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Abstract

To date, fluvoxamine is the only agent that has been demonstrated to be capable of augmenting clozapine efficacy under a well-designed study. Fluvoxamine could also reduce clozapine doses (and thus costs) needed. However, fluvoxamine inhibits clozapine metabolism and increases blood clozapine levels markedly, sometimes leading to hazardous reactions. Therefore, the dosing strategy for clozapine-fluvoxamine cotreatment needs to be determined. Twelve refractory schizophrenia inpatients received 100-mg/day clozapine from week −2 to week 8 and adjunctive 50-mg/day fluvoxamine at weeks 1-4. At weeks 5-8, the patients were randomly assigned into 2 groups: one group received a higher dose (100 mg/day) of fluvoxamine and the other continued the same dose. Plasma levels of clozapine and metabolites, side effects and clinical efficacy were monitored. After 2 weeks of 50-mg/day fluvoxamine coadministration, the mean plasma clozapine concentration rose to approximately 330 ng/mL, but without more changes at week 4. Afterwards, the mean clozapine concentration increased further to around 460 ng/mL in the 6 patients receiving the higher dose (100 mg/day) of fluvoxamine but remained constant in others. Fluctuation of plasma norclozapine levels was similar to (but relatively modest compared with) that of clozapine levels. Plasma levels of clozapine N-oxide remained unchanged throughout. The regimens were generally tolerable and efficacious. These preliminary results suggest that low-dose (100 mg/day) clozapine plus 50-100 mg/day of fluvoxamine could yield therapeutic plasma clozapine levels and favorable clinical outcome in general patients. Further studies with longer-term observation and double-blind designs are warranted.

Key Words**:** *Clozapine; Combined treatment; Dose effect; Drug interaction; Fluvoxamine*

Introduction

Clozapine holds the promise of improving the outcome of refractory schizophrenia patients.[1] Unfortunately, it still fails to bring sufficient therapeutic response in a substantial portion of patients even if a threshold plasma drug concentration (350-420 ng/mL) has been attained.[2-5] To date, poor responders of clozapine have little option in further pharmacotherapy. Remarkably, Silver and Shmugliakov[6] demonstrated that coadministration of fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), could augment clozapine efficacy (especially for negative symptoms of schizophrenia) in a controlled study. In contrast, fluoxetine, another SSRI, is incapable of enhancing clozapine's effectiveness.[7] Besides, addition of agonists or partial agonists of the glycine site at the N-methyl-D-aspartate receptor was also useless or even detrimental for clozapine-resistant patients.[8-10] In another controlled trial, sulpiride, a selective dopamine D_2 blocker, was superior to placebo in augmenting clozapine response; however, the sulpiride group of patients had revealed better clinical conditions at baseline, thus weakening the conclusion.[11] Other studies regarding combined therapy of clozapine and other psychotropic agents did not enroll controlled groups. For instance, 2 small-sized, open-labeled studies of clozapine plus risperidone revealed controversial findings.[12,13]

Adjunctive fluvoxamine has another benefit: it also reduces clozapine doses (and consequently costs) needed in refractory schizophrenia patients.[14,15] However, fluvoxamine inhibits clozapine metabolism both in vitro and in vivo and thus increases blood clozapine concentration significantly[16-22], sometimes leading to severe side effects.[23,24] Therefore, the dosing strategy for clozapine-fluvoxamine cotreatment needs to be established.

Methods

This prospective, open-labeled study was conducted in a research ward of the institute. The protocol was approved by the facility's institutional review board.

Subjects

The facility's Institutional Review Board approved the project. Chinese inpatients in Taiwan entered into this study if they (1) were physically healthy and had all laboratory parameters within normal limits, (2) aged 18-60 years, (3) satisfied DSM-IV criteria for schizophrenia, (4) were "treatment-resistant"[1] to classical antipsychotics, (5) had not received depot antipsychotics for the preceding 6 months, and (6) gave written informed consent and were competent to do so. Twelve Chinese male inpatients (mean ± SD age = 31.6 ± 8.5 years, mean ± SD body weight = 68.5 ± 18.4 kg) entered and completed this study. They were all smokers and consumed more than ten cigarettes per day.

Study design

The clozapine dose was gradually titrated to 100 mg/day at bedtime. This low dose was then maintained for 10 weeks (week −2 to week 8). Patients also received adjunctive 50-mg/day fluvoxamine at weeks 1-4. At weeks 5-8, they were randomly and equally assigned into 2 groups: one group received a higher dose (50 mg b.i.d.) of fluvoxamine and the other continued the same dose. On day −7 and day 0 (before fluvoxamine addition) as well as days 14, 28, 42, and 56, blood samples for plasma levels of clozapine and metabolites were obtained in the morning, 12 hours after the evening drug administration.

Clinical assessments

Drug safety was rigorously monitored. Daily vital signs were measured. Hematology, physical and neurological examinations were repeated weekly. The Extrapyramidal Symptom Rating Scale (ESRS)[25] and the UKU Side Effect Rating Scale[26] were used biweekly for evaluating exprapyramidal symptoms and other side-effect profiles. Electrocardiogram (ECG),

urinalysis, and biochemistry were rechecked at the study's endpoint.

General psychopathology and functioning were also biweekly assessed with Clinical Global Impression Scale (CGI)[27] and Global Assessment of Functioning Scale (GAF) (DSM-IV axis V). These 2 efficacy scales, the ESRS, and the UKU Side Effect Rating Scale were performed by an experienced research psychiatrist throughout.

Laboratory assessments

The venous blood was collected into an EDTA tube and centrifuged at 3000 rpm for 15 minutes. The plasma samples were stored at −60°C until assayed. Plasma levels of clozapine, norclozapine, and clozapine N-oxide were then determined by high performance liquid chromatography with ultraviolet detection.[28,29] The intraassay and interassay coefficients of variation were <10% for clozapine and its metabolites. The lower limit of detection for clozapine was 1 ng/mL, and for the metabolites was 2 ng/mL.

Statistical analyses

Differences in plasma clozapine, norclozapine, and clozapine N-oxide concentrations and norclozapine/clozapine ratios at specific time points within and between groups were assessed using analysis of variance (ANOVA) for repeated measures. The clinical manifestations were compared before and after the comedication by repeated-measures ANOVA. When ANOVA results showed significant differences, post hoc multiple comparisons were performed using the least-significant-difference test. An α level of 0.05 for type I errors was employed, and two-sided statistical tests were performed.

Results

The plasma concentrations of clozapine and its 2 metabolites at baseline (day 0) were similar to those on day −7 (data not shown), indicating that a steady state had been attained

prior to fluvoxamine initiation.

Low-dose fluvoxamine interaction with low-dose clozapine

After the first 2 weeks of 50-mg/day fluvoxamine coadministration in the 12 patients, the mean ± SD plasma clozapine concentration increased 2.39-fold from 137.1 ± 69.9 ng/mL to 327.3 ± 140.6 ng/mL ($p < 0.001$). Mean plasma norclozapine concentrations also increased from 65.5 ± 40.1 ng/mL to 116.3 ± 42.2 ng/mL ($p < 0.01$). Further increases in plasma clozapine and norclozapine concentrations were not observed on day 28. From day 0 to day 28, mean plasma clozapine N-oxide concentrations remained unchanged. Although both plasma clozapine and norclozapine levels were elevated with fluvoxamine, the increase in the metabolite concentration was relatively modest. Consequently, both plasma norclozapine/clozapine ratios and clozapine N-oxide/clozapine ratios declined significantly after fluvoxamine comedication (Table 1). These ratios remained stable from day 14 to day 28.

Dose effects of fluvoxamine

In the 6 patients receiving the higher dose (100 mg/day) of fluvoxamine at weeks 5-8, plasma levels of clozapine and norclozapine, but not clozapine N-oxide, increased further and reached a new plateau on day 42 (14 days after fluvoxamine dose increments) (Table 1). The average plasma clozapine levels were approximately 480 ng/mL on day 42 and 440 ng/mL on day 56. Although both plasma clozapine and norclozapine levels were further elevated after fluvoxamine dosage titration, the increment in the metabolite concentration was smaller compared to the parent compound (Table 1).

In contrast, in the group continuing 50-mg/day fluvoxamine (N = 6), plasma levels of clozapine and metabolites remained rather constant from day 28 to day 42 (Table 1). On both

day 42 and day 56, plasma clozapine concentrations differed significantly between the 2 groups of patients (both p values < 0.05), and so did plasma norclozapine (both $p < 0.05$).

Safety and efficacy

This novel cotreatment regimen was well tolerated in all patients. No patients withdrew from the trial due to side effects. During weeks 1-4 of 50-mg/day fluvoxamine cotreatment, adverse events included sedation (N = 3), weight gain (N = 3), hypersalivation (N = 2), constipation (N = 2), and postural hypotension (N = 2) among all 12 patients. During weeks 5-8, the adverse events in the low-dose fluvoxamine group (N = 6) included weight gain (N = 2), hypersalivation (N = 1), polyuria (N = 1), and constipation (N = 1). The events in the high-dose fluvoxamine group (N = 6) were sedation (N = 3), tachycardia (N = 1), hypersalivation (N = 1), weight gain (N = 1), and constipation (N = 1). These adverse reactions were mostly mild and usually disappeared spontaneously. Seizures, motor symptoms, or agranulocytosis did not occur in our patients. No clinically relevant abnormal laboratory or ECG results were found.

After fluvoxamine comedication, the mean ± SD CGI in the patients showed a significant improvement (4.64 ± 0.52 on day 0 vs. 3.92 ± 0.29 on day 28, $p < 0.01$), and so did the GAF (46.7 ± 8.9 on day 0 vs. 60.8 ± 4.4 on day 28, $p < 0.01$). The CGI and the GAF also tended to improve from day 28 to day 56, but without achieving statistical significance in either group of patients.

Discussion

Researchers have reported relationships between clozapine levels and treatment responses. If most of the dose is given in the evening, a threshold level of 350-420 ng/mL should be attained in any patient who is not showing a good response.[2-5] In the current study, combined

treatment of 50-mg/day fluvoxamine and 100-mg/day clozapine yielded a mean plasma clozapine level of around 330 ng/mL and a favorable clinical response. When the fluvoxamine dose was increased to 100 mg/day, the mean clozapine level rose further to around 440-480 ng/mL, tending to generate better response. These findings could be applied in the dosing strategy for fluvoxamine-clozapine cotherapy. Clinicians could start the treatment with 50-mg/day fluvoxamine plus 100-mg/day clozapine. If the patients tolerate the doses but show unsatisfactory response, the SSRI dose could be raised to 100 mg/day under careful clinical observation. Certainly, monitoring of blood clozapine concentrations are strongly recommended.

Another new finding is that, in our patients receiving 8-week, 50-mg/day fluvoxamine, plasma levels of clozapine and metabolites remained rather constant throughout, implying that the inhibitory effects of fluvoxamine may persist up to 8 weeks. Longer-term fluvoxamine effect on clozapine disposition remains to be ascertained. Of note, this study focused on male, smoker, and Chinese patients; all 3 variables may predict lower blood levels of clozapine.[3,14,30,31] Further studies are warranted for other populations.

Although our patients showed clinical improvement with the combined treatment, this finding is limited by the small sample size, lack of control groups, and a short study period (8 weeks). Previous studies recommended that the optimal period for a trial of clozapine is around 12-24 weeks or even longer.[1,5] Therefore, longitudinal effectiveness of fluvoxamine-clozapine cotreatment requires characterization too.

Consistent with earlier findings[17,21], plasma norclozapine to clozapine ratios declined under fluvoxamine cotreatment. Norclozapine has been suggested to be more toxic than the parent compound and may be related with agranulocytosis or granulocytopenia.[23,32] No hematological side effects were found in our patients; nonetheless, larger sized studies are needed to testify this potential benefit of this novel strategy. Regarding other side-effect profiles, not only pharmacokinetic but also pharmacodynamic interactions should be considered. For instance, certain patients may experience motor symptoms upon fluvoxamine addition to clozapine therapy, even without significant alteration in blood

clozapine/metabolites levels.[24] SSRIs can enhance the inhibition of the dopaminergic system and lead to extrapyramidal side effects in some patients.[33] When the SSRI is added to clozapine, the increased serotonin might intensify the modest dopamine inhibition by clozapine, increasing the risk of the motor symptoms.[24] In the present study, however, no extrapyramidal side effects were evident before or under the add-on SSRI. Other adverse reactions that occurred during the cotreatment period of this study were mild, tolerable, and short-lived.

This preliminary study suggests that fluvoxamine's inhibition for low-dose clozapine metabolism exhibits dose effects in refractory schizophrenia patients. Addition of 50 mg/day and then 100 mg/day of fluvoxamine to 100-mg/day clozapine could raise the average plasma clozapine level to 330 ng/mL and then around 460 ng/mL. Further studies with larger samples and controlled groups, various fluvoxamine and clozapine doses, and longer treatment duration are necessary. The results could be applied in refining dosing strategies for fluvoxamine-clozapine cotherapy in clinical practice.

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TABLE 1. Clozapine plasma metabolic profiles (mean ± SD) before and during comedications with different fluvoxamine doses.

	Clozapine (ng/mL)	Norclozapine (ng/mL)	Clozapine N-Oxide (ng/mL)	Norclozapine /Clozapine Ratios	Clozapine N-Oxide/Clozapine Ratios
Day 0					
Group 1[a]	130.4 ± 75.8	63.3 ± 42.1	23.2 ± 14.3	0.54 ± 0.23	0.20 ± 0.10
Group 2[b]	143.8 ± 70.1	67.7 ± 41.8	23.0 ± 10.9	0.45 ± 0.12	0.17 ± 0.09
Day 14					
Group 1	298.5 ± 138.6[c]	108.5 ± 40.3[c]	24.0 ± 9.8	0.39 ± 0.11[d]	0.09 ± 0.03[c]
Group 2	356.0 ± 149.3[c]	124.2 ± 46.4[c]	24.8 ± 9.6	0.37 ± 0.11[d]	0.09 ± 0.05[c]
Day 28					
Group 1	282.1 ± 132.8[c]	106.8 ± 47.0[c]	24.7 ± 13.2	0.39 ± 0.09[d]	0.09 ± 0.04[c]
Group 2	331.0 ± 109.3[c]	103.1 ± 41.3[c]	23.2 ± 10.5	0.33 ± 0.09[d]	0.10 ± 0.06[c]
Day 42					
Group 1	478.7 ± 150.3[c, e]	151.2 ± 50.1[c, f]	29.3 ± 11.5	0.32 ± 0.05[d]	0.06 ± 0.02[c]
Group 2	306.7 ± 98.2[c]	94.5 ± 38.6[c]	25.1 ± 10.7	0.34 ± 0.10[d]	0.10 ± 0.07[c]
Day 56					
Group 1	438.5 ± 123.5[c, e]	152.4 ± 55.0[c, f]	27.9 ± 9.4	0.35 ± 0.09[d]	0.06 ± 0.02[c]
Group 2	298.3 ± 96.3[c]	93.4 ± 37.8[c]	28.7 ± 9.6	0.33 ± 0.09[d]	0.10 ± 0.07[c]

[a]Group 1: clozapine 100-mg/day coadministered with fluvoxamine 50-mg/day from day 1 to day 28,

then fluvoxamine 100-mg/day from day 29 to day 56.

[b]Group 2: clozapine 100-mg/day coadministered with fluvoxamine 50-mg/day from day 1 to day 56.

[c]$p < 0.001$; [d]$p < 0.05$ for within-group comparisons versus day 0.

[e]$p < 0.01$; [f]$p < 0.05$ for within-group comparisons versus day 28.

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