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Time-Dependent Clearance Decrements of Fluvoxamine in Depressed Inpatients

A Clinical Evaluation

To the Editors:

The selective serotonin reuptake inhibitor, fluvoxamine, is used in the treatment of depressive and anxiety disorders. Fluvoxamine is well absorbed after oral administration. Because of rapid and extensive hepatic first-pass biotransformation, the amount of unchanged drug reaching the systemic circulation is approximately 53%. The plasma protein binding is low (77%). The mean half-life is 15 hours.[1]

In a case report of fluvoxamine intoxication, in which fluvoxamine concentrations were followed for 1 week, nonlinearity was present at serum levels of more than 150 ng/mL.[2] This plasma concentration is well inside the range of steady-state concentrations reached after therapeutic dosages.[3] In a study with 10 healthy volunteers, fluvoxamine was administered in increasing doses.[4] In this study, fluvoxamine also exhibits time-dependent kinetics within the dose range of 25 mg/d during the first week, with increasing dosage per week until 200 mg/d in the fourth week. This nonlinear increase is significantly more pronounced in men than in women with subtherapeutic dosages.[5]

This indicates that there can be a considerable variability in plasma levels relative to the treatment dose. As the dose increases, the plasma level of fluvoxamine increases more than would be predicted from the lower dose. Because only limited data are available on the pharmacokinetics of fluvoxamine in depressed patients, we calculated fluvoxamine dose to fluvoxamine plasma concentrations as ratios for each patient participating in a double-blind trial with fluvoxamine after attaining a predefined plasma level.[6] Plasma levels of fluvoxamine were obtained weekly during this trial. If the plasma level increases more compared with the dosage, the ratios over time would change accordingly, and time-dependent steady-state plasma concentrations were assumed to be present.

The study was performed at the department of Psychiatry of the Erasmus Medical Center in Rotterdam (EMCR). Patients participated in a double-blind, randomized, controlled trial comparing fluvoxamine with imipramine after a single-blind placebo run-in period of 4 days.[6] Dosages of drugs prescribed for somatic indication were optimized before the trial and remained at the same dosage during the trial. The smoking habits of the patients were not assessed; the smoking habits of the patients remained unchanged during this study. Included were patients aged 18 to 65 years who had a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnosis of depressive disorder and a Hamilton Rating Scale for Depression score of 17 or higher.[7]

Starting with 75 mg, tablets of fluvoxamine were administered once a day at 10 PM. After 2 days, the dose was doubled unless severe side effects were observed. The pharmaceutical laboratory of the EMCR monitored blood levels once a week. Blood samples were collected 12 hours after the last evening dose. The hospital pharmacist advised on the adjustment of the dosage based on the targeted plasma level according to a predefined dosage table. This was communicated to the treating physician in percentages to prevent unblinding. The treating physicians were not involved in the ratings of this study. Doses of fluvoxamine were adjusted to obtain predefined plasma levels. The predefined plasma level for fluvoxamine was 150 to 200 ng/mL (100% equals 175 ng/mL).[8]

Fluvoxamine plasma concentrations were measured using a high-performance liquid chromatographic method with ultraviolet detection at 260 nm. Fluvoxamine and internal standard amitriptyline were extracted from 1 mL plasma by using Bond Elut TCA columns (Varian, Middelburg, The Netherlands). After application of the plasma, the column was washed with 1 mL acetonitrile (20% vol/vol), and fluvoxamine and internal standard were eluted with 600 μL 0.6% (wt/vol) diethylamine in methanol. The eluate was evaporated to dryness under nitrogen. Finally, the residue was reconstituted in 300 μL of mobile phase ([480 mL 0.01 M phosphate buffer + 4 mL butylamine + phosphoric acid 85% to pH 7.3] + 300 mL methanol + 220 mL acetonitrile), and a sample of 100 μL was injected into the analytical column (ChromSpher, Varian). The limit of quantification for fluvoxamine was 10 ng/mL. In the range of 50 to 300 ng/mL, interassay and intra-assay coefficients of variation were less than 5%.

Outcome was assessed 4 weeks after attaining these predefined plasma levels. If patients achieved remission, fluvoxamine and the weekly monitoring of the plasma level continued until discharge. Concurrent psychotropic drugs were not allowed except for 1 to 6 tablets a day containing 45 mg of an extract of valerian in case of severe anxiety or insomnia; this extract was assumed to be without antidepressant effect. According to the protocol, in exceptional cases, lorazepam (1–3 mg/d for intolerable anxiety) or haloperidol (1–10 mg/d in case of intolerable psychotic symptoms) was allowed. A research nurse systematically assessed side effects.

Time dependency of steady-state plasma concentrations of fluvoxamine was assumed to be present if a positive time trend of ratios between steady-state plasma concentrations and fluvoxamine doses could be demonstrated. All

plasma levels and doses available after attaining the first predefined adequate plasma level for all patients were used for the statistical analysis of the kinetics. Using a random coefficients model, we tested against an average linear trend in time (measured in weeks) of the logarithm of these ratios. Our model is described as the logarithm of the ratio that is the intercept or the first plasma level with addition of a coefficient of the slope times weeks and, additionally, a residue (log[ratio] = a + b × weeks + residue). The intercept and slope with time were assumed to be randomly (normally) distributed between patients. Sex was included in the model as a fixed factor allowing the testing of the modification by sex of the slope with time. The within-patients residual term was assumed to have a week-to-week autocorrelation according to a first-order autoregressive structure. Statistical significance was defined as $P < 0.05$. For evaluating the random coefficient model, SAS version 8 (PROC MIXED) was used.

The ethics committee of the EMCR approved the protocol. The protocol was carried out in accordance with the ethical standards laid down in the Declaration of Helsinki.

The mean time to reach the predefined plasma levels was 12.6 days (SD, ±6.2 days; range, 4–33 days) for fluvoxamine. The mean daily dose during the 4 weeks after attaining the first predefined plasma level for fluvoxamine was 287.5 mg/d (SD, ±265.8 mg/d; range, 150–800 mg/d), with a mean plasma level of 215.0 ng/mL (SD, ±39.98 ng/mL; range, 108.6–325.0 ng/mL). The number of patients was 39, of whom 80% were women (n = 31), mean age was 49 years (SD, ±17 years), and range was 34 to 65 years. The maximum number of weeks to estimate the ratio between steady-state plasma levels and doses of fluvoxamine was 23 weeks; the mean numbers of weeks was 11.5 (SD, ±6.93). The average dosage during this period for the participating patients (n = 39) was 214.6 mg/d (SD, ±153.77 mg/d); the average plasma level was 186.0 ng/mL (SD, ±70.38 ng/mL).

On average, the ratio of steady-state plasma levels to doses of fluvoxamine increased by 2.2% per week (95% confidence interval [CI], 1.3–3.1; $P < 0.0001$) across both sexes. In men, this was 3.5% (95% CI, 1.3–5.6; $P = 0.002$), and in women, this was 1.7% (95% CI, 1.2–2.2; $P < 0.0001$); the difference between the sexes was not significant ($P = 0.12$).

Figure 1 shows the mean observed ratios of the plasma level compared with the dosage per week. We back-transformed the logarithm of the ratios as predicted by our model and also plotted these results in Figure 1.

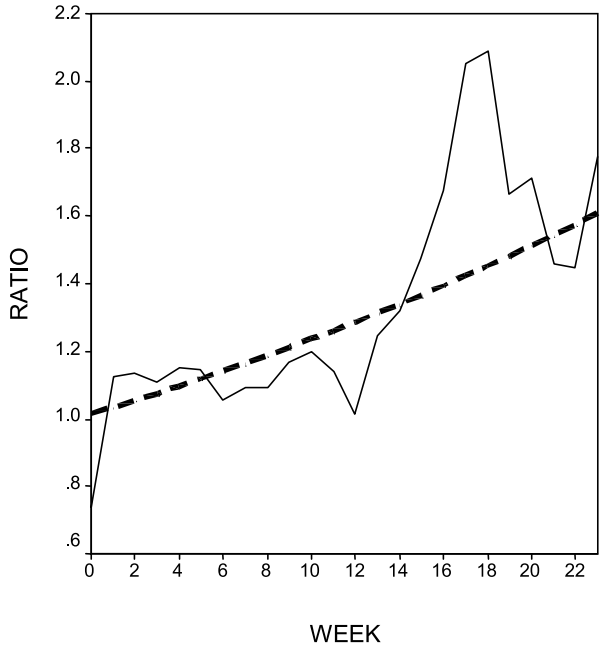

FIGURE 1. The mean observed ratios ((mg/day)/(ng/mL)) of fluvoxamine dose (mg/day) to fluvoxamine plasma concentrations (ng/mL) per week (solid line) and the predicted logarithmic ratio (dotted line), using all the plasma levels obtained during the trial.

DISCUSSION

This is the first study that demonstrates that time-dependent kinetics of fluvoxamine occur in depressed inpatients observed during an average period of 11 weeks. An earlier study used healthy subjects with weekly dosage increments from 25 up to 200 mg/d during 4 weeks without reaching steady state.[4]

The present study demonstrates that the fluvoxamine dosage has to decrease to attain the used predefined plasma level range used in this study. The logarithm of the ratios of plasma level with fluvoxamine dosage increased by 2.2% per week during an average period of 11 weeks. In our population, we could not detect a plateau phase to this increment; a longer period of measurement may be needed to establish the existence of a plateau phase. The mean plasma level during the 4 weeks after attaining the first predefined plasma level for fluvoxamine was 215.0 ng/mL (SD, ±39.98 ng/mL; range, 108.6–325.0 ng/mL). This level was well outside the predefined range of 150 to 200 ng/mL. The latter can be due to the difficulty of dosing a drug with time-dependent pharmacokinetics.

The study also shows that the dose of fluvoxamine has to be relatively high to obtain the targeted plasma level compared with average dosages used in clinical practice and research. This was also clinically shown in a trial in which

high dosages of fluvoxamine were effective in the treatment of psychotic depressed patients.[9] The reason for time-dependent clearance of fluvoxamine before reaching a steady state can be nonlinearity. This nonlinearity is not the Michaelis-Menten saturation kinetics of a single metabolic pathway, but a more complex metabolic picture involving multiple pathways.[4]

Because marked sex differences in pharmacokinetics were found (with women developing higher plasma concentrations), we estimated the ratios for both sexes. No significant difference in ratio was found. This could be due to the sex difference being shown to exist at a dosage of 100 mg/d and disappeared after the dosage was doubled.[5] Our dosages were mostly far more than 100 mg/d, and this could have influenced the nonsignificant difference in ratio between men and women. The disappearance of the difference in pharmacokinetics between men and women at a higher dosage suggests the participation of a saturable enzyme that is more active in male than in female subjects. Two studies have reported that a higher plasma concentration of fluvoxamine is associated with more adverse effects.[3,4] Techniques to improve individual dosing should provide the means to decrease the incidence of side effects and increase the response rates. These techniques should involve plasma level determination over an extended period of treatment considering that steady-state plasma concentrations of fluvoxamine are time-dependent. It is not clear, however, which plasma levels should be aimed at because data on the relation between plasma levels and effect are scarce.[8,10] In this respect, the range for a maximum response with fluvoxamine of 160 to 220 ng/mL reported by Foglia et al[8] may prove to be useful.

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