	21.61 (8.46)	9.00 (3.67)	17.43(11.87)	8.86(3.08)
		t=6.93, p<0.001		t=2.51, p<0.05
Gen-Psy PANSS	34.22 (11.66)	25.91 (9.36)	26.71 (8.12)	27.60(8.46)
		t=5.00, p<0.001		t=0.19, Not significant
Composite Index	-9.34 (11.66)	-0.80 (3.37)	-10.71 (10.19)	4.57 (3.78)
		t=4.43, p<0.001		t=3.86, p<0.01

FIGURE PANSS SCORE OVER 10 WEEKS



of positive symptoms and so no significant change in general psychopathology (Gen-Psy) subscale of PANSS was observed. The substantial improvement in negative symptoms is also reflected in positive shift in composite index (Table).

Out of the 7 patients, 4 patients had increase in rating on suspiciousness and hostility and two patients reported auditory hallucinations. One patient developed delusions and conceptual disorganization along with suspiciousness and hostility.

On review of literature we found another report by Cung and Stimmel (1997) who have also reported the reemergence of positive symptoms, especially auditory hallucinations after 8 months and again after 24 months of risperidone therapy.

Risperidone's antiserotonergic activity is hypothesized to potentiate the dopamine release in the prefrontal cortex and enhance dopaminergic neurotransmission in the basal ganglia, thereby alleviating the negative symptoms and minimizing the extrapyramidal symptoms (Kapur & Remington, 1996). However, a similar potentiation in dopamine release at the mesolimbic region may counteract the primary

antipsychotic activity, resulting in a reemergence of positive symptoms. In a recent radioligand binding study by Volonte *et al.* (1997), it has been demonstrated that subcutaneous risperidone in rates stimulates dopamine release in the medial prefrontal cortex, nucleus accumbens and the lateral striate cortex to a similar extent.

The other possibility is that the discontinuation of conventional antipsychotics may have lead to reemergence of positive symptoms in these patients. This is however unlikely as risperidone has been reported to be useful in negative as well positive symptoms (Carmen *et al.*, 1995).

The probability of inadequate dosage in these 7 patients is also unlikely as the mean dose of risperidone received by these 7 patients was 6.9 mg/day which was comparable to the mean dose of 6.2 mg/day received by the other 23 patients who did not develop positive symptoms.

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