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Clozapine 併用 fluvoxamine 對於難治型精神分裂症患者之療效研究

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計畫主持人：盧孟良
共同主持人：郭豐榮

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Background: Adjunctive fluvoxamine inhibits clozapine metabolism, reduces the clozapine dose needed for schizophrenia treatment, and decreases plasma norclozapine (a toxic metabolite of clozapine) to clozapine ratios. This study aimed to testify fluvoxamine effects on clozapine-related weight gain, hyperglycemia, and lipid abnormalities and to evaluate the influences of plasma clozapine and norclozapine levels on body weight and metabolism changes.

Method: Sixty-eight treatment-resistant schizophrenia inpatients were randomly assigned into two treatments for 12 weeks. The monotherapy group (N = 34) received clozapine alone (≤ 600 mg/day). The coadministration group (N = 34) received fluvoxamine (50 mg/day) plus low-doe clozapine (≤ 250 mg/day).

Results: The two groups were similar in demographic data, baseline body weight and BMI, baseline serum glucose, triglycerides and cholesterol, and steady-state plasma clozapine concentration. The monotherapy patients (but not the coadministration patients) had significantly higher body weight, BMI, serum glucose and triglycerides after treatment than at baseline. At week 12, the monotherapy patients also had significantly higher glucose, triglycerides, and norclozapine (and numerically higher cholesterol) levels than the cotreatment patients. The changes in weight and serum levels of sugar and triglycerides were significantly correlated to the plasma norclozapine concentration, but not to plasma clozapine.

Conclusion: These results suggest that fluvoxamine cotreatment can attenuate weight gain and metabolic disturbances in clozapine-treated patients. Plasma levels of norclozapine, but not clozapine, are associated with the increases in weight and serum levels of sugar and triglycerides.

Key words: Clozapine, Fluvoxamine, Metabolic Disturbance, Weight Gain.

INTRODUCTION

Clozapine, an atypical antipsychotic drug, can improve the outcome of refractory schizophrenic patients[1,2] and decrease the economic burden on society.[3] However, it still fails to bring sufficient therapeutic response in a substantial portion of patients even if a threshold plasma drug concentration (350-420 mg/dL) has been attained.[4,5] Moreover, its usage has been limited because of side-effect profiles including hypotension, seizure, sedation, and hematological abnormalities.[6-8] Recently, clozapine induced weight gain,[9] serum triglycerides elevation,[10] hyperglycemia,[11,12] and new onset of Type II diabetes mellitus[13,14] have become the focus of attention.

Weight gain has been a documented side effect of antipsychotic drug use for over 40 years.[15,16] The consequences of excessive weight gain associated with antipsychotic drugs include poor compliance or even discontinuation of therapy by the patients.[17] Poor adherence almost always leads to relapse and a worsened long-term outcome. Since obesity is a common comorbid condition with schizophrenia,[18] schizophrenic patients are inherently at increased risk of developing obesity-related conditions such as cardiovascular disease and type II diabetes.[19] Fontaine et al.[20] found that 492 suicide deaths per 100,000 schizophrenic patients would be prevented over 10 years with the use of clozapine compared to 416 additional deaths due to antipsychotic induced weight gain. They suggested that the lives saved via clozapine may essentially be offset by the deaths due to weight gains.[20]

Accumulated experience has led experts to emphasize how difficult it is to achieve a stable normal weight once obesity is well established.[21] There are some inherent difficulties for schizophrenic patients to adhere to strict weight-loss programs. Therefore, management with specific diets[22] or adjuvant drugs to prevent or decrease antipsychotics-induced weight gain is a logical strategy. The agents that have been tested in antipsychotics-treated schizophrenic patients include amantadine,[23-25] metformin,[26,27] nizatidine,[28] orlistat,[29] and topiramate.[30,31] However, there is an understandable concern about the economic burden of

adding another drug, often expensive, with its own side effects, and with potential drug interaction to already poly-medicated patients.

Add-on selective serotonin reuptake inhibitors (SSRIs) may be tried when clozapine fails to bring sufficient therapeutic response,[8,32-34] especially with respect to depressive or negative symptomatology. Although several SSRIs, particularly fluvoxamine, interact pharmacokinetically and phramacodynamically with clozapine,[35-38] several pilot studies reported that addition of fluvoxamine to clozapine treatment was well tolerated and could improve the psychopathology of schizophrenic patients.[39-41] The two principal metabolites of clozapine, norclozapine and clozapine N-oxide, represent most of the total metabolite formation.[7] Clozapine N-oxide is a rather inactive compound.[7] Norclozapine, however, produces lower therapeutic activity and perhaps more adverse effects than the parent drug.[42] Norclozapine may be responsible for the myelotoxicity of clozapine treatment.[43-45] In addition, norclozapine, a more potent 5-HT_{2C} antagonist than clozapine itself,[46] may be more likely to generate such side effects as weight gain or convulsion.[47] In recent studies by our group,[41,48] coadministration of fluvoxamine could increase steady-state plasma clozapine levels, decrease plasma norclozapine/clozapine ratios, and reduce clozapine dose (and thus cost) needed in refractory schizophrenic patients.

Hinze-Selch et al.[49] compared the effects of coadministration of clozapine and fluvoxamine (N = 11) versus clozapine monotherapy (N = 12) on plasma levels of cytokines and body weight in schizophrenic patients after 6 weeks of medication. The results showed that coadministration of fluvoxamine enhanced and accelerated the clozapine-induced increase in plasma leptin levels without significant effect on clozapine-induced weight gain. Due to the relatively small sample size and the short duration of the study, the effects of coadministered fluvoxamine on clozapine-induced weight changes and metabolic disturbances require further elucidation. We hypothesized that fluvoxamine cotreatment could attenuate weight gain and serum levels of glucose, triglycerides, and cholesterol in clozapine

recipients.

METHOD

Subjects and procedures

The facility's institutional review board approved this prospective, randomized, open-label study. After a description of the study to the patients, written informed consent was obtained. Patients were evaluated by the research psychiatrists after a thorough medical and neurological workup. The Structured Clinical Interview for DSM-IV[50] was conducted for the diagnosis. All enrolled patients fulfilled the DSM-IV diagnosis of schizophrenia and were "treatment-resistant" to typical antipsychotics.[1] None were receiving clozapine or other atypical antipsychotics prior to initiation of clozapine treatment. None of the patients had been pretreated with depot antipsychotics during at least 6 months before study entry. Patients with Axis I diagnosis other than schizophrenia or medical or neurological illness were excluded. Subjects were excluded for medical conditions that could confound metabolic assessments. All were Han Chinese inpatients and aged 18-60 years.

A total of 68 inpatients were included into this study and were randomized into two treatment groups: clozapine monotherapy (N = 34) and fluvoxamine-clozapine coadministration (N = 34). The monotherapy patients received clozapine alone (up to 600 mg/day). The coadministration 34 patients received a fixed dose of fluvoxamine (50 mg/day) and low doses of clozapine (up to 250 mg/day). Clozapine dosage in each patient of both groups was individually titrated according to clinical efficacy and adverse effects. Since adjunctive fluvoxamine can increase plasma clozapine concentration by around 2.3 times,[41] we thus utilized a lower dose range of clozapine in the coadministration group. Medications (e.g., lithium, carbamazepine, valproic acid, propranolol, tricyclic antidepressants, or other SSRIs) that may influence body weight, glucose/lipid metabolism, or clozapine disposition

were not allowed.[51] Among the 68 patients, 53 did not smoke but the other 15 consumed more than ten cigarettes per day.

All patients were hospitalized during the study period and received a routine hospital diet. The body weight was measured every week. Fasting serum glucose, triglycerides, and cholesterol levels were assayed at baseline and the 12th week of treatment. Based on the standard guidelines set forth by the American Diabetes Association[52] and the National Cholesterol Education Program,[53] we defined clinical significance as fasting glucose ≥ 126 mg/dL, total cholesterol ≥ 200 mg/dL, and triglycerides ≥ 200 mg/dL. We then determined the percentage of patients who had clinically significant changes in glucose or lipid measurements. At week 12, plasma levels of clozapine, norclozapine, and clozapine N-oxide were also analyzed. Fasting blood samples and body weight 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 the fluvoxamine-clozapine coadministration. Daily vital signs were measured. Hematology, physical and neurological examinations were repeated weekly. The Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale[54] was used biweekly for monitoring both exprapyramidal symptoms and other side-effect profiles. Electrocardiogram (ECG), urinalysis, and biochemistry were checked at baseline and endpoint. General psychopathology and functioning were biweekly assessed with Clinical Global Impression Scale (CGI)[55] and Global Assessment of Functioning Scale (GAF) (DSM-IV axis V). The clinical assessment involving these two efficacy scales and the UKU Side Effect Rating Scale was performed by a research psychiatrist throughout.

Laboratory assessment

Plasma levels of clozapine, norclozapine, and clozapine N-oxide were determined by high performance liquid chromatography with ultraviolet detection.[56] The intraassay and interassay coefficients of variation were < 10% for clozapine and its metabolites. The lower limit of detection for clozapine was 1 mg/dL, and for the metabolites was 2 mg/dL. The serum levels of glucose, triglycerides, and cholesterol were measured by using the Ciba-Corning 550 express chemistry analyzer.

Statistical analyses

The Kolmogorov-Smirnov testing revealed a trend toward normality of distribution for all variables. Subgroups were compared using t-test for continuous variables and chi-square test for categorical variables. To explore the effect of the two treatment modalities on the time course of the variables, multivariate analysis of variance with repeated measurements and with a between-subject factor (for the two treatment modalities) was applied. When significant effects emerged, analysis of variance for repeated measures was applied to analyse the effect of time in each of the two treatments, respectively. To identify the time points of significant differences compared to baseline, within-group tests with simple contrasts were conducted. To identify the time points of significant differences, between-group t-tests were performed. A p-value of less than 0.05 was considered to have statistical significance.

RESULTS

The two groups were similar in gender, age, height, age of illness onset, smoking status, and plasma clozapine concentration (Table 1). The coadministration group, however, had significantly lower plasma levels of norclozapine and clozapine N-oxide (Table 1). This result supports previous study finding that add-on fluvoxamine decreases plasma norclozapine to

clozapine ratios.[41,48] Baseline body weight and BMI and fasting serum levels of glucose, triglycerides, and cholesterol were also comparable in the two groups (Tables 2 and 3). All subjects completed the 12-week trial.

Clozapine dose increased significantly across time in both treatment groups but was significantly lower in the patients on the coadministration treatment from week 2 onwards (Table 2). In accordance, antecedent studies suggest that add-on fluvoxamine can decrease the clozapine dose needed.[41,48]

Changes in weight, BMI, glucose, cholesterol, and triglycerides

As shown in Table 2, both body weight and BMI kept rather constant after treatment in the coadministration group. In the clozapine monotherapy group, however, body weight and BMI at weeks 4, 8, and 12 were significantly higher than the baseline values. No statistically significant difference in body weight or BMI was found between two groups at each time point. Eleven subjects in clozapine monotherapy group gained ≥ 7% in weight at 12 weeks compared to 3 subjects in coadministration group ($p = .03$).

Table 3 reveals the metabolic profiles. In the coadministration patients, fasting glucose, total cholesterol, and triglycerides levels did not have significant changes after treatment. In contrast, the monotherapy patients had significant increases in fasting glucose and triglycerides levels and trend (insignificant) increase in total cholesterol levels after treatment. Compared to the cotreatment patients, the monotherapy patients also had significantly higher levels of glucose and triglycerides at week 12.

The weight change was correlated to the change in serum glucose levels ($r = 0.70$, $p < .001$), in triglycerides ($r = 0.35$, $p = .003$), and in total cholesterol levels ($r = 0.40$, $p = .001$). The glucose level change was correlated to the changes in triglycerides ($r = 0.49$, $p < .001$) and in total cholesterol levels ($r = 0.62$, $p < .001$).

In the clozapine monotherapy group, the rates of hypertriglyceridemia increased from 8.8% (N = 3) at baseline to 11.8% (N = 4) at week 12 (X^2 = 4.63, df = 1, p = .03). In the coadministration group, the rates of hypertriglyceridemia were unchanged: 11.8% (N = 4) at baseline and 11.8% (N = 4) at week 12. The rate of hypercholesterolemia did not have significant change in both groups. In the monotherapy group, the rates of hypercholesterolemia were 17.6% (N = 6) at baseline and 20.6% (N = 7) at week 12. In the coadministration group, the rates of hypercholesterolemia were 11.8% (N = 4) at baseline and 11.8% (N = 4) at week 12 too. During the 12-week study, no patients experienced hyperglycemia.

Influence of plasma norclozapine levels

The weight change was correlated to the plasma level of norclozapine (N = 68, r = 0.27, p = .026), whereas no correlation was found between weight change and plasma clozapine level. The changes in blood sugar and triglycerides levels were also correlated to the plasma concentration of norclozapine (r = 0.34, p = .005; and r = 0.27, p = .028), but not to the plasma clozapine level. There was a tendency toward a correlation between the change in the total cholesterol level and the plasma level of norclozapine (r = 0.21, p = .07).

Safety and efficacy

The frequencies of other treatment-emergent adverse events in the cotreatment and monotherapy groups were similar: sedation (N = 10 and 12, respectively), hypersalivation (N = 6 and 9), constipation (N = 8 and 6), postural hypotension (N = 4 and 7), tachycardia (N = 4 and 5), accommodation disturbances (N = 2 and 5), and nausea (N = 2 and 0). These events were all mild and many of them disappeared spontaneously. Extrapyramidal symptoms, seizures or agranulocytosis did not occur in our patients.

The CGI scores in the cotreatment and monotherapy groups were similar (baseline: 4.54 ± 0.53 and 4.60 ± 0.51 in the 2 groups, respectively; endpoint: 4.04 ± 0.25 and 3.98 ± 0.27); and so were the GAF scores (baseline: 47.6 ± 9.3 and 47.0 ± 8.9; endpoint: 60.2 ± 3.4 and 59.5 ± 3.3).

DISCUSSION

Compared with the general population, schizophrenic patients suffer not only neurocognitive and functional impairments but also increased medical morbidity and mortality. Atypical antipsychotics may be contributors to the medical morbidity of schizophrenia patients. It has been recognized that there are differential effects among these agents on metabolic outcomes. The dibenzodiazepine-derived atypical antipsychotics (clozapine, olanzapine) are associated with greater adverse reactions on weight, glucose, and serum lipids than ziprasidone (benzisothiazolyl) or risperidone (benzisoxazole).[57] This study mainly aimed to compare the effects of clozapine monotherapy and clozapine-fluvoxamine coadministration on body weight and metabolic profiles.

As expected, the clozapine monotherapy group had statistically significant increases in weight, BMI, and serum levels of glucose and triglycerides and a trend increase in serum levels of total cholesterol from baseline. Our data further suggest that add-on fluvoxamine attenuates the effects of clozapine on body weight, BMI, and serum levels of glucose and triglycerides (and possibly levels of total cholesterol).

One possible explanation for the between-group differences could be that fluvoxamine itself can decrease body weight and serum levels of glucose and triglycerides (and possibly total cholesterol). Fluvoxamine could modulate CRH or CRH-like peptides and thus lead to significant weight loss in animal studies.[58] Some investigators also reported weight reduction effects and increased metabolic rates of fluvoxamine,[59,60] but others did not support it.[61] The ability of clozapine to stimulate insulin secretion directly from the beta cells may explain its

weight-gain and diabetogenic effects.[62,63] Insulin levels in the Zucker rats model were reduced following fluvoxamine administration.[58] Besides, fluvoxamine might also have a cholesterol-lowering effect.[61] Therefore, this coadministration strategy may neutralize the metabolic disturbances of clozapine medication. However, two recent studies suggest that coadministration of fluoxetine (another SSRI) cannot lessen olanzapine-induced weight gain.[64,65] Further studies are required to substantiate the weight effect of adjunctive fluvoxamine.

Another possible explanation is that fluvoxamine alters pharmacokinetic and/or pharmacodynamic characteristics of clozapine. Five cytochrome P450 (CYP) isoenzymes, 1A2, 2C9, 2C19, 2D6, and 3A4, are able to mediate the demethylation of clozapine, whereas only CYP3A4 catalyzes the formation of clozapine N-oxide.[66-68] Fluvoxamine inhibits the activities of all of these five isoenzymes.[38] The inhibition of clozapine metabolism is at least partly due to the inhibition of CYP isoforms.[38] Several studies reported that clozapine led to significant increases in serum levels of triglycerides and/or total cholesterol.[11,63,69] The effect of serotonin 5-HT_{2C} antagonism has been postulated as a pharmacological mechanism underlying generally greater weight gain experienced with atypical antipsychotics. Norclozapine is a more potent 5-HT_{2C} antagonist than clozapine itself.[46] Fluvoxamine coadministration can decrease the plasma norclozapine/clozapine ratio[41,48] and may thus attenuate the metabolic abnormalities in clozapine receivers. In accordance, the changes in weight and in serum levels of glucose, triglycerides, and perhaps total cholesterol in our subjects were correlated to plasma norclozapine levels, but not to plasma clozapine levels.

Several limitations in our study deserve attention. First, clinical variables (e.g., adverse reaction and psychopathology) were compared between the clozapine monotherapy and fluvoxamine-clozapine cotreatment groups under an open-label design. Second, some laboratory measurements (e.g., insulin, leptin) were unavailable.

Third, the study duration was limited to 12 weeks. Long-term effects of adjuvant fluvoxamine on clozapine-induced metabolic disturbances remain unclear.

Drug names: clozapine (Clozaril and others), fluvoxamine (Luvox).

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Table 1. Patient demographics at baseline and plasma levels of clozapine and metabolites at 12th week

	Coadministration Group	Monotherapy Group
Male:female, N	10:24	10:24
Age, mean ± SD, y	32.9 ± 8.5	35.1 ± 9.4
Height, mean ± SD, cm	165.3 ± 8.7	163.6 ± 6.0
Age of onset, mean ± SD, y	21.6 ± 4.8	21.0 ± 4.5
Smokers:nonsmokers, N	8:26	7:27
Plasma clozapine, mean ± SD, mg/dL	509.8 ± 281.1	502.0 ± 220.6
Plasma Norclozapine, mean ± SD, mg/dL[a]	179.0 ± 95.8	242.8 ± 100.3
Plasma Clozapine N-oxide, mean ± SD, mg/dL [a]	28.6 ± 15.9	61.2 ± 28.4

[a]Significant difference between treatment groups at the 12th week ($p < .05$)

Table 2. Body weight, BMI, and dosage of clozapine

	Baseline	Week 2	Week 4	Week 8	Week 12
Body weight, mean ± SD, kg					
Coadministration group	67.9 ± 14.1	68.1 ± 14.1	68.3 ± 14.0	68.6 ± 13.7	68.8 ± 13.5
Monotherapy group	65.3 ± 12.1	65.8 ± 12.1	66.3 ± 12.0[a]	67.2 ± 12.0[a]	68.5 ± 12.0[a]
BMI, mean ± SD, kg/m^2					
Coadministration group	24.8 ± 4.6	24.9 ± 4.6	24.9 ± 4.6	25.0 ± 4.4	25.1 ± 4.3
Monotherapy group	24.3 ± 3.3	24.5 ± 3.3	24.6 ± 3.3[a]	25.0 ± 3.2[a]	25.4 ± 3.2[a]
Clozapine dosage, mean ± SD, mg/d					
Coadministration group	-	102.2 ± 9.5	121.3 ± 40.9[b,c]	128.7 ± 52.3[b,c]	130.1 ± 56.3[b,c]
Monotherapy group	-	159.6 ± 44.0[c]	266.2 ± 74.6[b,c]	297.1 ± 104.9[b,c]	307.4 ± 120.8[b,c]

[a] Significant difference from baseline ($p < .05$)

[b] Significant difference from week 2 ($p < .05$)

[c] Significant difference between treatment groups at the same time point ($p < .05$)

Table 3. Serum levels of glucose, total cholesterol, and triglycerides at baseline and endpoint (week 12)

	Baseline	Endpoint
Glucose, mean ± SD, mg/dL		
Coadministration group	91.9 ± 7.3	92.3 ± 6.0
Monotherapy group	91.2 ± 7.1	95.6 ± 6.7[a,b]
Total Cholesterol, mean ± SD, mg/dL		
Coadministration group	178.8 ± 19.5	180.2 ± 23.9
Monotherapy group	181.8 ± 16.6	190.4 ± 21.5
Triglycerides, mean ± SD, mg/dL		
Coadministration group	107.7 ± 46.9	109.8 ± 46.2
Monotherapy group	108.6 ± 32.2	132.5 ±45.9[a,b]

[a] Significant difference from baseline ($p < .05$)

[b] Significant difference between treatment groups at the same time point ($p < .05$)