A Preliminary Study of Fluvoxamine Maleate on Depressive State and Serum Melatonin Levels in Patients after Cerebral Infarction

Eiko Sunami, Kazuhiro Usuda, Yutaka Nishiyama, Tatuo Otori, Kenichirou Katsura and Yasuo Katayama

Abstract

Objective Antidepressants have been recommended for the treatment of post-stroke depression (PSD). The purpose of this study was to evaluate the effect of fluvoxamine maleate, a selective serotonin re-uptake inhibitor (SSRI), on depressive state, sleep disturbance, and serum melatonin levels in patients with depressive state after cerebral infarction.

Methods Nineteen patients who were hospitalized for cerebral infarction and scored 40 points or higher on the Self Depression Scale (SDS) were enrolled in this study. Nine of the 19 patients received fluvoxamine as a treatment group and the other 10 patients were used as untreated controls. Before and after commencing the drug therapy, the patients were assessed by the SDS, Pittsburgh Sleep Quality Index (PSQI), Japan Stroke Scale for Depression (JSSD), and Japan Stroke Scale for Emotional Disturbance (JSSE), and their serum melatonin levels were measured. The control group underwent the same evaluations as the treatment group.

Results The SDS score improved in the treatment group at 1 week after the start of drug treatment, and in the control group at 1 and 2 weeks into the observation period. In the treatment group, the JSSD and PSQI scores improved and serum melatonin levels increased.

Conclusion The administration of fluvoxamine to patients with depressive state after cerebral infarction alleviated both the depressive state and sleep disturbances. Increased melatonin levels by the administration of fluvoxamine may contribute to improvement in sleep disturbance, one of the major symptoms of depression.

Key words: ischemic stroke, depression, sleep disturbance, fluvoxamine maleate, melatonin

Introduction

Stroke patients often develop post-stroke depression (PSD), a mood disturbance characterized by depressive state or reduced volition. The estimated incidence of PSD in stroke patients ranges from 12 to 64% (1). PSD is reported to increase stroke mortality by preventing recovery from the sequela of cerebrovascular impairment (2). This underlines the importance of appropriate diagnosis and treatment for PSD. Tricyclic antidepressants (3, 4) and selective serotonin re-uptake inhibitors (SSRIs) (5, 6) are reportedly effective for PSD, and antidepressants for PSD have been recommended. Sleep disturbance is a frequent complication in patients with depression, and one of the important symptoms of PSD. Many investigators have assumed that a depressive state can be improved by alleviating sleep disturbance.

Melatonin, a hormone secreted primarily from the pineal gland, is involved in the regulation of both sleep and mood. Depressed patients secrete decreased levels of melatonin at night (7) and exhibit an abnormal melatonin secretion rhythm phase (8). It thus appears that a change in melatonin secretion kinetics may contribute to the onset of depression. As described above, depression, sleep disturbance and serum melatonin levels are profoundly interrelated. Moreover, a limited number of antidepressants are reported to have an
effect of enhancing melatonin (9, 10). There is a report which shows that fluvoxamine maleate, an SSRI, inhibits the melatonin metabolism by suppressing CYP1A2 and CYP2C19 in the liver and eventually raises serum melatonin levels (9). The current study was undertaken by administering fluvoxamine to patients who contracted depressive state following cerebral infarction to investigate the effect of the drug to depression and sleep disturbance. Simultaneously, the study involved the measurement of serum melatonin levels aiming at assessing the influence of fluvoxamine to melatonin levels and to observe the relationship with depression and sleep disturbance.

Materials and Methods

The subjects were cerebral infarction patients who were hospitalized at Nippon Medical School Hospital during the period from November 2006 to September 2009. The cerebral infarctions were diagnosed using magnetic resonance imaging (MRI) of the brain. This study was approved in advance by the ethics committee of our facility.

A stroke patient was assumed to be depressed if he or she was free of consciousness disorders, aphasia, or apparent dementia and had a score of 40 points or higher on Self-rating Depression Scale (SDS) conducted at least 3 weeks following the infarction. SDS is a simple, self-rated evaluation scale to determine the severity of depression (11). Nineteen patients diagnosed with depression state were used for this study. The ischemic stroke subtype was classified by the clinical categories of the National Institute of Neurological Disorders and Stroke (NINDS-III). The National Institutes of Health and Stroke Scale (NIHSS) was evaluated on the day of admission.

The 19 patients were divided into two groups, a treatment group (n=9) and control group (n=10). These patients did not have a medical history of psychosis. Among nine patients in the treatment group, six patients were complicated with hypertension, two patients were complicated with dyslipidemia, four patients were complicated with diabetes mellitus, two patients were complicated with atrial fibrillation, and one patient was complicated with chronic heart failure. Among ten patients in the control group, six patients were complicated with hypertension, five patients were complicated with dyslipidemia, three patients were complicated with diabetes mellitus, three patients were complicated with atrial fibrillation, two patients were complicated with hypertrophic cardiomyopathy, one patient was complicated with dilated cardiomyopathy, one patient was complicated with old cardiac infarction, and one patient was complicated with old cerebral infarction.

The 9 patients in the treatment group were treated with fluvoxamine (Depromel®: Meiji Seika Pharma Co., Ltd., Tokyo, Japan) once a day after supper (7:00 pm) at doses of 25 mg/day on days 1-3 after the start of the treatment period, 50 mg/day on days 4-6, and 75 mg/day from day 7 onward. The SDS and PSQI assessments were conducted before the fluvoxamine was commenced, and at 1, 2, and 4 weeks into the treatment period. PSQI is a self-administered questionnaire which assesses sleep quality and disturbances (12). PSQI consists of seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score. These component scores were considered to be effective to interpret the efficacy of fluvoxamine on sleep disturbance. Therefore, although PSQI is generally used to evaluate the quality of the sleep of the previous month, in this study PSQI was evaluated once in 1 week or 2 weeks and it was used for the short-term evaluation.

Before and at 4 weeks after the fluvoxamine administration was commenced, the patients were assessed by the Japan Stroke Scale for Depression (JSSD), the Japan Stroke Scale for Emotional Disturbance (JSSE), the Japan Stroke Scale for Motor Function (JSSM), and the Mini Mental State Examination (MMSE). The JSSD, JSSE, and JSSM are quantitative evaluation scales developed by the Japan Stroke Association for the assessment of post-stroke depression, post-stroke emotional disturbance, and post-stroke motor dysfunction (13, 14).

The serum melatonin level was measured twice a day (6:00 am and 6:00 pm) before the fluvoxamine was commenced, and at 1 and 2 weeks into the treatment period. Venous samples were collected from the patients and the sera were freeze-preserved until used for measurement by the RIA2 antibody method (SRL Co., Ltd., Tokyo, Japan).

The 10 control patients, who received no fluvoxamine, were evaluated by the same assessment scales and melatonin measurements. The patient backgrounds in the treatment and control groups were analyzed and compared by the Fisher’s exact test, Mann-Whitney U test, and T-test. Changes over time were analyzed by the Wilcoxon rank sum test and Paired-t test. A level of p<0.05 was regarded as significant.

Results

The treatment group consisted of 9 patients (7 males and 2 females) with an average age of 74.4±8.9. The control group consisted of 10 patients (8 males and 2 females) with an average age of 75.4±7.9 years. No significant differences between the treatment and control groups were found in age or sex, in the serum melatonin level, in the ischemic stroke subtype or stroke location, or in the scores from the NIHSS, SDS, PSQI, JSSD, JSSE, JSSM, and MMSE assessments (Table 1).

Table 2 and Fig. 1-5 show the scores from the evaluation scales and the variation in melatonin levels over time. In the treatment group, the mean score for SDS was 47.1±6.2 (mean ± SD) before the fluvoxamine was commenced, and 37.7±5.7, 38.5±14.6, and 35.2±7.9 at 1, 2, and 4 weeks into the treatment period, respectively. Compared to the score before the fluvoxamine was commenced, the score was signifi-
Table 1. Characteristics of the Study Patients by Group

<table>
<thead>
<tr>
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<th>treatment group n=9</th>
<th>control group n=10</th>
<th>p value</th>
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</thead>
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<tr>
<td>Age(years)</td>
<td>74.4±8.9</td>
<td>75.4±7.9</td>
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<td>Gender(Men)</td>
<td>7(78%)</td>
<td>8(80%)</td>
<td>0.21^a</td>
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<td>NIHSS score</td>
<td>5.3±2.9</td>
<td>6±2.4</td>
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<tr>
<td>SDS</td>
<td>47.1±6.2</td>
<td>47.2±8.7</td>
<td>0.74^c</td>
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<tr>
<td>PSQI</td>
<td>10.3±4.5</td>
<td>7.5±4.5</td>
<td>0.21^a</td>
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<tr>
<td>JSSE</td>
<td>3.7±1.3</td>
<td>3.2±1.2</td>
<td>0.40^b</td>
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<td>JSSE</td>
<td>2±1.5</td>
<td>1.6±1.5</td>
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<tr>
<td>JSSD</td>
<td>10±11.7</td>
<td>8±10.6</td>
<td>0.935^b</td>
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<td>JSSM</td>
<td>25.6±3.9</td>
<td>21.9±7.8</td>
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<td>Melatonin P.M.(pg/mL)</td>
<td>9.6±10.3</td>
<td>16.0±33.3</td>
<td>0.585^b</td>
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<td>Melatonin L.M.(pg/mL)</td>
<td>2.8±1.0</td>
<td>3.3±1.6</td>
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<td>Ischemic stroke subtype</td>
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<td>other</td>
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<td>Stroke location</td>
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<td></td>
</tr>
<tr>
<td>brainstem</td>
<td>5</td>
<td>1</td>
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</table>

There were no significant differences between the fluvoxamine-treated group and control group in melatonin levels, ischemic stroke subtype, stroke location, or any of the evaluation scores, p values for differences between the fluvoxamine-treated group and control group. a: Comparisons are by Fisher’s exact test. b: Comparisons are by the Mann-Whitney U test. c: Comparisons are by the t-test.

NIHSS: National Institutes of Health and Stroke Scale, SDS: Self Depression Scale, PSQI: Pittsburgh Sleep Quality Index, JSSD: Japan Stroke Scale (Depression Scale), JSSE: Japan Stroke Scale (Motor Function), MMSE: Mini Mental State Examination

cantly improved at 1 week into the treatment period. In the control group, the score was 47.2±8.7 at the start of observation, and 37.2±6.9, 38.3±7.4, and 38.8±8.8 at 1, 2, and 4 weeks into the observation, respectively. Compared to the score before the observation began, the scores were significantly improved at 1 and 2 weeks into the observation period (Fig. 1).

In the treatment group, the mean score for PSQI was 10.3±4.5 before the fluvoxamine was commenced, and 5.1±2.5, 6.2±2.2, and 5.0±3.1 at 1, 2, and 4 weeks into the treatment period. Compared to the score before the drug was commenced, the score was significantly improved at 1, 2, and 4 weeks into the treatment period. In the control group, the mean score was 7.5±2.5 at the start of observation and 6.4±4.8, 6.0±3.7, and 4.2±1.7 at 1, 2, and 4 weeks, respectively, indicating no significant improvement (Fig. 2).

In the treatment group, the mean score for JSSD was 3.2±1.2 at the start of observation and 2.0±1.4 at 4 weeks into the observation period, indicating no significant improvement (Fig. 3). In the treatment group, the mean score for JSSE was 2.4±1.5 before the fluvoxamine was commenced and 0.6±1.9 at 4 weeks into the treatment period. In the control group, the score was 1.6±1.5 at the start of observation and 0.6±1.3 at 4 weeks into the observation period. Both groups tended toward improvement, but not significantly. The JSSM and MMSE scores at 4 weeks after the start of treatment were not significantly different from the pre-treatment scores in either the treatment group or control group.

In the treatment group, the morning melatonin level (at 6:00 am) was 9.6±10.3 pg/mL before the fluvoxamine was commenced, and 68.2±72.3 pg/mL and 86.2±76.9 pg/mL at 1 and 2 weeks into the treatment period, respectively. In the control group, the morning melatonin level was 16.0±33.3 pg/mL at the start of observation, and 15.0±28.5 pg/mL and 8.7±12.3 pg/mL at 1 and 2 weeks into the observation period, respectively, indicating no significant increase (Fig. 4).

In the treatment group, the evening melatonin level (at 6:00 pm) was 2.8±0.0 pg/mL before the drug was commenced, and 4.9±3.0 pg/mL and 87.4±7.7 pg/mL at 1 and 2 weeks into the treatment period. This indicated a tendency toward increase, but not a significant one. The evening melatonin level in the control group was 3.3±1.6 pg/mL at the start of observation, and 3.4±1.7 pg/mL and 2.9±0.3 pg/mL at 1 and 2 weeks. Again, there was no significant increase in melatonin compared to the pre-observation level in the control group (Fig. 5).

Discussion

Fluvoxamine is a selective serotonin re-uptake inhibitor and antidepressant that confers its antidepressant effect by enhancing the serotonin system. Fluvoxamine is used for the treatment of depression and associated conditions, obsessive-compulsive disorders, social anxiety disorders, and so on. It has also been reported to confer favorable effects on depressive state after cerebral infarction (15). In this study we investigated the effects of fluvoxamine on depression state, sleep disturbance, and serum melatonin levels in patients with depressive state after cerebral infarction.

Fluvoxamine significantly improved the SDS scores in the treatment group at 1 week after the beginning of treatment. The statistically significant improvement was not seen after 2 and 4 weeks following the administration of the drug. Meanwhile, the control group showed a comparable significant improvement at 1 and 2 weeks. These findings indicate that the depressive state might also have improved naturally.

The mean SDS scores in this study were 47.1±6.2 in the treatment group and 47.2±8.72 in the control group. These scores indicated that the depressive state was potentially mild enough to subside naturally, without medication. Additionally, there is a possibility that SDS scores improved naturally along with the improvement of the reduction of cerebral blood flow and metabolism caused by the cerebral impairment after stroke during the period of acute stage to
Changes of SDS scores. In the fluvoxamine-treated group, the scores at 1 week after fluvoxamine was commenced were significantly lower than those before treatment. There were no significant differences, however, in the scores between pre-treatment and at 2 or 4 weeks into the treatment period. In the control group, the scores at 1 and 2 weeks after the start of observation were significantly lower than those at baseline. There were no differences, however, between the score at the start of observation and that at weeks 4 into the observation period. *p<0.05.

Changes of PSQI scores. In the fluvoxamine-treated group, the scores at 1, 2, and 4 weeks after fluvoxamine was commenced were significantly lower than those before the treatment. In the control group, the scores at 1, 2, and 4 weeks after the start of observation were not significantly different from those at baseline. *p<0.05.
ment period, there was no significant improvement in the SDS compared to the pre-treatment level in either the treatment or control group.

The JSSD evaluates a patient’s depressive state after a stroke. At 4 weeks into the treatment period, the control group showed no significant improvement in the JSSD score, whereas the treatment group did. Differences in the evaluation for depressive state were found between the JSSD score and SDS score in the treatment group. The JSSD mainly scores for depressive moods, guilt feelings, anxiety, impatience, sleep disturbance, and a disappearance of interest or joy. The items evaluated in the JSSD are all assigned specific weightings, hence the JSSD might reflect depressive conditions more sensitively than the SDS. Moreover, SDS is a questionnaire which includes the physical status, constipation, appetite and palpitation and it is influenced by the motor impairment due to stroke. Accordingly, JSSD which is not influenced by the motor impairment is considered to have improved after 4 weeks.

JSSE evaluates emotional disorders after a stroke. The JSSE score after 4 weeks of fluvoxamine treatment declined from the pre-treatment levels in both the treatment group and control group, indicating a tendency towards improvement. This indicates that the emotional disorders after a stroke may be alleviated naturally in due course. JSSM evaluates locomotor disorders after the onset of a stroke. The JSSM score after 4 weeks of fluvoxamine treatment showed no change from the pre-treatment level in either the treatment or control group. This indicates that fluvoxamine conferred no effect on the locomotor disorders.

Neither group showed any change in cognitive functions evaluated by MMSE, which suggests that fluvoxamine elicited no cognitive effects. This is at variance with another study in which cognitive improvements in response to treatments for depression were confirmed (16). We speculate that the almost normal MMSE score in the present patients before treatment may explain the lack of cognitive improvement in response to the treatment.

The PSQI scores in the treatment group improved significantly compared to those in the control group, indicating that fluvoxamine was effective for sleep disturbance. The melatonin levels measured at 6:00 am in the treatment group were significantly increased, presumably in response to the action of fluvoxamine administered after supper.

Melatonin is secreted mainly from the pineal gland, but various organs of the body have recently been reported to produce it. Melatonin secretion is controlled by innervation of the suprachiasmatic nucleus, the brain region identified as the biological clock. Thus, the melatonin concentration in blood shows a clear circadian rhythm, rising and peaking at night and decreasing in daytime. Melatonin engages in
phase-change action of the biological clock and a sleep pro-
motion action (17).

Melatonin is thought to be involved in sleep and mood
regulation, and changes in melatonin secretion kinetics are
thought to be a pathologic factor underlying depression.
Many reports have shown the relation between depression
and melatonin: the melatonin level decreases at night (7);
the phase of melatonin production shifts (8); decreased
melatonin level induces a depressive tendency (18). Mela-
tonin is used for the treatment of insomnia and disorders of
the sleep-wake rhythm, as well as for depression accompa-
nying sleep phase delay syndrome (19). The hormone is also
confirmed to be effective for alleviating sleep disturbance
and depressive symptoms in patients with major depres-
sion (20). Apart from sleep disturbances, there have also
been many reports demonstrating the efficacy of melatonin
on depression. Two recent reports have demonstrated the ef-
icacy of agomelatine, a melatonin receptor agonist, for
sleep disturbance and depression (21, 22).

Although there have been only a few reports on the
melatonin-increasing effect of antidepressants, some antide-
pressants are reported to enhance melatonin effects (9, 10).
The SSRI fluvoxamine inhibits the melatonin metabolism by
suppressing CYP1A2 and CYP2C19 in the liver, which sub-
sequently increases melatonin concentration in the blood-
stream (9). Consistent with previous reports, fluvoxamine
treatment increased melatonin levels in our stroke patients
suffering from depressive state. In addition to the increased
melatonin levels, our treatment group also showed a signifi-
cant improvement in sleep disturbance. We presume that the
increased melatonin in response to fluvoxamine and the as-
associated improvement in the melatonin circadian rhythm al-
leviated the sleep disturbance. Melatonin has an effect of
sleep promotion and phase-change action of the biological
clock. The effect of melatonin on sleep disturbance needs to
be clarified by further investigation in details of the sleep
onset, time and quality.

Sleep disturbance and depression are deeply associated.
Sleep disturbance is a frequent complication in patients with
depression, and a history of insomnia is a risk factor for de-
pression (23-25). The present treatment group showed more
improvement in the PSQI score than in the SDS score, re-
vealing an apparent effect of fluvoxamine on sleep distur-
bance. While many investigators have assumed that a de-
pressive condition can be improved by alleviating sleep dis-
turbance, our results revealed a slight dissociation between
sleep disturbance and relief of depression as assessed by
SDS. Several reasons may explain this discrepancy. The
present subjects, for example, were patients who presented
not with endogenous depression, but with depression state
after cerebral infarction. Our follow-up period was also rela-
tively short compared to those in other studies, and we
worked with a relatively small number of cases.

Fluvoxamine increased melatonin levels in the blood-
stream, markedly alleviated sleep disturbances, and im-
proved PSQI scores in patients with a depressive state after
cerebral infarction. Fluvoxamine may confer an antidepress-
sant effect by alleviating sleep disturbance, one of the major
symptoms of depression, via the inhibition of melatonin me-
tabolism.

The authors state that they have no Conflict of Interest (COI).

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