BIOPHARMACEUTICS & DRUG DISPOSITION, VOL. 14, 291–296 (1993)

PHARMACOKINETICS OF FLUVOXAMINE MALEATE AFTER INCREASING SINGLE ORAL DOSES IN HEALTHY SUBJECTS

M. H. DE VRIES*, J. VAN HARTEN, P. VAN BEMMEL AND M. RAGHOEBAR

Clinical R&D Solvay Duphar B.V., P.O. Box 900, 1380 DA Weesp, The Netherlands

ABSTRACT

The pharmacokinetics of fluvoxamine after single oral administration of 25, 50, and 100 mg fluvoxamine maleate was studied in a three-way cross-over study in 12 healthy male subjects. Fluvoxamine was administered orally in a solution. For dose-proportionality, AUC, and C_{max}–dose relationships were evaluated by linear regression. Plasma concentrations increased in a linear dose-dependent manner in the dose range between 25 and 100 mg; $t_{½}$ and T_{max} showed no significant differences among treatments. Fluvoxamine was well tolerated.

KEY WORDS Fluvoxamine Pharmacokinetics Dose-dependency Human

INTRODUCTION

Fluvoxamine maleate is a potent and selective serotonin reuptake inhibitor[1] with documented antidepressant properties in humans.[2,3] In contrast to the first-generation tricyclic antidepressants, fluvoxamine has fewer anticholinergic, sedative, and cardiovascular side-effects.

The disposition of fluvoxamine in humans has been described in recent years.[2,4,5] The results of these studies indicate that fluvoxamine is completely absorbed from the gastrointestinal tract[4] and is metabolized in the liver to inactive metabolites, which are subject to renal excretion. Renal excretion of unchanged fluvoxamine is negligible. Plasma concentrations are not affected by concomitant food intake.[5] Binding to plasma proteins is moderate (77 per cent).[6] The purpose of this study was to evaluate the dose proportionality of 25, 50, and 100 mg single oral doses of fluvoxamine maleate.

*Addressee for correspondence.

0142-2782/93/040291-06$08.00

Received 4 February 1992
Revised 28 October 1992

MATERIALS AND METHODS

Twelve male volunteers ranging in age from 22 to 41 years (mean: 30 years) and in weight from 54 to 86 kg (mean: 73 kg), participated in this oral, triple cross-over study. The study was approved by an Institutional Review Board.

All volunteers signed an informed consent form before being included. The subjects were in good health as established by pre-study medical assessment which included medical history, physical examination, and laboratory tests.

Fluvoxamine maleate was supplied by Duphar B.V. in crystalline form in bottles, containing unit doses of either 25, 50 or 100 mg. One day before dosing, the contents of each bottle were dissolved in 100 ml water. The medication was randomized so that each of the six possible treatment sequences occurred twice. The time interval between successive drug intakes was 7 days for each subject.

Subjects selected for the study were admitted to the investigational unit for the first 24 h after each drug intake, after which they were allowed to resume their normal activities. The drug was administered in the morning. Subjects were required to abstain from alcohol during the 24 h before drug intake and until the last blood sample (at 72 h) had been drawn. No concurrent medication was allowed. The subjects fasted during the 10 h prior to drug intake.

The drug solution was taken with water so that the total fluid intake was 250 ml, after which no food or fluid was permitted for 3 h. A light breakfast was then taken and later on the first day a light lunch and supper was allowed.

Blood samples of 10 ml were drawn in heparinized syringes just before dosing and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 32, 48, and 72 h after dosing. The samples were centrifuged and the plasma was kept deep-frozen until analysis.

During each study period, subjects were asked to report any adverse events and the investigator was asked to record both these and any other signs observed by either the investigator or his staff.

Drug assay

Plasma concentrations of fluvoxamine were determined by electron capture gas chromatography,[7] using the structural analogue clovoxamine as internal standard.

This assay allows quantification of fluvoxamine (calculated as free base) in plasma down to 1 ng ml^{-1} (1 mg of the maleate corresponds to 0·733 mg of the free base).

Pharmacokinetic calculations

Maximum plasma concentration, C_{max}, was the highest experimental plasma concentration and T_{max} was the time for C_{max}. The areas under the plasma curves (AUC) were calculated using the modified trapezoidal method of Chiou[8]

and extrapolated to infinity by C_t/λ, where C_t is the last measurable plasma concentration and λ is the elimination rate constant.

The elimination rate constants were calculated by nonlinear regression of the plasma concentrations vs time curves, using the FORTRAN computer program NONLIN of Metzler *et al.*[9] Initial parameter estimates were obtained by means of the FORTRAN computer program CSTRIP of Sedman and Wagner.[10] The latter program indicated the best fit for an open one-compartment system, so this system was used for the nonlinear regression analysis.

Statistics

A preliminary inspection of the areas under the plasma curves (AUC) and the peak plasma levels (C_{max}) suggested that the variability in the observations, as could be expected, was roughly proportional to their magnitude. Therefore the data for both responses were subjected to an analysis of variance after logarithmic transformation, specifying effects for subjects, session, and treatments.

In the case of dose proportionality, the treatment means are expected to match closely with a straight line through the origin. Hence, the *F*-test for deviations from this regression served as a test for disproportionality. In addition, 90 per cent confidence intervals for the dose-normalized AUC and C_{max} ratios according to Schuirmann[11] were calculated (two one-sided tests). In bioequivalence studies, equivalence of doses within a range regarded as clinically relevant is usually tested by calculation of such confidence intervals. A clinically relevant

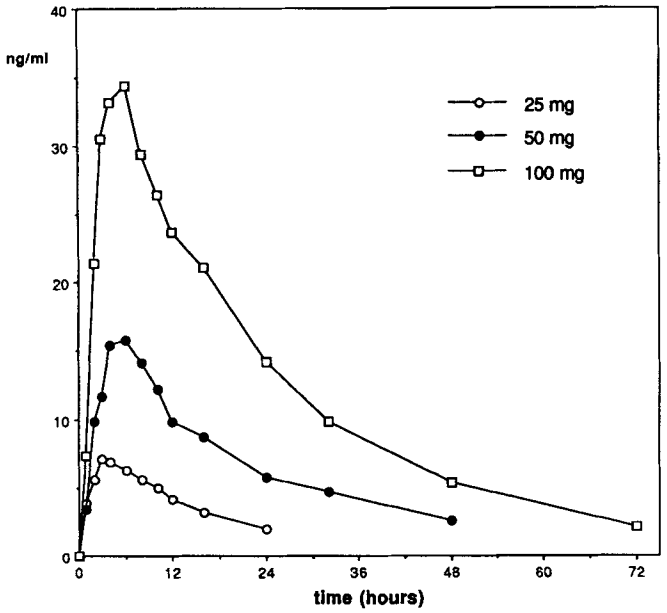

Figure 1. Mean fluvoxamine (calculated as free base) plasma concentrations after single oral administration of 25, 50, and 100 mg fluvoxamine maleate to 12 healthy subjects

interval for AUC and C_{max} is 80–125 per cent in the case of log-transformed data.[12] For T_{max} and $t_{½}$ an analysis of variance without logarithmic transformation was performed.

RESULTS

Dose-proportionality

The mean plasma concentration–time curves of fluvoxamine are shown in Figure 1. In Table 1 the mean pharmacokinetic parameters and their ranges are given.

Neither AUC nor C_{max} showed statistically significant period effects at the 10 per cent level. The F-test did not show significant dose disproportionality for both AUC and C_{max} (p-values for nonlinearity were 0·36 and 0·63, respectively). The linear relationship between these parameters and dose is further illustrated in Figure 2.

No significant differences in T_{max} and $t_{½}$ values were observed. In addition, the data were analysed using the two one-sided tests procedure. The results are shown in Table 2. All 90 per cent confidence intervals are within the 80–125 per cent range.

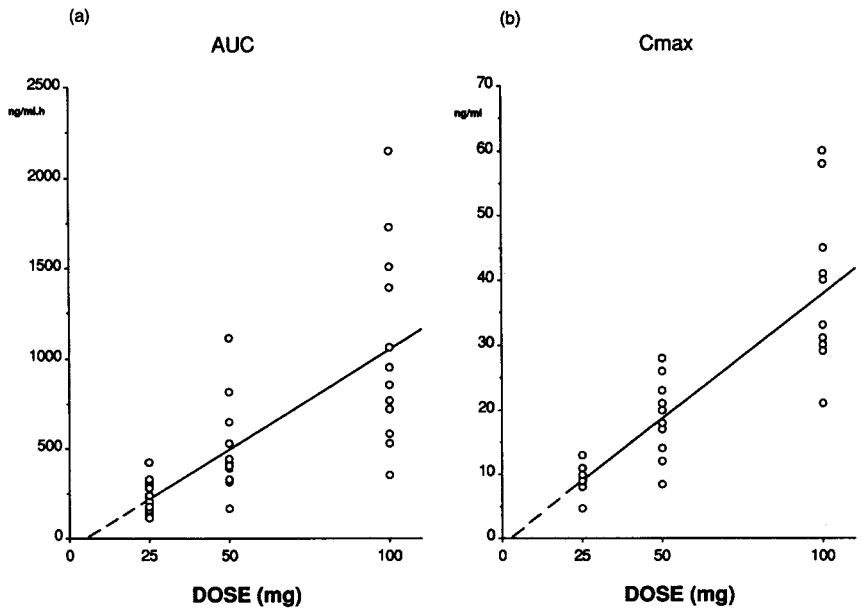

Figure 2. Relationship of fluvoxamine, calculated as free base (a) AUC and (b) C_{max} with the administered dose. The open circles represent individual data, the solid line represents the regression of the data

Table 1. Mean pharmacokinetic parameters (and ranges) obtained after oral administration of 25, 50, and 100 mg of fluvoxamine maleate as a single dose. The fluvoxamine plasma concentrations are expressed as the free base

Parameter	25 mg	50 mg	100 mg
AUC (ng ml^{-1}.h)	209 (117–425)	448 (166–1115)	927 (352–2146)
normalized to 25 mg	209	224	232
C_{max} (ng ml^{-1})	8·8 (4·7–13)	17 (8·4–28)	36 (21–60)
normalized to 25 mg	8·8	8·5	9·1
T_{max} (h)	5·0 (1–8)	4·8 (2–8)	4·5 (3–6)
$t_{½}$ (h)	14·3 (10·6–26·0)	15·3 (7·9–28·2)	15·7 (9·3–25·6)

Note: geometric means for AUC, C_{max} and $t_{½}$; arithmetic for T_{max}.

Table 2. Ratios (per cent) and 90 per cent confidence intervals (CI) for AUC and C_{max}

Parameter	Dose comparison (mg)	Ratio (%)	90% CI (%)
AUC	50/25	107	95–120
	100/25	110	98–124
	100/50	103	92–116
C_{max}	50/25	97	86–109
	100/25	104	92–117
	100/50	107	95–121

Adverse reactions

There were few reports of adverse reactions. However, at 100 mg an increase in reporting was seen. Five subjects reported symptoms at the low dose (25 mg) and nine subjects at the high dose (100 mg) and the latter tended to be more severe. Insomnia was the most frequent complaint and increased in incidence with increasing dose. Other reported symptoms were varied, mild, and infrequent.

DISCUSSION

The linearity of kinetics of fluvoxamine after single oral doses of 25 mg, 50 mg, and 100 mg fluvoxamine maleate was investigated. Both the *F*-test and the two one-sided tests procedure according to Schuirmann (90 per cent confidence intervals) did not show significant disproportionality. Thus, plasma concentrations of fluvoxamine increased in a linear dose dependent manner, as assessed with AUC and C_{max} determinations. Fluvoxamine plasma concentrations peaked at 1–8 h, independent of the dose. The parameter reflecting elimination ($t_{½}$) was independent of dose. The major pharmacokinetic processes thus seem to be of first order.

The mean $t_{1/2}$ of 15 h is consistent with the half-lives measured in other single (15–17 h) and multiple dose studies (20–22 h) (Solvay Duphar; data on file), suggesting a once or twice daily dosage regimen from a pharmacokinetic point of view.

The present study was carried out with oral solutions of fluvoxamine maleate. The pharmacokinetic parameters are, however, in close agreement with those estimated after administration of solid formulations.[5]

In conclusion, the pharmacokinetics of fluvoxamine are linear in the single dose range between 25 and 100 mg. Fluvoxamine was well tolerated.

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