Fluvoxamine Reduces the Clozapine Dosage Needed in Refractory Schizophrenic Patients

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Background: Concomitant fluvoxamine use can potentially reduce the dosage of clozapine needed in treatment-refractory patients with schizophrenia. Previous reports have shown that fluvoxamine can increase plasma clozapine concentrations by inhibition of cytochrome P450 (CYP) 1A2. We evaluated the safety and efficacy of fluvoxamine, 50 mg/day, coadministration with clozapine, 100 mg/day, in refractory schizophrenic patients.

Method: In this prospective study, 18 treatment-refractory patients with DSM-IV schizophrenia (10 nonsmokers and 8 smokers) were treated with clozapine at a target dose of 100 mg h.s. After steady-state conditions of clozapine had been reached, 50 mg/day of fluvoxamine was then added. Plasma levels of clozapine, norclozapine, and clozapine *N*-oxide were measured prior to fluvoxamine addition and on days 14 and 28 during combined treatment. Side effects and efficacy were monitored with standardized rating instruments.

Results: After 14 days of combined treatment, the mean ± SD plasma clozapine level increased 2.3-fold to 432.4 ± 190.9 ng/mL without further elevation on day 28. All patients completed the study without significant adverse side effects. Twelve of the 18 patients achieved plasma clozapine concentrations of at least 350 ng/mL. While plasma norclozapine levels also rose (but to a smaller extent), plasma clozapine *N*-oxide levels remained unchanged after the add-on therapy. Patients who smoked had 34% lower plasma clozapine concentrations than nonsmokers (NS). Three of the 4 patients who did not reach clozapine plasma levels of at least 300 ng/mL were smokers. Plasma norclozapine/clozapine ratios, especially in smokers, declined significantly with fluvoxamine addition.

Conclusion: The addition of fluvoxamine, 50 mg/day, to low-dose clozapine, 100 mg/day, can raise plasma clozapine levels to at least 300 ng/mL in most patients. Only slight dosage adjustments with clozapine may be needed after fluvoxamine coadministration in some patients who smoke. Plasma clozapine levels remained stable after 14 days of fluvoxamine addition. The combined treatment was well tolerated, and clinical improvement was observed in our patients. Further long-term studies with this drug combination are needed to determine its economic impact.

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Schizophrenia, especially treatment-resistant schizophrenia, is extremely expensive in direct and indirect costs.[1,2] Clozapine, an atypical antipsychotic agent, holds the promise of improving the outcome for refractory schizophrenic patients[3,4] and thus decreasing the economic burden on society.[2,4] Clozapine remains an expensive therapeutic intervention with direct costs that include medication and laboratory expenses. Clozapine also carries risks of dose-related and non–dose-related adverse reactions.[5,6] Strategies to reduce its expense and, if possible, its side effects can improve clozapine utilization in this difficult population.

Addition of selective serotonin reuptake inhibitors (SSRIs) may be tried when clozapine monotherapy fails to bring sufficient therapeutic response,[7,8] especially with respect to depressive or negative symptomatology. However, SSRIs, with the exception of citalopram, were reported to increase plasma clozapine concentrations.[9,10] Numerous cases of fluvoxamine interacting with clozapine have been reported.[11] Recently, the interaction between fluvoxamine and clozapine was carefully evaluated in a single-dose pharmacokinetic clozapine study[12] in schizophrenics in which the mean area under the plasma concentration time curve (AUC) increased by a factor of 2.58. When fluvoxamine, 50 mg/day, was added to clozapine-treated patients, mean plasma clozapine concentrations increased 2.87-fold after steady-state conditions during coadministration.

Most clinicians and investigators have reported that the minimal threshold for therapeutic benefit in plasma cloza-

pine concentrations is 350 to 420 ng/mL.[5] We hypothesized that fluvoxamine addition to clozapine at about one third of recommended doses could yield therapeutic plasma clozapine levels. This strategy could result in lower medication costs of clozapine. Clozapine is mainly metabolized by cytochrome P450 (CYP) isozymes 3A4 and 1A2 to 2 principle metabolites: norclozapine and clozapine *N*-oxide.[13–15] The interaction between clozapine and fluvoxamine occurs via inhibition of CYP1A2.[11] The impact of fluvoxamine on plasma levels of clozapine and its metabolites during low-dose clozapine therapy remains to be ascertained. This prospective study aimed to investigate the effect of 50 mg/day of fluvoxamine on steady-state plasma clozapine concentrations in treatment-refractory schizophrenic patients taking low-dose (100 mg/day) clozapine.

METHOD

This prospective, open-label study was conducted in a research ward at Taipei City Psychiatric Center, Taipei, Taiwan. The facility's institutional review board approved the project.

Subjects

All subjects gave informed consent to participate in this study. They met DSM-IV diagnostic criteria for schizophrenia and were treatment resistant according to the guidelines proposed by Kane et al.[3] The participants were physically healthy, and all their laboratory test results were within normal limits. None of the patients had been treated with depot antipsychotics during at least 6 months before study entry. Eighteen Chinese inpatients (2 women, 16 men; mean ± SD age = 30.1 ± 7.1 years, mean ± SD body weight = 70.5 ± 15.4 kg) entered and completed this study. Among them, 10 did not smoke, but the other 8 consumed more than 10 cigarettes per day.

Study Design

Clozapine dose was gradually titrated in each patient, starting at 25 mg/day to 100 mg/day at bedtime. This clozapine dosage was maintained for 14 days before fluvoxamine was started. Fluvoxamine, 50 mg h.s., was coadministered for 28 days. Other medications were not allowed during the study period. On days –7 and 0 (before fluvoxamine addition) as well as days 14 and 28 of the coadministration, blood samples were obtained to measure plasma clozapine, norclozapine, and clozapine *N*-oxide levels. Samples were obtained in the morning 12 hours after the bedtime drug administration.

Clinical Assessment

Drug safety was rigorously evaluated by the investigators at baseline (day 0) and under fluvoxamine-clozapine coadministration. Daily vital signs were measured. Hematologic, physical, and neurologic examinations were repeated weekly. The UKU Side Effect Rating Scale[16] was used every 2 weeks for monitoring both extrapyramidal symptoms and other side effect profiles. Electrocardiogram (ECG), urinalysis, and biochemistry were rechecked at the study's endpoint.

General psychopathology and functioning were assessed every 2 weeks with the Clinical Global Impressions scale (CGI)[17] and the Global Assessment of Functioning scale (GAF; DSM-IV Axis V).[18] The clinical assessment involving these 2 efficacy scales and the UKU Side Effect Rating Scale was performed by a research psychiatrist throughout.

Laboratory Assessment

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 determined by high performance liquid chromatography with ultraviolet detection.[19,20] The intra-assay and inter-assay coefficients of variation were < 10% for clozapine and its metabolites. The lower limit of detection for clozapine was 1 ng/mL and for its metabolites, 2 ng/mL.

Statistical Methods

Plasma clozapine, norclozapine, and clozapine *N*-oxide concentrations and norclozapine/clozapine ratios were compared within and between groups by t tests (paired and unpaired). The clinical manifestations were also compared before and after the comedication by a paired t test. An α level of 0.05 for type I errors was employed, and 2-sided statistical tests were performed.

RESULTS

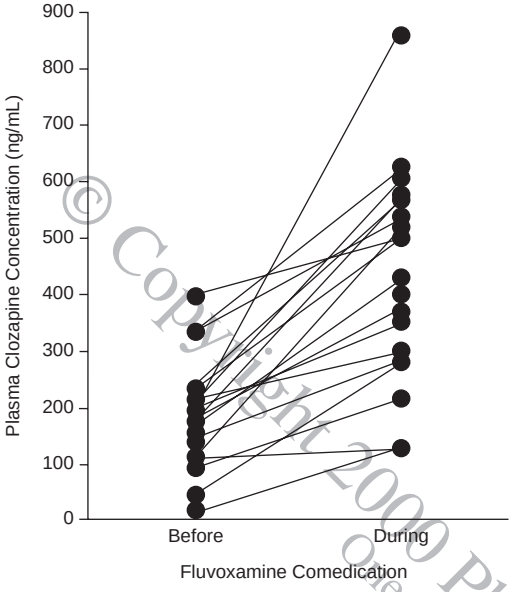
The plasma concentrations of clozapine and its 2 metabolites determined at baseline (day 0) were similar with those on day –7 (data not shown), indicating that a steady state had been attained before the comedication started. On day 0, the plasma clozapine levels displayed large interindividual variation (Figure 1).

Fluvoxamine Effects on Plasma Clozapine and Metabolites

The addition of 50 mg/day of fluvoxamine to 100 mg/day of clozapine treatment led to substantial increments in the plasma levels of clozapine and norclozapine, but not clozapine *N*-oxide (Table 1 and Figure 1). The increase in plasma levels was highly variable. It ranged from 1.3- to 6.4-fold for clozapine and 1.1- to 5.1-fold for norclozapine after 28-day cotreatment (data not shown).

The inhibitory effect of fluvoxamine on clozapine metabolism reached a plateau by day 14 of the comedication (see Table 1). Mean plasma clozapine concentration mark-

Figure 1. Plasma Levels of Clozapine Before (Baseline) and 14 Days After Start of Fluvoxamine Comedication in 18 Schizophrenic Patients



edly increased 2.32-fold from 185.8 ± 98.9 ng/mL to 432.4 ± 190.9 ng/mL ($p < .001$). Only 6 patients shown in Figure 1 had plasma clozapine concentrations less than 350 ng/mL despite fluvoxamine coadministration. Mean plasma norclozapine concentrations also increased from 73.4 ± 37.2 ng/mL to 134.5 ± 43.8 ng/mL ($p < .001$). Further increases in plasma clozapine and norclozapine concentrations were not observed on day 28 (see Table 1). During the study, mean plasma clozapine *N*-oxide concentrations remained unchanged during fluvoxamine coadministration.

Although both plasma clozapine and norclozapine levels were elevated with fluvoxamine, the increase in the metabolite concentration was relatively modest compared with that of the parent compound, as shown in Table 1. Consequently, the plasma norclozapine/clozapine ratios, an indicator of *N*-demethylation, declined slightly but statistically significantly after fluvoxamine coadministration ($p < .05$). These ratios remained stable from day 14 to day 28.

Effects of Smoking

Plasma clozapine levels at baseline were 34% lower in smokers than in nonsmokers; however, the difference did not reach statistical significance (Table 2). Four of 6 patients who had plasma clozapine concentrations below 350 ng/mL (see Figure 1) were smokers. Plasma clozapine concentrations in 3 of those patients after fluvoxamine addition were 283 ng/mL, 128.4 ng/mL, and 128 ng/mL, respectively. In contrast, the plasma norclozapine and clozapine *N*-oxide levels were very similar between smokers and nonsmokers. Accordingly, smokers had significantly higher norclozapine/clozapine ratios at baseline.

After fluvoxamine coadministration, plasma clozapine and norclozapine (but not clozapine *N*-oxide) levels increased remarkably in both smokers and nonsmokers (see Table 2). However, the *N*-demethylation ratio diminished significantly only in smokers but not in nonsmokers. That is, the baseline (day 0) *N*-demethylation difference between smokers and nonsmokers was largely curtailed with the combined therapy (see Table 2).

Table 1. Plasma Clozapine, Norclozapine, and Clozapine *N*-Oxide Concentrations and Norclozapine-to-Clozapine Ratios Before and During Fluvoxamine Comedication in 18 Schizophrenic Patients

	Baseline		Day 14		Day 28	
Measurement	Mean	SD	Mean	SD	Mean	SD
Plasma concentrations (ng/mL)						
Clozapine	185.8	98.9	432.4	190.9[a]	408.0	207.8[a]
Norclozapine	73.4	37.2	134.5	43.8[a]	128.6	50.5[a]
Clozapine *N*-oxide	26.2	11.7	25.8	9.9	25.2	9.3
Norclozapine/clozapine ratio	0.42	0.15	0.34	0.11[b]	0.35	0.14[b]

[a] $p < .001$ for within-group comparisons versus baseline.
[b] $p < .05$.

Table 2. Metabolic Profiles of Clozapine Before and During Fluvoxamine Comedication in 18 Schizophrenic Patients Stratified by Smoking Status

	Smokers (N = 8)		Nonsmokers (N = 10)	
Measurement	Mean	SD	Mean	SD
Plasma concentrations (ng/mL)				
Clozapine				
Baseline	153.5	99.4	211.6	95.5
Day 28	371.0	229.4[a]	437.7	196.1[a]
Norclozapine				
Baseline	69.6	45.2	76.5	31.8
Day 28	123.2	58.4[a]	132.9	46.1[a]
Clozapine *N*-oxide				
Baseline	26.1	12.9	26.3	11.5
Day 28	24.2	7.4	26.0	10.9
Norclozapine/clozapine ratios				
Baseline	0.50	0.20[b]	0.37	0.07
Day 28	0.39	0.17[c]	0.33	0.10

[a] $p < .001$ for within-group comparisons versus baseline.
[b] $p < .01$ for between-group comparisons at the same point of time.
[c] $p < .01$.

Safety and Efficacy

This novel regimen was well tolerated in all patients. From baseline to day 14 of fluvoxamine supplementation, the following adverse events were reported: sedation (N = 6), hypersalivation (N = 4), constipation (N = 4), weight gain (N = 2), and postural hypotension (N = 2). From day 14 to day 28, the incidence of sedation (N = 2) and hypersalivation (N = 2) decreased, while postural

hypotension ceased. The prevalence of weight gain and constipation remained unchanged. Significant differences in adverse side effect frequency between smokers and nonsmokers were not found.

These events were all mild, and many of them disappeared spontaneously. Extrapyramidal symptoms, seizures, and agranulocytosis did not occur in our patients. Blood chemistry and ECG findings after 4 weeks of the cotreatment remained unchanged and were all within the normal ranges.

One nonsmoking patient (shown in Figure 1) had plasma clozapine concentrations increase 4.53-fold from 189.3 ng/mL to 857.7 ng/mL (day 14) and 815.3 ng/mL (day 28). During this time period, this patient experienced only mild sedation and hypersalivation and completed the study without further problems. Plasma norclozapine concentrations increased from baseline levels of 71.6 ng/mL to 170.2 ng/mL and 158.6 ng/mL for days 14 and 28, respectively, for this patient, and *N*-oxide plasma clozapine concentrations remained unchanged from baseline (23.4 ng/mL) to day 28 (21.9 ng/mL).

After the fluvoxamine comedication, the CGI score showed a significant improvement (baseline mean ± SD score = 4.44 ± 0.51, endpoint score = 3.94 ± 0.24; $p < .01$), as did the GAF (baseline score = 47.5 ± 9.4, endpoint score = 60.0 ± 3.4; $p < .001$).

DISCUSSION

Recently, it has been proposed that concomitant fluvoxamine treatment could reduce clozapine doses (and costs) needed to generate therapeutic blood concentrations.[14] This prospective study supports those previous findings using low-dose clozapine, 100 mg/day, in refractory schizophrenic patients. Addition of fluvoxamine, 50 mg/day, elevated mean plasma clozapine levels by at least 2-fold to over 400 ng/mL. Only 4 patients did not reach the threshold range of 350 to 420 ng/mL recommended for clinical response.[21–23] Three of these patients were smokers.

These preliminary results support a potentially cost-sparing strategy.[24] The cost of 100-mg tablets of clozapine is $352/100 (U.S., average wholesale price). In our previous study,[25] most Taiwanese and Chinese patients (139/162, 85.8%) were treated with clozapine doses of greater than 300 mg, and only 7 patients (4.3%) used 100 mg/day. Fluvoxamine 50-mg tablets costs $252/100 (U.S., average wholesale price). The additional use of fluvoxamine more than offsets the costs of clozapine, and lower clozapine doses can be employed in this treatment strategy. To calculate the cost saved by the combined treatment, we found that the mean plasma clozapine concentration (432.4 ng/mL) obtained by this cotreatment strategy is very close to that (404 ng/mL) produced by 300-mg/day clozapine monotherapy in one of our previous studies.[25] Therefore, this cotreatment strategy could reduce direct treatment cost by about 40%. It would be interesting to examine whether we would get further savings by using lower doses of clozapine and higher doses of fluvoxamine. Further studies are warranted. Similar cost-saving tactics have been applied in cardiac transplant patients who are treated with cyclosporine, an expensive immunosuppressive agent, which is metabolized by CYP3A3/4.[26] Ketoconazole, a potent inhibitor of CYP3A3/4, greatly decreased the doses of cyclosporine required for achieving the therapeutic range after being added to cyclosporine.[26,27]

Plasma concentrations of clozapine, norclozapine, and clozapine *N*-oxide remained constant from day 14 to day 28 of fluvoxamine supplementation (see Table 1). Our findings are similar to those of Wetzel et al.[28] Their results indicate that steady-state conditions with clozapine can be reached within 2 weeks after the addition of 50 mg/day of fluvoxamine.[28] Further studies are warranted to clarify long-term safety and efficacy of fluvoxamine and clozapine use in schizophrenic patients.

Previous studies reported that adjunctive fluvoxamine treatment could reduce adverse effects of ordinary-dose clozapine and improve efficacy,[7,29] whereas others revealed contradictory results.[30,31] Our regimen of fluvoxamine plus low-dose (100 mg/day) clozapine produced increased plasma clozapine concentrations, but a wide interpatient variation was found (shown in Figure 1). Clinicians must be cautious and patients be carefully monitored when this drug combination is employed since some case reports showed that plasma clozapine levels may be elevated more than 2- to 3-fold.[32,33] Several reasons could explain this occurrence since clozapine disposition displays a large interpatient variability due to the CYP isozymes. Clozapine is converted to norclozapine by CYP3A4 and 1A2 and to clozapine *N*-oxide by CYP3A4. However, in vitro models also showed that clozapine is metabolized by CYP2D6, 2C9, and 2C19 isozymes and the flavin monooxygenase system.[13–15,34] The contributions of these other isozymes can vary between individuals in clozapine disposition. Finally, when clozapine is metabolized to clozapine *N*-oxide, a portion of the *N*-oxide metabolite is converted back to clozapine, indicating a reversible metabolic process.[35] All these metabolic factors can contribute toward the wide interpatient variability found in plasma clozapine concentrations of schizophrenic patients.

Cigarette smoking can induce CYP1A2 activities and increase the clearance of the CYP1A2-metabolized drug.[36] Patients in our study who smoked had lower plasma concentrations of clozapine than nonsmokers, a result that has been found by others.[5,37] As previously mentioned, 4 of 6 patients who had plasma clozapine levels below 350 ng/mL were smokers. These 4 patients represented 50% of the total smokers in this study. Therefore, clozapine dos-

ages may need to be adjusted in some smokers after fluvoxamine coadministration. With clozapine monotherapy, plasma norclozapine/clozapine ratios were found to be higher in smokers than in nonsmokers.[28] Fluvoxamine is a potent CYP1A2 inhibitor, which can produce a greater decrease in the norclozapine/clozapine ratios in smokers than in nonsmokers.[28] Our study showed similar findings for norclozapine/clozapine ratios, indicating CYP1A2 in the *N*-demethylation pathway of clozapine. Although our study had only 2 female participants, previous studies have reported that gender is a significant factor on plasma clozapine concentrations.[38,39]

In addition to the pharmacokinetic interaction between these 2 agents, the possibility of pharmacodynamic interactions must be considered.[31] We recently described 2 schizophrenic patients who experienced extrapyramidal symptoms upon fluvoxamine addition to clozapine therapy.[37] Their plasma clozapine concentrations were only moderately elevated; therefore, a possible pharmacodynamic interaction might have contributed to the increased motor side effects.[38] SSRIs can enhance the inhibition of the dopaminergic system and lead to extrapyramidal side effects in some patients.[40,41] However, for the majority of patients, the extent of dopamine inhibition induced by the SSRIs does not cross the extrapyramidal symptom threshold.[31,40] When an SSRI was added to clozapine, the increased serotonin might have intensified the modest dopamine inhibition by clozapine, increasing the risk of the motor symptoms.[31] In the present study, no extrapyramidal side effects were evident before or during treatment with the add-on SSRI. Other adverse side effects that occurred during the cotreatment period in this study were mild, tolerable, and short-lived and lessened over time.

With this combined treatment regimen, our patients showed improvement in overall functioning in terms of 2 global rating scales, CGI and GAF. The application of these preliminary findings to the schizophrenic population is limited by our small sample size and the lack of control groups. Moreover, SSRIs can enhance the inhibition of the dopaminergic system and may affect the therapeutic efficacy of clozapine. Further studies are needed to clarify the effects of fluvoxamine on the therapeutic efficacy of clozapine.

In summary, the addition of fluvoxamine, 50 mg/day, to clozapine, 100 mg/day, can increase plasma clozapine levels to the minimum therapeutic threshold in most patients. If clinicians decided to utilize this drug combination, plasma clozapine concentrations should be obtained prior to and after 14 days of treatment. Additional plasma concentrations may be indicated when clozapine dosages are adjusted. Plasma drug samples can be obtained simultaneously with the hematologic tests. Careful patient monitoring and selection is important. Patients must be compliant with medications and have proper family and social services support. Further studies are warranted to testify to the effect of fluvoxamine on metabolism of low-dose clozapine and to substantiate the safety and efficacy of this potential cost-reducing regimen in various populations.

Drug names: citalopram (Celexa), clozapine (Clozaril and others), cyclosporine (Sandimmune and others), fluvoxamine (Luvox), ketoconazole (Nizoral and others).

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