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BIOAVAILABILITY OF FLUVOXAMINE GIVEN WITH AND WITHOUT FOOD

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ABSTRACT

The influence of concomitant food intake on plasma concentrations of the antidepressant drug fluvoxamine maleate was investigated in a two-way, crossover study design. Eight male and four female healthy, young volunteers received a single oral dose of fluvoxamine maleate (50 mg, tablet) on two occasions: after an overnight fast and immediately after a breakfast. Food did not affect maximum fluvoxamine plasma levels (C_{max}), or the time to reach C_{max} (t_{max}). The plasma AUC of fluvoxamine was on average 7 per cent lower in the fed than in the fasted state. It is concluded that the effect of food on the pharmacokinetics of fluvoxamine is negligible.

KEY WORDS Fluvoxamine maleate Food interaction Pharmacokinetics

INTRODUCTION

Fluvoxamine maleate (Figure 1) is a selective serotonin reuptake inhibitor[1] with antidepressant properties in humans.[2] In contrast to the first-generation tricyclic antidepressants, fluvoxamine has much less anticholinergic, sedative, and cardiovascular side-effects. In addition, onset of action of fluvoxamine seems more rapid. Side-effects of fluvoxamine include nausea and vomiting, mainly during the first days of therapy.

Fluvoxamine is completely absorbed from the gastrointestinal tract[3] and is nearly completely metabolized in the liver. Approximately 4 per cent of an oral dose is excreted unchanged in urine (Duphar, data on file). Also metabolites are excreted in urine.[3] The elimination half-life of the parent compound is about 15 h. The absolute bioavailability of fluvoxamine is not yet known, because of the unavailability of a parenteral formulation. Since fluvoxamine is generally administered with food to avoid gastrointestinal side-effects, a study

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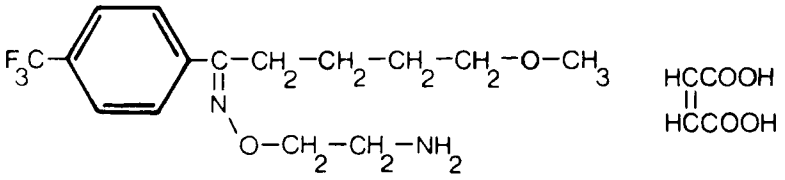

Figure 1. Structure of fluvoxamine maleate

was conducted to assess the influence of concomitant food intake on the plasma concentration profile of fluvoxamine.

METHODS

Subjects

Twelve healthy volunteers (eight males, four females), aged 18 to 30 years with body weights 55 to 91 kg, participated in this study. Cardiovascular and other relevant diseases were excluded by medical history, physical examination, and appropriate laboratory tests. Females had a negative pregnancy test. None were on any medication (including oral contraceptives) during the study or (at least) in the preceding week. Beverages containing alcohol were not permitted in the period from 24 h preceding to 48 h after each fluvoxamine dose; caffeine was not permitted on the days when fluvoxamine was taken.

The protocol was approved by an appropriate Institutional Review Board. All subjects gave written informed consent before entering the study.

Protocol

In an open, randomised, crossover study design the participants received on two occasions, separated by a 1-week washout period, a single, oral dose of 50 mg of fluvoxamine maleate. The drug was given as an instant-release tablet, coated with hydroxypropylmethylcellulose (HPMC), which was developed to mask the bitter taste of fluvoxamine maleate.

The experiments started after an overnight fast. An indwelling cannula with a heparin lock was inserted in a forearm or elbow vein of the subjects. On one occasion the subjects received, 15 min before fluvoxamine dosing, a standardized breakfast consisting of 2 eggs, 2 slices of white toast, 1 tablespoon of margarine, 1 tablespoon of jam, 240 ml orange juice and 240 ml water. The fluvoxamine tablet was taken either with the water or with the orange juice, at the end of breakfast. Two hours after dosing, they drank another 240 ml water. On the other occasion, the subjects remained fasting, and swallowed the tablet with 480 ml water. Two hours after dosing, they drank 240 ml orange juice.

Apart from these dietary differences, the two study sessions were identical. Five hours after dosing all participants received a standardized lunch. After

that no further food restrictions existed. Eight hours after dosing, the participants left the clinical unit.

Blood samples (10 ml) for determination of plasma concentration of fluvoxamine were taken before dosing and 1, 2, 3, 4, 5, 6, 8, 12, 24, 32, 48, and 72 h after drug intake. Samples up to 8 h were drawn through the indwelling cannula, in heparinised syringes; the remaining samples were taken at the clinical unit, by venepuncture (heparinised Venoject® tubes).

Plasma was promptly separated by centrifugation and frozen (−20°C) in labelled polycarbonate tubes for transport to Duphar, Weesp, The Netherlands. Plasma concentrations of fluvoxamine were determined by a specific gas chromatographic assay with electron capture detection. This assay allows quantification of fluvoxamine in plasma down to 2 ng ml^{-1}.[4]

Data evaluation

Observed values of the peak plasma concentrations, and time of peak were used as estimates of C_{max} and t_{max}, respectively. The area under the plasma concentration–time curve, AUC, was calculated by the lin-log trapezoidal method. For each individual, AUCs reported are those values obtained under fed and fasting conditions up to the last common time point at which there were measurable plasma levels of fluvoxamine. This was considered a valid approach, since from 5 h after dosing onwards, the experimental conditions were the same in the two sessions and on all occasions, except one, plasma levels could be measured up to at least 24 h.

In essence, AUC and C_{max} data were treated as if generated in a two-period, crossover bioequivalence study with fluvoxamine alone and fluvoxamine with food as the two dosage forms. The US Food and Drug Administration (FDA) has adopted the two one-sided tests procedure,[5] and this procedure (which is operationally identical to the procedure of declaring equivalence if the 90 per cent confidence interval for the difference between two dosage forms is contained in the equivalence interval, e.g. 0·80–1·20) was used for evaluation of the data from this study.

The analysis of AUC and C_{max} was done after logarithmic transformation of the data,[6] because logarithmic values of fluvoxamine AUC and C_{max} are more normally distributed than untransformed values, and because normality is a prerequisite for application of ANOVA.

Since AUC values have not been evaluated after extrapolation to infinity, but up to the last common time point in the individual's two curves, separate analyses have been carried out for subjects having t_{last} not later than 24 h after dosing ($n=6$), and for subjects with t_{last} at 32 h or later ($n=6$).

The partial imbalance due to mistakenly reversing the planned treatment sequence for one subject was accounted for by using the type III SS of SAS®—procedure GLM[7,8]; t_{max} values were compared using Wilcoxon's Signed Rank test.

RESULTS

A representative pair of individual plasma concentration vs time curves is shown in Figure 2. Maximal plasma concentrations were reached in 4 to 12 h, the peak plateau being relatively broad. As could be expected in this study design, the terminal parts of the two curves paralleled.

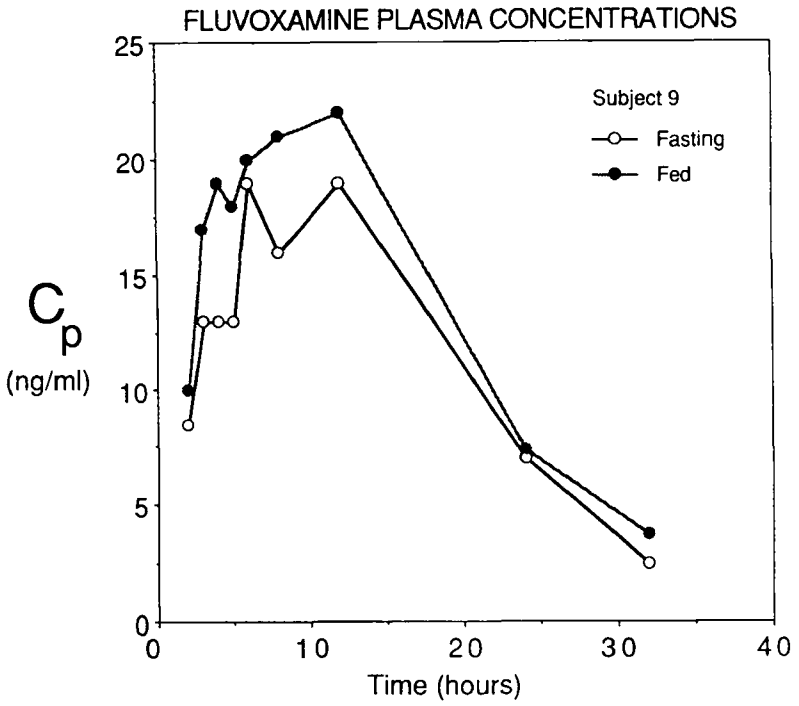

Figure 2. Plasma concentrations of fluvoxamine after oral administration under fasting (open circles) and fed conditions (closed circles)

Individual plasma pharmacokinetics of fluvoxamine, including descriptive statistics, is given in Table 1. Median values for C_{max} and t_{max} of fluvoxamine with and without concomitant food intake were essentially the same. The median AUC-ratio fed over fasted was equal to one. For the six subjects with $t_{last} \leq 24$ h, the AUC-ratio (with 90 per cent confidence limits) was 0·90 (0·60–1·32). For the six subjects with $t_{last} \geq 32$ h, these values were 1·00 (0·87–1·14). Because these ratios were not significantly different, all AUC-data were combined for the final analysis, which is given in Table 2. On average, the AUC of fluvoxamine in the fed state was 7 per cent lower than in the fasted state. C_{max} values were, on average, 3 per cent higher in the fed state. Intra-

individual comparisons of C_{max}, t_{max}, and AUC did not show an influence of concomitant food intake on the pharmacokinetics of fluvoxamine. Fluvoxamine, at single doses of 50 mg, was very well tolerated.

Table 1. Pharmacokinetic parameters of fluvoxamine after oral administration to fasting and fed subjects

Subject	C_{max} (ng ml^{-1}) Fasting	Fed	t_{max} (h) Fasting	Fed	AUC (ng h ml^{-1}) Fasting	Fed	t_{last} (h)	AUC-ratio fed/fasting
1	19	17	6	12	571	587	72	1·03
2	23	22	6	6	439	415	32	0·94
3	23	29	8	3	360	376	32	1·05
4	15	14	5	3	102	65	12	0·63
5	21	32	3	2	397	314	32	0·79
6	11	11	8	5	114	135	24	1·18
7	12	11	12	8	240	236	32	0·98
8	7·5	18	4	2	102	155	24	1·51
9	19	22	6	12	341	405	32	1·19
10	12	10	3	8	167	125	24	0·75
11	27	14	5	5	360	176	24	0·49
12	9·5	12	3	12	150	184	24	1·23
Arithmetic mean	17	18			279	264		0·98
Median	17	16	6	6				1·01

Table 2. Summary statistics (ANOVA) for AUC and C_{max}, after logarithmic transformation of AUC and C_{max} values

Source	d.f.	ln (AUC) mean square	Pr(F)	ln (C_{max}) mean square	Pr(F)
Subjects	11	0·732	<0·001	0·247	0·02
Periods	1	0·044	0·37	0·175	0·11
Fed vs fasting	1	0·033	0·44	0·007	0·74
Within subjects	10	0·050		0·058	
Ratio fed/fasting		0·93		1·03	
90% Confidence limits		0·78–1·10		0·86–1·24	

DISCUSSION

This study was designed to establish the influence of concomitant food intake on the pharmacokinetics of orally administered fluvoxamine maleate. C_{max}, t_{max}, and AUC were chosen as useful indicators. A difficulty in the interpretation

of AUC values was that it turned out to be impossible to measure the concentration–time profile up to 72 h after dosing, or to extrapolate AUC to infinity by linear regression analysis of the terminal part of the curve. However, it was judged reasonable to compare AUC values up to the same time point of both curves since, if differences existed, they would be observed during the gastrointestinal transit of fluvoxamine. The participants received a lunch 5 h after dosing, and therefore differences in terminal concentration decay are likely to depend on factors other than gastrointestinal absorption of fluvoxamine. In the present study, the mean *intra*-individual coefficient of variation in AUC was 22 per cent, which is somewhat higher than the *intra*-individual coefficient of variation of about 14 per cent which was found in a three-way, crossover study with three (bioequivalent) dosage forms, i.e. an oral solution, a hard gelatin capsule, and the same kind of tablet formulation as used in the present study (Duphar, data on file). This means that, as could be expected, the *intra*-subject variation is increased when an additional experimental variable (food) is introduced.

Fluvoxamine is usually given chronically. However, this does not mean that the data generated in this study are not applicable to multiple dosing conditions, since bioequivalence is basically a matter of rate and extent of absorption and of first-pass metabolism of unit doses of the active drug.

The basic clinical question underlying this study was whether concomitant food intake could reduce the incidence of nausea and vomiting in patients taking fluvoxamine. As a consequence, it needed to be assessed whether plasma concentrations (and hence possibly therapeutic efficacy) would be affected by concomitant food. Clearly it has not been possible in this study to address the question whether the incidence of nausea and vomiting was indeed reduced when fluvoxamine was taken with food.

It is concluded that the effect of food on the pharmacokinetics of fluvoxamine is negligible.

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