Onset of Clinical Effects and Plasma Concentration of Fluvoxamine in Japanese Patients

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It is widely accepted that selective serotonin reuptake inhibitors (SSRIs) require 2 to 4 weeks of administration before improvements in emotional symptoms of depression are seen. We evaluated whether early monitoring of Hamilton Rating Scale for Depression (HAMD) scores in patients treated with the SSRI fluvoxamine could predict antidepressant response, and also assessed the relationship between the onset of clinical response following the start of fluvoxamine administration and its plasma concentration. Twelve depressed patients (baseline HAMD score ≥15) received an initial dose of fluvoxamine (50 mg/d) followed by an optimized maintenance dose according to their clinical symptoms after 7 d. HAMD scores and plasma drug concentrations were determined at 7 and 28 d after the first administration. There were 7 responders and 5 non-responders on day 28, as evaluated by HAMD scores. The HAMD score for the responders was significantly lower than that for the non-responders on day 7 (mean±S.D., 11.6±6.1 vs. 26.6±6.5, p<0.006). Thus, the reduction in HAMD score on day 7 was clearly divided between responders and non-responders. On day 28, the plasma concentration of fluvoxamine in responders was lower than that in non-responders (14.2±10.5 ng/ml vs. 44.2±28.1 ng/ml, p=0.051). Furthermore, receiver operating characteristic curve analysis conducted on day 28 revealed an upper concentration threshold of 28.2 ng/ml (p=0.042), with none in the responder group above that level. Our results suggest that HAMD score after the first week of treatment with fluvoxamine and the upper threshold of plasma drug concentration could predict whether a patient is a non-responder.

Key words fluvoxamine; antidepressant response; Hamilton Rating Scale for Depression; plasma concentration

Depression is a common and major psychiatric disorder that affects as many as 20% of individuals within their lifetime.1,2) Those who suffer from major depression experience significant and pervasive symptoms, and, unfortunately, suicide is often the result of major depression that has not been diagnosed and treated adequately. A wide variety of pharmaceuticals are available for treating depression, including tricyclic antidepressants, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors (SSRIs). Although antidepressants are some of the most commonly prescribed drugs, inadequate treatment remains a serious concern, despite recent advances.3) In addition, it is widely accepted that antidepressants require approximately 2 to 4 weeks of treatment before improvements in emotional symptoms are seen.4–6) Such delayed onset of effect is clinically problematic, as it prolongs the impairments associated with depression, leaves patients vulnerable to an increased risk of suicide, increases the likelihood that a patient will prematurely discontinue therapy, and increases medical costs associated with severe depression.7)

Fluvoxamine is an SSRI that is widely used for treatment of depression and other psychiatric disorders, and has been suggested to have early effects when used as an antidepressant drug.8,9) In addition, the results of some trials have shown that significant improvements in Hamilton Rating Scale for Depression (HAMD) total scores achieved in the first few weeks were maintained after 6 weeks of treatment.10,11) Results of a recent meta-analysis also suggest that treatment with the SSRI leads to symptomatic improvements in patients with depression by the end of the first week of use.12) However, other studies failed to find statistically significant benefits of fluvoxamine over a placebo until after several weeks of treatment.13,14) Thus, a key question for physicians, pharmacists, and patients is whether the early effects of SSRIs such as fluvoxamine are clinically observable.

Therapeutic drug monitoring for tricyclic antidepressants has been well documented to improve the use of these agents for therapeutic management of depression15) and the plasma concentration of fluvoxamine has been correlated to clinical effect in several studies. However, others have reported a wide variability in the range of plasma concentrations among responders and found no correlation with dosage.16,17) Thus, available data do not indicate benefits from routine monitoring of plasma fluvoxamine concentration.

In the present study, we determined HAMD scores on days 7 and 28 after treatment with fluvoxamine in Japanese patients, and evaluated whether such score monitoring after the first week could predict antidepressant response. In addition, we assessed the relationship between the onset of clinical response of fluvoxamine and its plasma concentration.

MATERIALS AND METHODS

Drugs The study patients were treated with fluvoxamine...
Subjects Eighteen Japanese patients with depression being treated at the outpatient clinic of the Hamamatsu University School of Medicine from September 1999 to June 2000 were initially enrolled in this study. Six were later dropped from the study, as they did not continue the follow-up examinations. Thus, 12 patients (3 males, 9 females; 39.1±13.0 years old; body weight 53.4±9.6 kg) completed the trial (Table 1). Each met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)\(^{18}\) criteria for mood (n=8), anxiety (n=3), and eating (n=1) disorders (single or recurrent) with a minimum score of 15 on the 17 item version of the HAMD.\(^{19}\) None of the study patients were administered an antidepressant for the present episode. All were free of any significant health problems, as determined by clinical laboratory tests. The study protocol was approved by the Ethics Committee of Hamamatsu University School of Medicine and written informed consent was obtained from each patient. The initial dose of fluvoxamine was 50 mg/d, given in two equally divided doses after breakfast and dinner for the first week. Patients then received an optimized maintenance dosage according to their clinical symptoms after the first week. Benzodiazepines and digestive enzyme preparations were allowed during the study according to the clinical symptoms of the patient.

Depressive symptoms were evaluated by scores for the 17 item version of the HAMD on days 0 (baseline), 7, and 28 after starting administration. Treatment compliance was monitored by detailed interviews with patients. A patient with a 50% or greater reduction in HAMD score on day 28 as compared to their baseline score was defined as a responder, according to the practice guideline for the treatment of patients with major depressive disorder published from American Psychiatric Association.\(^{20}\) On days 7 and 28, blood (7 ml) was collected before the morning dose and plasma samples were stored at \(-80^\circ\)C until determination of fluvoxamine concentration.

**Determination of Plasma Concentration of Fluvoxamine** The concentration of fluvoxamine in plasma was determined using high-performance liquid chromatography/tandem mass spectrometry (LC/MS/MS), as previously described.\(^{21}\) Briefly, an internal standard solution of clovoxamine fumarate was added to 0.5 ml of human plasma, then the plasma was eluted with 4 ml of diethyl ether and the organic phase was dried under nitrogen at 40 °C. The residue thus obtained was dissolved in 200 μl of a mobile phase (methanol containing 0.1% acetic acid), and 20 μl of that sample was injected into the LC/MS/MS system. A reverse phase column (Waters SYMMETRY C8, 3.5 μm, 2.1×100 mm) was employed for liquid chromatography and the sample was eluted with a mobile phase at a rate of 0.2 ml/min. Mass spectrometry was performed with ionization in electrospray ionization mode, and the monitoring ion was m/z 319→71 for fluvoxamine and m/z 285→71 for clovoxamine for monitoring positive ions. The detection limit was 0.5 mg/ml of fluvoxamine.

**Data Analysis** Data are shown as the mean±S.D. in the text. All statistical analyses and receiver operating characteristic (ROC) curve analysis were conducted using JMP (ver. 8, SAS Institute Inc., Cary, NC, U.S.A.). The significance of differences between groups was assessed using a Mann–Whitney U test. Pearson’s correlation coefficients were used to assess the interrelationships between plasma concentration of fluvoxamine and clinical response. Based on the ROC curve, the threshold concentration of fluvoxamine (cutoff point) for therapeutic response (reduction in HAMD score) was calculated from the maximum percent difference between responders and non-responders.\(^{22}\) The sensitivity and specificity of the ROC curve was assessed by \(\chi^2\) analysis. A p-value of 0.05 or less was considered statistically significant.

**RESULTS**

Of the 12 patients who finished the trial, 7 patients were classified as responders (58.3%; 2 males, 5 females) and 5 patients as non-responders (41.7%; 1 male, 4 females), as evaluated by HAMD scores obtained on day 28. There was no significant difference for the HAMD scores at baseline (day 0) between the responders and non-responders (Table 2). The HAMD score for responder patients decreased during fluvoxamine treatment, while the score for non-responders was unchanged, and significantly lower for responders than non-responders on days 7 (11.6±6.1 vs. 26.6±6.5, \(p=0.006\)) and 28 (7.7±6.5 vs. 21.4±8.8, \(p=0.023\)). In addition, the reduction in HAMD score as compared to the baseline in the

<table>
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<th>Patient No.</th>
<th>Gender</th>
<th>Age (year)</th>
<th>Body weight (kg)</th>
<th>DSM IV criteria</th>
<th>Dose of fluvoxamine (mg/d)</th>
<th>HAMD score</th>
<th>Responder/ non-responder</th>
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<tr>
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responders group was significant as compared to the non-responders on day 7 (55.0 ± 23.2% vs. −24.2 ± 43.9%, Fig. 1). Thus, the reduction in HAMD score on day 7 was clearly divided between responders and non-responders, as each of the patients in the former group showed a greater than 31% reduction, while each patient in the latter group showed a less than 19% reduction.

Plasma concentrations of fluvoxamine were determined before the morning dose on days 7 and 28. There was no significant difference between responders and non-responders on day 7 (10.0 ± 3.2 ng/ml vs. 9.6 ± 5.3 ng/ml, p = 0.75, Fig. 2a), while the concentration in responders tended to be lower than that in non-responders (14.2 ± 10.5 ng/ml vs. 44.2 ± 28.1 ng/ml, p = 0.051, Fig. 2b) on day 28. We used an ROC curve to arrange the plasma concentrations of fluvoxamine on day 28 in ascending order, which represented an upper concentration threshold of 28.2 ng/ml (p = 0.042) between responders and non-responders, with no patient in the responder group found above this level (Fig. 3). There was no significant correlation between the plasma concentration of fluvoxamine and reduction in HAMD score on day 7 (r = 0.285, p = 0.369, Fig. 4a) or 28 (r = 0.523, p = 0.081, Fig. 4b).

**DISCUSSION**

This study aimed to evaluate whether early monitoring of HAMD score for depressed patients receiving treatment with fluvoxamine could predict an antidepressant response. We determined HAMD scores on days 7 and 28 after starting the treatment in Japanese patients, and also assessed the relationship between the onset of clinical response to fluvoxamine and its plasma concentration. Our results showed that the reduction in HAMD score 7 d after the start of treatment with fluvoxamine in responders was significantly higher than that in non-responders, indicating that HAMD scores after the first week of treatment of fluvoxamine can identify depressed patients who respond to the drug. Some trials reported that significant improvements in HAMD total score achieved in the first few weeks after beginning treatment were maintained after 6 weeks.10,11) In addition, results of a recent meta-analysis showed that treatment with an SSRI was associated with symptomatic improvement in depression by the end of the first week of use and the improvement continued at a decreasing rate for at least 6 weeks.12) The present findings were in line with those previous reports.

The plasma concentration of fluvoxamine in the responders on day 28 was significantly lower than that in the non-responders, whereas there was no significant difference between the groups on day 7. According to the protocol of this
study, the maintenance dose of fluvoxamine was adjusted based on clinical symptoms after the first week of treatments and it is likely that the attending physicians increased the dose for non-responders in order to obtain sufficient effects to improve their depressive symptoms. In fact, 4 of 5 patients in the nonresponder group had their fluvoxamine dose increased from 50 to 100 mg/d. Interestingly, our ROC analysis represented an upper concentration threshold of 28.2 ng/ml, increased from 50 to 100 mg/d. Similarly, Härtter et al. found that the upper threshold of fluvoxamine concentration was 85 ng/ml in German patients with depression by using ROC analysis conducted on day 14. Moreover, the plasma concentrations of fluvoxamine in our study did not show a significant relationship with clinical response in any of the present patients (Fig. 4). Therefore, our results suggest that a high plasma concentration of fluvoxamine does not provide superior results, and that monitoring of the concentration as early as 2 or 4 weeks after beginning treatment would be useful to predict whether a patient is a non-responder.

The findings in this study are limited by the relatively small sample size. In addition, we performed this open-label trial without a placebo, because it was conducted in a clinical setting, and cannot exclude the possibility that the improvement of symptoms in some patients was the result of a placebo effect. Additional controlled studies with larger numbers of patients conducted over a longer period are necessary to evaluate whether HAMD score monitoring after the first week can predict an antidepressant response to fluvoxamine treatment and assess the benefits of therapeutic drug monitoring.

In conclusion, our findings suggest that the results of HAMD score after the first week of treatment with fluvoxamine and an upper threshold of plasma drug concentration are able to identify responders to the drug.

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REFERENCES