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Fluvoxamine augmentation in risperidone-resistant schizophrenia: An open trial

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We investigated the efficacy and safety of augmenting risperidone with fluvoxamine for the treatment of residual positive and negative symptoms in patients with chronic schizophrenia who had shown an incomplete response to risperidone. A total of 30 patients completed the open trial over a 12-week period during which fluvoxamine was added to risperidone. The result from the positive and negative syndrome scale (PANSS) and Simpson-Angus extrapyramidal effects (S-A) scale were examined at baseline, 1, 2, 4, 8 and 12 weeks of treatment. There were no significant differences in PANSS positive, negative and general psychopathology scores, or in S-A scale scores at any point during the treatment. These results suggest that fluvoxamine appears to be ineffective in augmenting the risperidone treatment response in chronic schizophrenic patients. Further controlled trials will be needed to confirm this observation. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS — SSRI augmentation; risperidone; fluvoxamine; schizophrenia; treatment resistance

INTRODUCTION

Several studies have suggested the beneficial effect of augmenting typical antipsychotics, including haloperidol, with selective serotonin reuptake inhibitors (SSRIs) for treatment of both positive and negative symptoms (Goff *et al.*, 1990; Thakore *et al.*, 1996), or negative symptoms alone (Silver and Nassar, 1992; Silver and Shmugliakov, 1998; Silver *et al.*, 2000; Spina *et al.*, 1994) in chronic schizophrenic patients. Although atypical antipsychotics, including clozapine, risperidone and olanzapine, have been reported to be more effective than typical antipsychotics in reducing these symptoms, pharmacotherapy with these agents is not always successful (Breier *et al.*, 1994; Carman *et al.*, 1995; Tollefson and Sanger, 1997). Treatment of schizophrenic patients who have failed to respond to atypical antipsychotics presents a clinical challenge.

As is the case with typical antipsychotics, some case reports and open-label studies have shown good clinical response when adding an SSRI, such as paroxetine or fluvoxamine, to clozapine-resistant schizophrenic patients (Anghelescu *et al.*, 1998; Silver *et al.*, 1995, 1996).

The exact mechanisms whereby adjunctive SSRIs improve the symptoms of treatment-refractory schizophrenic patients are unknown. In preliminary findings, fenfluramine, a serotonin-releasing agent improved negative symptoms, although this is not a consistent finding (Stahl *et al.*, 1985; Alphs *et al.*, 1989; Marshall *et al.*, 1989). On the other hand, among direct serotonin antagonists both the non-selective agent, cyproheptadine (Silver *et al.*, 1989) and the selective serotonin-2/1C antagonist, ritanserin (Duinkerke *et al.*, 1993) have been associated with therapeutic effects. The findings that agents which have serotonin-agonistic or antagonistic property ameliorate certain symptoms of schizophrenia provide evidence of a dysfunctional serotonergic system in schizophrenia. Therefore, the addition of an SSRI to typical antipsychotics may induce adjustment of serotonergic and dopaminergic balance, resulting in improved response in some treatment-refractory patients. Although clozapine itself has a serotonin-antagonistic property, 'fine tuning' of the serotonin and dopamine balance may also be associated

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with a good clinical effect of adjunctive SSRIs to clozapine.

The effect of an augmentation strategy of typical or atypical antipsychotics with SSRIs is inconsistent. Some double-blind studies, however, have found no clinical advantages of adding SSRIs to typical antipsychotics in patients with chronic schizophrenia and treatment-refractory positive and negative symptoms (Salokangas *et al.*, 1996; Lee *et al.*, 1998). A double-blind, placebo-controlled trial found that adding fluoxetine, an SSRI, to clozapine was ineffective in improving residual positive and negative symptoms in chronic schizophrenia with an incomplete response to clozapine (Buchanan *et al.*, 1996).

To our knowledge, no studies have been performed to examine the clinical effect of adjunctive SSRIs to risperidone when risperidone treatment has failed to induce a sufficient therapeutic response in chronic schizophrenia. Therefore, we conducted an open trial to investigate the efficacy and safety of adjunctive fluvoxamine for risperidone-resistant chronic schizophrenia using the 30-item positive and negative syndrome scale (PANSS) (Kay *et al.*, 1987); positive scale (item P1–P7); negative scale; (item N1–N7); general psychopathology (item G1–G16), and Simpson-Angus extrapyramidal effects (S-A) scale (Simpson and Angus, 1970).

METHOD

The subjects in this study were inpatients at the Yokote-Kosei Psychiatric Hospital. All patients had test procedures fully explained to them and gave written informed consent before participating in the study. They were free to withdraw from the study at any time for any reason. Inclusion criteria were: (1) diagnosis of schizophrenia (DSM-4 criteria) with a history of at least 2 years of illness, (2) history of incomplete response to different typical antipsychotics for at least 12 weeks each, and subsequently risperidone for at least 12 weeks, (3) current state sufficiently severe to require treatment for both positive and negative clinically significant symptoms, despite good compliance with risperidone at adequate doses (2–6 mg/day) before this trial. Because depression or extrapyramidal symptoms cause secondary negative symptoms, we excluded patients who have a score of 2 or more in the depression item (G6) on the PANSS, or a score of 4 or more on the S-A scale. Patients with concurrent alcohol or substance abuse, mood disorder, organic brain disorder, mental retardation or any active major medical problems were also excluded.

The dosage of fluvoxamine was 50 mg/day during the first week and 100 mg/day during the second and subsequent weeks of the 12-week study. All patients were treated with risperidone 2–6 mg/day. Some patients received concurrent medication such as anticholinergics (e.g. biperiden) and/or benzodiazepines (e.g. diazepam, triazolam). Patients continued with their regular medications and the dose was kept constant for at least 4 weeks prior to the study and throughout the study period.

Patients were rated for psychopathology at baseline, 1, 2, 4, 8 and 12 weeks of treatment. Positive and negative syndrome scale (PANSS) and S-A scale were used. These ratings were performed by the psychiatrist (H. Takahashi).

Statistical analysis of these rating scores was made by one-way repeated measures of the analysis of variance (ANOVA).

RESULTS

Thirty-five (12 female, 23 male) patients entered the study, and 30 patients completed the 12-week trial. Three patients dropped out within the first week of the trial: two complained of epigastric discomfort, and one complained of headache and drowsiness. Two patients withdrew, one on day 11 and the other on day 14, because of development of extrapyramidal symptoms. One developed akinesia and rigidity (increased score on S-A scale from 0 to 2), while another developed parkinsonism (increased score on S-A scale from 0 to 3). These two patients who developed extrapyramidal symptoms had been receiving risperidone at a dose of 6 mg/day. The dropouts did not differ from those who completed the study in mean age, risperidone dosage or score on any of the baseline rating scales. Demographic and clinical characteristics of patients who completed the study are presented (Table 1). Compared with the baseline,

Table 1. Demographic and clinical characteristics of patients

Parameter		
	n	
Patients entered	35	
Sex (M/F)	23/12	
Patients evaluated	30	
Patients on anticholinergics	6	
	Mean	SD
Age (years)	46.2	8.6
Duration of illness (years)	13.0	6.2
Duration of current hospitalization (years)	5.3	2.4
Risperidone dose (mg/day)	3.6	1.4

Table 2. Time course of PANSS and S-A scale scores

	PANSS positive	PANSS negative	PANSS general	S-A scale
Baseline	24.6 (4.9)	23.1 (4.1)	38.4 (7.5)	1.0 (1.1)
Week 1	25.0 (4.5)	23.0 (4.2)	38.6 (7.0)	1.1 (1.1)
Week 2	25.1 (4.4)	23.1 (3.7)	39.0 (7.3)	1.1 (0.9)
Week 4	24.6 (4.6)	23.6 (3.5)	39.0 (6.8)	1.2 (0.8)
Week 8	25.1 (4.2)	23.3 (4.2)	38.4 (6.8)	1.0 (0.8)
Week 12	24.6 (3.8)	23.3 (3.7)	38.7 (6.8)	1.1 (0.8)
One-way repeated-measures ANOVA	NS	NS	NS	NS

PANSS, positive and negative syndrome scale; S-A, Simpson-Angus; ANOVA, analysis of variance; NS, not significant.
Data are expressed as mean (SD).

there were no significant differences on any of the measures such as PANSS positive (df 5, F 0.83, $p = 0.53$), negative (df 5, F 1.21, $p = 0.30$), and general psychopathology factors (df 5, F 0.95, $p = 0.45$), and S-A scale (df 5, F 0.93, $p = 0.47$) at any point (Table 2). Subjects who completed the trial reported adverse effects including nausea (three patients), nervousness and sweating (two patients). These side effects were of short duration, well tolerated and self-limiting. No patients showed deterioration of psychotic symptoms (worsening of >20% in PANSS positive factors) during the study.

DISCUSSION

Our findings suggest that adjunctive fluvoxamine to risperidone treatment appeared to be ineffective for reducing positive and negative symptoms in patients who have had an incomplete response to risperidone. This result, however, can only be considered preliminary and will need to be replicated by double-blind, placebo-controlled studies.

The maximum dose of risperidone 6 mg/day in this study seems to be low for gaining the maximum clinical effect from this drug. However, Marder *et al.* suggested in the double-blind study which included 388 schizophrenic patients drawn from 20 sites in the United States that a dose of 6 mg/day of risperidone was as effective as a dose of 16 mg/day in reducing positive and negative symptoms, and that the incidence of extrapyramidal symptoms in patients receiving 6 mg/day was no higher than those receiving placebo (Marder and Meibach, 1994). Therefore, we decided on 6 mg/day of risperidone as the maximum dose in this study, if patients tolerated this dose.

The failure to observe a good clinical response of fluvoxamine augmentation for chronic schizophrenic patients receiving risperidone treatment is inconsistent with previous reports that found adjunct SSRIs effective when added to typical antipsychotics. The selection of the patients may be one explanation for this difference. The patients included in the study were those who had shown an incomplete response not only to typical antipsychotics from some different classes but also to an atypical antipsychotic, risperidone, which has been reported to have a beneficial effect for treatment-refractory schizophrenia (Wirshing *et al.*, 1999). It may be difficult for these severely ill, highly treatment-resistant patients to respond to pharmacological intervention, including augmentation strategy with SSRIs. This observation is consistent with the negative result from the double-blind trial of fluoxetine augmentation for chronic schizophrenic patients who responded incompletely to some typical antipsychotics and subsequently to clozapine (Buchanan *et al.*, 1996).

Another possible explanation is the differing action of fluvoxamine and risperidone on serotonergic symptoms. Fluvoxamine is an SSRI which enhances serotonergic neurotransmission, whereas risperidone has a potent serotonin-antagonistic property. Therefore, the potential benefit from adjunctive fluvoxamine may be cancelled out.

Although the maximum dose of fluvoxamine of 100 mg/day and the 12-week length of the trial were determined according to previous studies suggesting that fluvoxamine augmentation is effective in chronic schizophrenic patients (Silver and Nassar, 1992; Silver and Shmugliakov, 1998; Silver *et al.*, 2000), we can not rule out the possibility that an insufficient dose and/or the short study period would contribute to the lack of beneficial effects of fluvoxamine augmentation to risperidone. An additional replication study that includes a higher dose of fluvoxamine and a longer trial duration will be needed to resolve this important issue.

We observed the emergence of severe extrapyramidal symptom after adding fluvoxamine to risperidone in two patients. This phenomenon may be associated with the pharmacokinetical interaction between fluvoxamine and risperidone. Fluvoxamine is not only a potent inhibitor of CYP1A2 but also a moderate inhibitor of CYP3A and a mild inhibitor of CYP2D6 (Naranjo *et al.*, 1999). Bork *et al.* suggested that drugs which inhibit CYP3A and CYP2D6 might significantly increase the plasma risperidone level (Bork *et al.*, 1999). Unfortunately, plasma concentrations of risperidone were not measured in this study. Therefore, it is difficult to identify the exact mechanisms of this phenomenon.

Risperidone itself is also known to increase serum prolactin levels, inducing some clinical problems associated with hyperprolactinaemia including sexual dysfunction, amenorrhoea and galactorrhoea. Given the fact that the extrapyramidal symptoms developed after adding fluvoxamine to risperidone, there is a possibility that hyperprolactinaemia-associated side effects occurred due to the pharmacokinetical interaction between these drugs. Patients included in this study, however, reported no clinical problems related to hyperprolactinaemia. Plasma levels of prolactin were not measured in this study. Therefore, further studies are needed to confirm whether plasma prolatin levels increase after fluvoxamine addition to risperidone.

Even though it is difficult to draw conclusions from any open study, the addition of fluvoxamine to risperidone does not appear to improve residual positive and negative symptoms in chronic schizophrenic patients who have failed to respond sufficiently to risperidone.

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