Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Effects of adjunctive fluvoxamine on metabolic parameters and psychopathology in clozapine-treated patients with schizophrenia: A 12-week, randomized, double-blind, placebo-controlled study

Mong-Liang Lu [a,b], Tzu-Ting Chen [c], Po-Hsiu Kuo [d,e], Ching-Chi Hsu [f], Chun-Hsin Chen [a,b,*]

[a] Department of Psychiatry, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan
[b] Department of Psychiatry, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[c] Department of Psychiatry, National Taiwan University Hospital Yun-Lin Branch, Yunlin County, Taiwan
[d] Department of Public Health & Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan
[e] Research Center for Genes, Environment and Human Health, National Taiwan University, Taipei, Taiwan
[f] Department of Psychiatry, Wizcare Hospital, Taichung, Taiwan

ARTICLE INFO

Article history:
Received 13 February 2017
Received in revised form 17 June 2017
Accepted 18 June 2017
Available online xxxx

Keywords:
Clozapine
Fluvoxamine
Metabolic parameter
Psychopathology
Schizophrenia

ABSTRACT

Objective: Numerous studies have demonstrated that fluvoxamine has considerable pharmacokinetic and pharmacodynamic interactions with clozapine. We conducted a 12-week, randomized, double-blind, placebo-controlled study to evaluate the effects of fluvoxamine on metabolic parameters and psychopathology in clozapine-treated patients with schizophrenia.

Methods: We recruited 85 patients who received a DSM-IV diagnosis of schizophrenia. Eligible patients were randomized to receive fluvoxamine 50 mg/day plus clozapine 100 mg/day or clozapine 300 mg/day. We studied metabolic parameters, psychopathology, and drug levels at baseline and 4, 8, and 12 weeks after the intervention. Plasma levels of clozapine, norclozapine, clozapine N-oxide, and fluvoxamine were determined using high-performance liquid chromatography with ultraviolet detection.

Results: No significant difference was observed in baseline characteristics between the two groups. Clozapine–fluvoxamine combined treatment significantly attenuated the increments in body weight, insulin resistance, and levels of insulin, glucose, and triglycerides compared with clozapine monotherapy. Both groups exhibited significant improvements in their Positive and Negative Syndrome Scale (PANSS) total and negative scores. The combined treatment group showed significant reduction in the PANSS general psychopathology scores compared with the monotherapy group. No difference was observed in the plasma clozapine level between the two groups. The monotherapy group showed higher levels of norclozapine and clozapine N-oxide than the combined group.

Conclusions: Compared with clozapine monotherapy, treatment with adjunctive fluvoxamine with clozapine for 12 weeks can alleviate body weight gain and metabolic abnormalities in patients with schizophrenia, without sacrificing the clinical effect. Clinicians should interpret these findings cautiously considering the short duration of this study.

The study was registered at www.clinicaltrials.gov (NCT01401491).

1. Introduction

Schizophrenia is characterized by a wide range of behavioral, emotional, and cognitive abnormalities that often do not resolve completely with treatment (Kane and Correll, 2010). The development of new drugs in recent decades has not produced dramatic improvements in treating schizophrenia (Swartz et al., 2003). An estimated 20%–30% of people with schizophrenia are treatment-refractory (Kane et al., 1988). Clozapine can improve the clinical outcomes of patients with treatment-refractory schizophrenia (Buchanan, 1995; Stroup et al., 2016). However, growing concerns about clozapine treatment are related its metabolic side effects such as weight gain, metabolic syndrome, type II diabetes mellitus, and hyperlipidemia (Newcomer, 2007; Rummel-Kluge et al., 2010; Stroup et al., 2016). In addition, 40%–70% of patients with treatment-resistant schizophrenia still fail to respond to or are only partially responsive to clozapine even if a threshold plasma drug level of 350–420 mg/dL is achieved (Lieberman et al., 1994; Perry et al., 1991).

* Corresponding author at: Department of Psychiatry, Wan Fang Hospital, Taipei Medical University, #111, Section 3, Xing-Long Road, Taipei 116, Taiwan.
E-mail address: chchen@tmu.edu.tw (C.-H. Chen).

http://dx.doi.org/10.1016/j.schres.2017.06.030
0920-9964/

In clinical practice, clozapine is frequently augmented with another drug despite the paucity of evidence that an additional drug enhances antipsychotic efficacy (Porcelli et al., 2012). Combination therapy for managing treatment-refractory schizophrenia may offer therapeutic advantages, but this therapy increases the potential for pharmacokinetic interactions. Clozapine is metabolized to *N*-desmethylclozapine (norclozapine) by cytochrome P450 1A2 (CYP1A2) and CYP3A4 and to clozapine N-oxide by CYP3A4 (Eiermann et al., 1997). Norclozapine has been shown to be more cytotoxic than clozapine in PC12 cultured cells (Dwyer et al., 2003).

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) that has been approved for psychiatric disorders such as major depressive episodes by the European Medicines Agency and for obsessive–compulsive disorder by the US Food and Drug Administration (van Harten, 1995). It is a potent inhibitor of CYP1A2 and can inhibit the metabolism of clozapine, resulting in higher plasma clozapine levels and clozapine–norclozapine ratios (Fabrazzo et al., 2000; Lu et al., 2000; Olesen and Linnet, 2000). In addition to inhibiting serotonin reuptake, fluvoxamine is a potent agonist of endoplasmic reticulum (ER) protein sigma-1 receptors, which play a role in the pathophysiology of many psychiatric and neurodegenerative disorders (Hashimoto, 2009; Niitsu et al., 2012). A recent meta-analysis demonstrated that patients treated with fluvoxamine add-on antipsychotic medication showed improved overall psychopathology and negative symptoms compared with controls, and fluvoxamine add-on therapy had no significant effects on positive symptoms, depressive symptoms, weight, and discontinuations from any cause or adverse events (Kishi et al., 2013). Some studies have also reported that adjunctive fluvoxamine attenuated weight gain and metabolic disturbance in clozapine-treated patients (Lu et al., 2004) and improved clinical efficacy (Lammers et al., 1999; Lu et al., 2004; Polcwiartek and Nielsen, 2016; Silver et al., 1996; Szegedi et al., 1999; Wetzel et al., 1998). However, other studies have presented contradictory findings (Hinze-Selch et al., 2000; Peritogiannis et al., 2005).

We previously completed a 12-week open trial that showed fluvoxamine could attenuate weight gain and metabolic abnormalities in clozapine-treated patients (Lu et al., 2004). Until now, no double-blind randomized-controlled trial has evaluated the effects of adjunctive fluvoxamine with clozapine on metabolic profiles and clinical efficacy. Thus, in this double-blind, randomized, placebo-controlled study, we examined the augmentation effects of fluvoxamine on metabolic parameters and psychopathology in clozapine-treated patients with schizophrenia. Body weight change was the primary outcome, and changes in metabolic parameters and psychopathology were the secondary outcomes. Furthermore, we examined the effects of fluvoxamine augmentation on pharmacokinetic parameters.

2. Methods

This study was performed in accordance with the World Medical Association Declaration of Helsinki regarding human experimentation and was approved by the Institutional Review Board of Taipei Medical University-Wan Fang Hospital and participating hospitals. The study was registered at www.clinicaltrials.gov (NCT01401491).

2.1. Design and participants

In this 12-week, double-blind, randomized, placebo-controlled trial, patients with schizophrenia received adjunctive fluvoxamine with clozapine. After a detailed description of this study was provided to the patients, written informed consent was obtained from them. The patients were evaluated by research psychiatrists after a thorough medical workup. To determine patient diagnoses, the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) was conducted. The inclusion criteria were age of 20–65 years; fulfilling the DSM-IV diagnostic criteria for schizophrenia; treatment-resistance to typical antipsychotics, which was modified from the criteria proposed by Kane et al. (1988), Conley and Kelly (2001) and Treatment Response and resistance in Psychosis Working Group Consensus Guidelines on Diagnosis and Terminology (Howes et al., 2017). The patients satisfied the treatment-resistance criteria for unambiguous lack of improvement when they had at least 6 weeks of continuous treatment with two or more typical or atypical antipsychotics at doses of at least 600 mg of chlorpromazine equivalents, a poor level of functioning over the last 5 years, and persistent psychotic symptoms of at least moderate severity (as indexed by Positive and Negative Syndrome Scale [PANSS] scores (Kay et al., 1987) on two or more positive subscale measures). The exclusion criteria were an Axis I diagnosis other than schizophrenia or a medical condition that could confound medical assessment, a history of clozapine use, and treatment with depot antipsychotics in the 6 months before the trial.

After baseline evaluation, the patients were randomized to receive clozapine monotherapy or clozapine–fluvoxamine combined treatment under double-blind conditions by using a randomization automated system on a 1:1 basis. Blocks of randomization numbers based on a computer-generated permuted-block randomization schedule were assigned to each study center. Randomization was stratified by site in blocks of 10. All patients, caregivers, and investigators were masked to the randomization. Placebos of clozapine and fluvoxamine, manufactured according to the Good Manufacturing Practices by Johnson Chemical Pharmaceutical Works Co., Ltd. (New Taipei City, Taiwan), were identical in appearance (including size, shape, and color) to the clozapine and fluvoxamine tablets, respectively. To ensure the concealment of the randomization, the clozapine, fluvoxamine, and placebo tablets were provided in coded containers. Given that the average clozapine dose is 318 mg/day in Taiwanese patients with schizophrenia (Bai et al., 2009), the target dose of clozapine monotherapy was set to 300 mg/day. Because adjunctive fluvoxamine at 50 mg/day can increase the plasma level of clozapine by approximately 2.3 times (Lu et al., 2000; Lu et al., 2004), we utilized a low-clozapine dosing strategy in the combined treatment group to achieve similar plasma clozapine levels in both groups. In the first 2 weeks, we slowly titrated clozapine to 100 mg/day in both the monotherapy and combined treatment groups. In the third week, clozapine was gradually titrated to 300 mg/day in the monotherapy group, and clozapine at 100 mg/day and an additional placebo of clozapine were administered to the combined treatment group. In addition, in the third week, fluvoxamine was gradually titrated to 50 mg/day in the combined treatment group, and a placebo of fluvoxamine was administered to the monotherapy group. All doses were taken at bedtime and were maintained until the end of the trial at week 12. Simultaneously, previous antipsychotics were tapered as follows: during week 1, the dosage of previous antipsychotics was reduced to 50% of the original dose; during week 2, the dosage was decreased to 25%; and at the start of week 3, previous antipsychotics were totally discontinued. The patients were not allowed to take medication (e.g., lithium, valproic acid, other SSRIs, and other antipsychotics) that might influence their body weight, glucose and lipid metabolism, or clozapine disposition. Limited use of benzodiazepines was permitted for severe anxiety, agitation, or insomnia.

At each patient visit, pill counts and medication reviews were conducted to assess treatment adherence. In addition, for all patients, an adherence plan that included medication checks by family members, residence staff, or caregivers who had extensive contact with them was implemented. Patient adherence to the study medication was defined as having taken >80% of the prescribed study drug dosage.

2.2. Assessments

Vital signs, including body weight, heart rate, temperature, and blood pressure, were recorded weekly. A digital scale was used to record the weight of the patients to the nearest 0.1 kg. An electrocardiogram was recorded at screening to confirm normal cardiac function. The white blood cell (WBC) count was evaluated every week. Fasting

Please cite this article as: Lu, M.-L., et al., Effects of adjunctive fluvoxamine on metabolic parameters and psychopathology in clozapine-treated patients with schizophrenia: A ..., Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.06.030