ABSTRACT

Obsessive compulsive symptoms have been reported to occur in high proportion in schizophrenia. Presence of obsessive compulsive symptoms in schizophrenia has poor prognostic significance. Because of the antiobsessional effect of the fluoxetine, present study was undertaken as preliminary investigation in cases of schizophrenia with obsessive compulsive symptoms. We conducted an open trial of 12 weeks duration in which fluoxetine was added up to 80 mg to the maintenance neuroleptic medication of outpatients of schizophrenia with obsessive compulsive symptoms diagnosed by DSM-IV criteria. Five patients showed a significant reduction in scores of Positive and Negative Syndrome Scale, Yale Brown Obsessive Compulsive Scale and Clinical Global Impression Scale. Two patients did not show any response. Fluoxetine was well tolerated by all the patients. The positive findings of this preliminary investigation supports the further investigations of fluoxetine as potential treatment in the obsessive compulsive symptoms in schizophrenia.

Key words: Fluoxetine, obsessive compulsive symptoms, schizophrenia

The presence of obsessive compulsive (OC) symptoms in schizophrenic patients have been reported for decades. Recent studies have reported that OC symptoms occur in large number of schizophrenic patients varying from 13-25% (Berman et al., 1995; Cossof et al., 1998; Fenton & McGlashan, 1986). Presence of persistent OC symptoms represents an indicator of poor prognosis (Fenton & McGlashan, 1986; Samuel et al., 1993). These patients have been reported to be more socially isolated, less likely to work and need longer hospitalization than non-OC schizophrenic patients (Fenton & McGlashan, 1986; Samuel et al., 1993). Fluoxetine has been reported to improve negative symptoms when added to neuroleptics in schizophrenic patients (Goff et al., 1995). However, later studies have failed to find any improvement in positive or negative symptoms when fluoxetine was added to Clozapine and conventional antipsychotics (Arango et al., 2000). There are several case reports that described patients who showed improvement in OC symptoms when fluoxetine was added to their ongoing neuroleptic medication (Sewell et al., 1994, Tejera et al., 1994). However there is no study in literature that confirms the efficacy of fluoxetine in OC symptoms in schizophrenic patients. We report an open pilot study in which fluoxetine was added to the ongoing neuroleptic medication of schizophrenic patients with OC symptoms.

MATERIAL AND METHOD

Seven outpatients (6 male, 1 female) with mean±SD age 25.7±6.6 years (range 16-35 years) were included in the study. The diagnosis of schizophrenia was confirmed by information from relatives of the patients, chart review and clinical interview of the patients using DSM-IV criteria. OC symptoms were diagnosed by Fenton and McGlashan (1986) criteria. Patients
with comorbid axis I disorders and clinically significant physical illness were excluded. Patients were stable on same dosage of their neuroleptic medication at least for one month prior to inclusion in the study. All the patients or their relatives (whichever applicable) gave written informed consent for participation in the study after being provided details of procedure. Detailed history was taken and physical examination was carried out. Routine blood investigations were carried out. Patients were assessed on Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), Yale Brown Obsessive Compulsive Scale (YBOCS; Goodman et al., 1989), Clinical Global Impression scale (CGI; NIMH 1985) and Dosage Record Treatment Emergent Symptom Scale (DOTES; Campbell and Palij 1985) at baseline and thereafter at every two weeks throughout the study period of 12 weeks. All the scales were administered to the patients by one clinician (first author) throughout the study. 20 mg fluoxetine was added to their neuroleptic medication in first two weeks then increased to 40 mg from 3rd week, thereafter doses of fluoxetine were increased on the basis of clinical judgement to 60 mg from 5th week and 80 mg from 9th week. Compliance was ensured through counselling of the patient and family members taking care of the patient. Drugs were administered to the patient daily under direct supervision of close family member taking care of the patient. Baseline scores of PANSS, YBOCS and CGI were compared with the final scores at 12th week using paired t test (two tailed).

RESULTS

All the patients completed the study period of 12 weeks. Mean duration of illness was 7.35±4.9 years. Mean dose of fluoxetine was 74 mg/day (range 40-80 mg). The antipsychotics given to the patients were haloperidol (n=1), trifluoperazine (n=1), injection fluphenazine (n=1), risperidone (n=3) and clozapine (n=1). Concomitant medication given were antiparkinsonian (n=3) and benzodiazepine (n=1). Five patients showed response in both OC and schizophrenic symptoms while 2 did not show any response.

Ratings on YBOCS (Table) at 12 weeks showed a significant improvement (p <0.01) as compared to baseline. Total scores on PANSS also showed a significant improvement (p<.004). Further analysis of PANSS subscales showed significant improvement in positive symptoms (p<0.01), negative symptoms (p<.006) and general psychopathology (p<.004) as compared to baseline. Score of severity of illness on CGI showed a significant reduction (p<.01). Ratings of patients on CGI global improvement of individual patient showed very much improvement in 1, much improvement in 3, minimal improvement in 1 and no change in 2 patients. All patients tolerated fluoxetine well.

| Scales | Baseline | 12th Week | p     |
|--------|----------|-----------|-------|
|        | Mean±SD  | Mean±SD   |       |
| YBOCS  | 30.3±4.9 | 14.1±10.9 | 0.01  |
| PANSS  |          |           |       |
| Positive | 10.0±1.7 | 7.7±1.5 | 0.01  |
| Negative | 16.7±7.1 | 14.1±7.7 | 0.006 |
| General | 28.1±2.8 | 23.0±4.7 | 0.004 |
| Psychopathology | | | |
| Total   | 54.8±6.6 | 44.8±13.0 | 0.004 |
| CGI     | 5.5±0.8  | 3.8±1.6  | 0.01  |

YBOCS : Yale Brown Obsessive Compulsive Scale, PANSS : Positive and Negative Syndrome Scale, CGI : Clinical Global Impression

Two patients developed restlessness and palpitation in first week which subsided in one week. Two patients complained of mild anorexia while one developed moderate anorexia which gradually decreased after four weeks. Two patients developed mild tremors and occasional headache tolerance to which developed in four weeks. None of the patient developed worsening of psychotic symptoms.

DISCUSSION

Evidence from this preliminary open trial suggest that fluoxetine was effective in reducing OC symptoms in schizophrenic patients.
OBSESSIVE COMPULSIVE SYMPTOMS IN SCHIZOPHRENIA

improvement in residual schizophrenic symptoms was also observed. It also improved the global picture of the schizophrenic patients. The findings are interesting with the current evidence of dysfunction of serotonin in schizophrenia (Roth & Meltzer, 1995) and obsessive compulsive disorder (Pigott, 1996). Also OC symptoms respond to serotonergic drugs like fluoxetine (Montgomery et al., 1993, Tollofson et al., 1994) and clomipramine (Clomipramine Collaborative Study Group 1991). Findings of our study suggest that OC symptoms in schizophrenic patients respond to fluoxetine in much the same way as OC symptoms in non schizophrenic patients. The improvement in residual schizophrenic symptoms is less clear. One possible explanation for improvement in schizophrenic symptoms could be the increase in the blood levels of neuroleptics because fluoxetine may increase the blood levels by inhibition of cytochrome p450 2d6 enzyme (Arango et al., 2000; Jefferson, 1998). As other than two non-responders none of the patient was treatment resistant so higher dose of neuroleptics may cause an improvement in schizophrenic symptoms. Improvement in general symptoms could be explained by reduction in depression and anxiety associated with obsession. Another possible mechanism of improvement in schizophrenic symptoms could be the effect of serotonin on dopaminergic system as there is evidence that serotonin may modulate dopaminergic system physiologically at various levels in brain (Roth & Meltzer,1995). Whatever the mechanism the fluoxetine was effective and well tolerated by the patients.

Both the non-responders were male and treatment resistant patients. One showed response to clozapine and was maintained on clozapine 500 mg while other had history of non-response to clozapine. Their OC symptoms were present prior to the administration of clozapine. The mechanism of non response in one patient could be the antagonistic effects of fluoxetine and clozapine on the serotonin system. It is also possible that they may respond to a different antiobsessional agent as both of them were given fluoxetine as a first antiobsessional agent.

The major limitations of the study were open trial, absence of the comparison group and small sample size. The preliminary findings suggest that fluoxetine was safe and effective in treatment of OC symptoms in schizophrenia. However there is the need of controlled trials on larger sample to confirm the findings of this study.

REFERENCES

Arango,C., Kirkpatrick,B. & Buchanan, W.R. (2000) Fluoxetine as an adjunct to conventional antipsychotic treatment of schizophrenia patients with residual symptoms. Journal of Nervous and Mental Disease, 188, 50-53.

Berman,l., Kalinowski,A., Berman,S.M., Lengua,J. & Green,A.I. (1995) Obsessive and compulsive symptoms in chronic Schizophrenia. Compr Psychiatry, 36, 6-10.

Campbell,M. & Pallij,M. (1985). Measurement of side effects including tardive dyskinesia. Psychopharmacology Bulletin, 21, 4, 1063-1066.

Clomipramine Collaborative Study Group (1991) Clomipramine in the treatment of patients with obsessive compulsive disorder. Archives of the General Psychiatry, 48, 730-738.

Cosoff,S.J. & Hafner,J. (1998) The prevalence of comorbid anxiety in schizophrenia, schizoaffective disorder and bipolar disorder. Australia and New Zealand Journal of Psychiatry, 32, 67-72

Fenton,W.S. & Mcglashan,T.H. (1986) The Prognostic significance of obsessive compulsive symptoms in Schizophrenia. American Journal of Psychiatry, 143, 437-441.

Goff,D.C., Midha,K.K., Sarid Segal,O., Hubbard,J.W. & Amlco,E. (1996) A Placebo controlled trial of fluoxetine added to neuroleptic...
in patient with schizophrenia. *Psychopharmacology* (Berl), 117, 417-423.

Goodman, W.K., Rasmussen, S.A., Price, L.H., Mazure, C., Heninger, G.R. & Charney, D.S. (1989) Yale Brown Obsessive Compulsive Scale: development, use, reliability. Archives of the Gen Psychiatry, 46, 1006-1016.

Jefferson, J.W. (1998) Drug interactions—friends or foe? *Journal of the Clinical Psychiatry*, 59, (Suppl. 4), 37-47.

Kay, S.R., Flezbein, A. & Opier, L.A. (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, 13, 261-267.

Montgomery, S.A., McIntyre, A., Osterheider, M., Sarteschi, P., Zitterl, W., Zohar, J., Birkett, M. & Wood, A.J. (1993) A double blind, placebo controlled study of fluoxetine in patients with OCD. The Lilly European OCD Study Group. *European Neuropsychopharmacology*, 3, 143-152.

National Institute of Mental Health (1985) Clinical Global Impression scale. *Psychopharmacology Bulletin*, 21, 4, 839-843.

Pigott, T.A. (1996) OCD: Where the serotonin selectivity story begins. *Journal of Clinical Psychiatry*, 57, (Suppl 6), 11-20.

Roth, B.L. & Meltzer, H.Y. (1995) The role of serotonin in schizophrenia. In: *Psychopharmacology the Fourth Generation of Progress*, (Eds) Bloom, F.E. & Kupfer, D.J., pp 1215-1227, Raven Press.

Samuel, J., Nesadat, G., Wolyniec, P., Adler, L., Liang, K.Y. & Pulver, A.E. (1993) Obsessive compulsive symptoms in schizophrenia. *Schizophrenia Research*, 9, 139.

Sewell, D.D., Lopez, W.M., Paulsen, J. & Gilbert, P. (1994) Treatment of obsessive-compulsive symptoms in schizophrenia with a neuroleptic selective serotonin reuptake inhibitor combination: Two case reports. *Journal of Nervous and Mental Disease*, 182, 12, 725-727.

Tejera, C.A., Mayerhoff, D.S., Safferman, A.Z., Ramos-Lorenczi, J.R. (1994) Fluoxetine for obsessional symptoms in schizophrenia. *American Journal of Psychiatry*, 15, 1, 149-150.

Tollofson, G.D., Rampey, A.H. & Potvin, J.H. (1994) A multicenter investigation of fixed dose fluoxetine in the treatment of obsessive compulsive disorder. *Archives of the General Psychiatry*, 57, 559-567.