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ORIGINAL INVESTIGATION

Norio Yasui-Furukori · Tsuyoshi Kondo · Kazuo Mihara · Yoshimasa Inoue · Sunao Kaneko

Fluvoxamine dose-dependent interaction with haloperidol and the effects on negative symptoms in schizophrenia

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Abstract Augmentation with low-dose fluvoxamine (50–100 mg/day) to antipsychotic treatment may improve the negative symptoms in schizophrenic patients, but involves a risk of drug-drug interaction. We studied the effects of fluvoxamine on plasma concentrations of haloperidol and reduced haloperidol, and their clinical symptoms, in haloperidol treated patients. Twelve schizophrenic inpatients with prevailingly negative symptoms receiving haloperidol 6 mg/day were additionally treated with incremental doses of fluvoxamine for 6 weeks (25, 75 and 150 mg/day for 2 weeks each). Plasma drug concentrations were monitored together with clinical assessments before and after each phase of the three fluvoxamine doses. Geometric mean of haloperidol concentrations during coadministration of fluvoxamine 25, 75 and 150 mg/day were 120% (95%CI; 114–127%), 139% (95%CI; 130–149%), and 160% (95%CI; 142–178%) of those before fluvoxamine coadministration, respectively. We found positive correlations between increase in plasma haloperidol concentrations and plasma fluvoxamine concentrations. Scores in negative symptoms were significantly reduced after fluvoxamine coadministration, whereas no changes were observed in the other psychiatric symptoms or any subgrouped side effects. Therefore, this study indicates that fluvoxamine increases plasma haloperidol concentrations in a dose-dependent manner. However, relatively small elevations in haloperidol concentration did not lead to the development of extrapyramidal symptoms under the conditions of this study.

Keywords Haloperidol · Fluvoxamine · Drug interaction · Dose effect

N. Yasui-Furukori (✉)
Department of Clinical Pharmacology,
Hirosaki University School of Medicine,
Hirosaki, 036-8562, Japan
e-mail: yasufuru@cc.hirosaki-u.ac.jp
Tel.: +81-172-395352
Fax: +81-172-395352

N. Yasui-Furukori · S. Kaneko
Department of Neuropsychiatry,
Hirosaki University School of Medicine,
Hirosaki, Japan

T. Kondo · K. Mihara
Department of Psychiatry, Faculty of Medicine,
University of the Ryukyus,
Okinawa, Japan

Y. Inoue
Pharmaceutical Research Division,
Mitsubishi Pharma Corporation,
Fukuoka, Japan

Introduction

There is some evidence that adding fluvoxamine, an antidepressant drug belonging to the group of selective serotonin reuptake inhibitors (SSRI), improves negative symptoms of schizophrenia (Silver 2001). Lower doses of fluvoxamine than those usually used in the treatment of depression have been recommended for augmentation therapy with respect to safety and tolerability (Silver 2001). In a double-blind, placebo controlled study, addition of fluvoxamine (50–100 mg/day) to antipsychotic therapy was associated with significant improvement in negative symptoms compared with placebo (Silver et al. 2000).

Several reports have shown that fluvoxamine coadministration increases plasma concentrations of the antipsychotic drugs clozapine (Markowitz et al. 1996; Armstrong et al. 1997; Heeringa et al. 1999; Fabrazzo et al. 2000), olanzapine (de Jong et al. 2001; Weigmann et al. 2001; Hiemke et al. 2002), and thioridazine (Carrillo et al. 1999). In addition, Daniel and coworkers (1994) reported a pharmacokinetic interaction of relatively high-dose fluvoxamine (100–300 mg/day) with haloperidol, which is still one of the most widely used antipsychotic drugs in the treatment of schizophrenia and other psychiatric disorders (Santamaria et al. 2002), in a small-sized study with three schizophrenic patients. Based on these findings, it is presumed that plasma haloperidol concentrations would be elevated in proportion to the

dose of coadministered fluvoxamine, although there has been no comprehensive information indicating the relationship between haloperidol concentration and dose or plasma concentration of fluvoxamine.

Therefore, this study aimed to examine the dose effects of fluvoxamine on steady-state plasma concentrations of haloperidol and its reduced metabolite intraindividually during incremental doses of fluvoxamine. In addition, changes in psychiatric symptoms and neuroleptic side effects occurring contemporaneously with concomitant administration of fluvoxamine were evaluated.

Materials and methods

Subjects

Twelve schizophrenic inpatients with prevailingly negative symptoms (ten females and two males) who fulfilled the criteria for schizophrenia, according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, participated in the study. The median (range) of age, body weight, and duration of illness were 49 (22–59) years, 54 (40–95) kg, and 150 (15–362) months, respectively. The study was approved by the Ethics Committee of Hirosaki University Hospital, and written informed consent to participate in this study was obtained from the patients and their families.

Protocol

Before fluvoxamine coadministration, subjects receiving haloperidol 3 mg twice a day (8 a.m. and 8 p.m.) were recruited because it is more likely that high doses of haloperidol have sedative effects, which prevent the efficacy of adding fluvoxamine. Dose of haloperidol was fixed for 3–18 weeks. The elimination half-lives of haloperidol and reduced haloperidol were reported to be 22 and 34 h, respectively (Tsang et al. 1994). Therefore, plasma concentrations of these compounds had already reached steady state in all of the subjects before initiating the study. The drugs coadministered were flunitrazepam 2–6 mg/day in seven cases, biperiden 2–6 mg/day in eight cases, sennoside 24 mg/day in one case, diazepam 8–10 mg/day in two cases and quazepam 30 mg/day in two cases. The doses of these coadministered drugs were fixed throughout the study period. Female patients did not receive oral contraceptives. Fluvoxamine 25 mg once a day (8 p.m.) was coadministered to all the subjects for the first 2 weeks, followed by 75 mg/day for the next 2 weeks and finally 150 mg/day for the last 2 weeks.

Plasma sample collections were performed before and 2 weeks after each dosage sequence of 25, 75, and 150 mg/day of fluvoxamine coadministration. On the same days as the blood samples, psychiatric symptoms and side effects were evaluated by the Brief Psychiatric Rating Scale (BPRS) classified by Bech and coworkers (1986), where each of 18 items was assessed by five-point steps from 0 (not present) to 4 (extremely severe) and the Udvalg for Kliniske Undersøgelser (UKU) side effects rating scale (Lingjaerde et al. 1987), respectively. Patients were evaluated by the same investigator. This investigator, from another hospital, was not involved in the study patient care and was blind to drug regimens and results of drug concentrations. However, he had access to the nursing charts.

The 18 items of the BPRS were divided into five clusters: positive (exaggerated self-esteem, suspiciousness, hallucinations, unusual thought content); excitement (hostility, uncooperativeness, psychomotor agitation); cognitive (conceptual disorganization, specific motor disturbances, disorientation); negative (emotional withdrawal, psychomotor retardation, blunted affect); and anxiety-depression [somatic concern, anxiety (mental), self-depreciation, anxiety (somatic), depressive mood] symptoms as classified by Lindenmayer and coworkers (1995). Nineteen items were selected from the UKU side effect rating scale to assess the side effects of haloperidol, which were further divided into three subgroups: psychic (concentration difficulties, asthenia, sleepiness, failing memory, depression, tension); extrapyramidal (dystonia, rigidity, hypokinesia, hyperkinesia, tremor, akathisia, increased salivation); and autonomic (accommodation disturbances, reduced salivation, constipation, micturition disturbances, orthostatic dizziness, palpitations).

Assay

The plasma concentrations of haloperidol and reduced haloperidol were measured in duplicate using high-performance liquid chromatography (HPLC) as described by Hikida and coworkers (1989). The lowest limits of detection were 0.3 ng/ml, and the values of the inter-day coefficient of variation were less than 5% at concentrations of 1.1 ng/ml for both haloperidol and reduced haloperidol.

Plasma concentration of fluvoxamine was determined using the following HPLC methods developed in our laboratory. After sample alkalization with 0.5 ml NaOH (2.5 M), fluvoxamine and internal standard, alprazolam, were extracted from 1000 μl of plasma using chloroform-n-heptane (30:70, v/v). The organic phase was evaporated to dryness, and the residue was dissolved with 800 μl of mobile phase. A 500 μl aliquot of the solution was injected into a C_{18} STR ODS-II analytical column (5 μl, 150×4.6 mm ID) (Shinwa Chemical Industry, Kyoto, Japan). The mobile phase consisted of phosphate buffer (0.02 M, pH 4.6), perchloric acid (6 M) and acetonitrile (58.93:0.07:41, v/v) and was delivered at a flow rate of 0.6 ml/min. The peak was detected using a UV detector (Shimazu SPD-10Avp, Kyoto, Japan) set at 254 nm for fluvoxamine. The method was validated for the concentration range 1–100 ng/ml, and good linearity (r>0.999) was confirmed. Intra- and inter-day of coefficient variations were less than 2.9% at a concentration of 16 ng/ml for the test compound. Relative errors ranged from –5 to 10%, and mean recoveries were 87–95%. The limit of quantification was 0.8 ng/ml for fluvoxamine.

Statistical analyses

The repeated measurement of analysis of variance followed by paired t-test and Freidman test with Bonferroni's correction was used for the comparison of the plasma drug concentrations and scores of clinical assessments, respectively, among four phases, i.e. before and during fluvoxamine coadministration at 25, 75, and 150 mg/day. Correlations between the changes in plasma concentrations of haloperidol and reduced haloperidol and dose or plasma concentration of fluvoxamine were tested using linear regression analysis. A P value of 0.05 or less was regarded as significant. SPSS 7.5.1 for Windows (SPSS Japan Inc., Tokyo) was used for these statistical analyses.

Results

All patients completed this study, although excitement symptoms deteriorated during fluvoxamine treatment in three patients who had average negative symptoms.

Plasma haloperidol concentrations during coadministration of fluvoxamine 25, 75 and 150 mg/day, respectively, were significantly higher than those before fluvoxamine coadministration (Table 1). Geometric mean haloperidol concentrations during fluvoxamine coadministration at the above-mentioned doses were 120% [95%CI (confidence interval); 114–127%], 139% (95%CI; 130–149%), and 160% (95%CI; 142–178%) of

Table 1 Changes in drug concentrations, BPRS and UKU scores before and after coadministration with incremental doses of fluvoxamine in 12 schizophrenic patients. *BRPS* Brief Psychiatric Rating Scale, *UKU* Udvalg for Kliniske Undersøgelser side effect rating scale. Data are shown as mean±SD (range)

	Before fluvoxamine	Daily fluvoxamine dose		
		25 mg	75 mg	150 mg
Drug concentrations (ng/ml)				
Haloperidol	3.7±4.4 (1.9–6.9)	4.4±1.7 (2.4–7.9)***	5.2±2.3 (2.5–10.0)**	6.0±3.0 (2.7–12.6)**
Reduced haloperidol	1.5±1.7 (0.5–3.1)	1.7±0.9 (0.6–3.8)*	1.9±1.1 (0.8–4.5)*	2.3±1.2 (0.9–4.6)**
Fluvoxamine	–	16.9±9.8 (4.5–37.5)	55.2±27.8 (15.4–110)	139.0±57.5 (47.6–336)
BPRS scores				
Total	14.4±6.1 (5–24)	13.2±5.4 (2–23)	12.6±6.6 (1–25)	12.5±7.4 (2–26)
Positive	4.0±3.2 (0–9)	3.9±3.0 (0-9)	3.9±3.5 (0–9)	4.0±3.9 (0–11)
Excitement	0.3±0.6 (0–2)	0.3±0.6 (0–2)	0.9±1.9 (0–7)	0.9±1.7 (0–6)
Cognitive	0.5±0.9 (0–2)	0.2±0.4 (0–1)	0.2±0.6 (0–2)	0.3±0.8 (0–2)
Negative	5.6±1.9 (2–9)	5.0±2.2 (1–8)	4.3±2.0 (1–8)	3.4±1.9 (1–8)*
Anxiety-depression	4.0±2.4 (1–9)	3.8±2.7 (0–8)	3.3±2.7 (0–10)	3.0±2.9 (0–8)
UKU scores				
Total	4.8±4.2 (0–15)	4.6±4.3 (0–15)	5.1±2.7 (0–9)	6.2±3.7 (0–12)
Psychic	2.9±3.4 (0–10)	2.8±3.2 (0–9)	3.3±2.8 (0–8)	4.0±3.8 (0–12)
Extrapyramidal	0.9±1.1 (0–3)	0.7±1.0 (0–3)	0.4±0.6 (0–2)	0.5±0.8 (0–2)
Autonomic	1.0±1.1 (0–3)	1.1±1.2 (0–3)	1.4±1.0 (0–3)	1.7±1.2 (0–4)

* $P<0.05$, ** $P<0.01$, *** $P<0.001$, compared with values before fluvoxamine

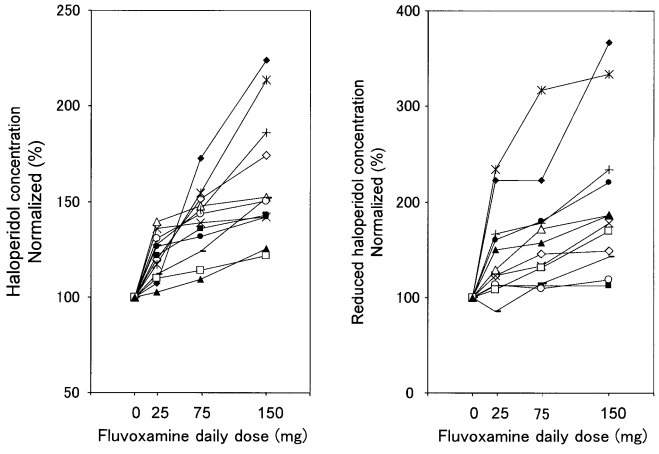

Fig. 1 Intraindividual changes in normalized plasma concentrations of haloperidol (*left*) and reduced haloperidol (*right*) during coadministration with incremental doses of fluvoxamine (n=12)

those before fluvoxamine coadministration, respectively (Table 1). Likewise, the corresponding values for reduced haloperidol concentrations were 138% (95%CI; 113–162%), 156% (95%CI; 125–187%), and 187% (95%CI; 144–230%), respectively. Most subjects showed intra-individual fluvoxamine-dose-dependent elevation in plasma concentrations of haloperidol and reduced haloperidol, but there was large inter-individual variability in the increase in haloperidol concentrations (Fig. 1). Significantly positive correlations ($r\geq0.97$) in seven out of 12 patients were found between increase in haloperidol concentrations and plasma fluvoxamine concentrations within each phase of three different fluvoxamine doses, whereas there were no correlations (r=0.64–0.87) in the remaining five subjects. The increase in haloperidol concentrations did not correlated with plasma fluvoxamine concentration during 25 (r=–0.02), 75 (r=0.20) or 150 mg/day (r=0.20) fluvoxamine coadministration.

Scores of negative symptoms were significantly reduced after 2 weeks of fluvoxamine coadministration, while those in total BPRS, positive, excitement, cognitive, and anxiety-depression symptoms were unchanged (Table 1). No significant changes were found in scores of total UKU, psychic symptoms, extrapyramidal symptoms or autonomic symptoms throughout the study period (Table 1).

Discussion

The present results showed that additional treatment with fluvoxamine resulted in a significant increase in the steady-state plasma concentrations of haloperidol and reduced haloperidol. These findings are consistent with a previous report (Daniel et al. 1994). However, plasma haloperidol concentration significantly increased even at 25 mg/day fluvoxamine coadministration. Therefore, a significant pharmacokinetic interaction should be kept in mind when even lower doses of fluvoxamine are concomitantly administered with haloperidol.

The dose effect of fluvoxamine on elevations in the steady-state plasma concentration of haloperidol was evident in this study. This was in line with previous interaction studies indicating that dose or plasma concentration of fluvoxamine correlated well with the degree of inhibition in the metabolism of various drugs such as clozapine (Markowitz et al. 1996; Fabrazzo et al. 2000), melatonin (von Bahr et al. 2000) and omeprazole (Christensen et al. 2002). In addition, we found positive correlations between increase in haloperidol concentra-

tions and plasma fluvoxamine concentrations within each phase of three different fluvoxamine doses. Thus, it is suggested that haloperidol concentration monitoring is required during incremental doses of coadministered fluvoxamine, especially with development or worsening of extrapyramidal symptoms after fluvoxamine coadministration.

Fluvoxamine is known as not only a potent inhibitor of CYP1A2 and CYP2C19 (Christensen et al. 2002), but also a moderate inhibitor of CYP3A4, based on in vivo (Fleishaker et al. 1994) and in vitro (von Moltke et al. 1995) interaction studies between fluvoxamine and alprazolam, which is a specific substrate of CYP3A4 (Yasui et al. 1996). In a previous study, we found that itraconazole, a potent inhibitor of CYP3A4, elevated haloperidol concentration, indicating the involvement of CYP3A4 in the metabolism of haloperidol (Yasui et al. 1999). Moreover, several in vitro studies have also demonstrated that N-dealkylation and oxidation to pyridinium metabolite are catalyzed by CYP3A4 (Fang et al. 1997; Kudo et al. 1998). In contrast with clozapine-fluvoxamine interaction due to CYP1A2 inhibition, it is therefore most likely that fluvoxamine increased haloperidol concentration via an inhibitory effect on CYP3A4 in the present study. Since it has been suggested that neuroleptics such as quetiapine (Caccia 2000), zotepine (Caccia 2000) and ziprasidone (Caccia 2000) are at least partly metabolized by CYP3A4, plasma concentrations of these neuroleptics may be also elevated with additional fluvoxamine treatment.

Negative symptoms were finally ameliorated after 2 weeks of fluvoxamine coadministration, when the dose was maintained at 150 mg/day. It should be noted that the results might have clinical implications although this study was not performed in a double-blind, placebo-control manner. The efficacy of fluvoxamine on negative symptoms was partly confirmed by the present finding, which probably resulted from the activating effect of fluvoxamine itself, and not from the small elevation of plasma haloperidol concentration. However, it is unclear whether this augmentation effect of fluvoxamine was dose- or time-dependent. Extrapyramidal symptoms were not exacerbated throughout the study period, despite the elevated haloperidol concentrations. As plausible explanations for this negative result, coadministration of anticholinergics, short period (2 weeks) of maximal dose (150 mg/day) of fluvoxamine coadministration, pharmacodynamic insensitivity due to long-term neuroleptic treatment, and relatively low haloperidol concentrations even after fluvoxamine coadministration should be considered.

In conclusion, the present study indicates that fluvoxamine increases plasma haloperidol concentrations in a dose-dependent manner, and that elevation in haloperidol concentrations is apparent even at lower doses of fluvoxamine. However, relatively small elevations in haloperidol concentrations did not lead to the development of extrapyramidal symptoms under the conditions of this study.

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