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Comparative bioavailability of a new formulation of fluoxetine drops

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Abstract. – **Fluoxetine drops and marketed fluoxetine capsules had quite the same C_{max} (50.25 ± 4.43 vs 47.55 ± 5.29 ng/ml), but significantly different AUC_{0-t} (717.27 ± 71.29 vs 644.91 ± 78.91 ng/ml/h). Furthermore the drops were characterised by a very early T_{max} (4.61 ± 0.85 hours) with a highly significant difference in comparison to the capsules reference compound (6.72 ± 1.23 hours).**

After log transformation 90% C.I. for C_{max}, AUC 0-t and AUC_{0-}. were 1.05, 1.11, 0.82 respectively. The two products, therefore, cannot be considered bioequivalent.

Our results demonstrate that fluoxetine drops and capsules significantly differ for their pharmacokinetics, with an earlier T_{max} and a higher AUC_{0-t} after the administration of the drops preparation.

Key Words:

Fluoxetine, Bioequivalence, Antidepressants, Depression, Pharmacokinetics.

Introduction

Fluoxetine, a selective Serotonin reuptake inhibitor (SSRI) at the central nervous system receptor sites[1,2], exerts antidepressant effects in man[2-4]. Although its pharmacokinetics seems to be very favourable for long term therapy[1], there are strong indications that individually high plasma concentration levels of the drug may be ineffective[1]. Montgomery et al[5] proposed the existence of a therapeutic window for Fluoxetine, because they observed a negative relationship between plasma drug concentrations and the therapeutic response. Therefore, the introduction of a new Fluoxetine preparation allowing for flexible dose schedules could be useful in order to reach the optimal individual therapeutic dose.

In this study we examined the pharmacokinetics of a new Fluoxetine drops formulation, containing 1 mg of active ingredient per drop, and its biodisponibility in comparison to the market standard drug in capsules.

Materials and Methods

Eighteen healthy volunteers of both gender (M:F = 1:1) took part to study. The experiment was planned and performed according to the Helsinki Declaration and its amendments. Before starting the trial, all subjects had given their written consent. The mean age for men was 36 ± 7.74 years and 32 ± 7.2 years for women, the mean weight was 75.4 ± 7.1 kg and 65.7 ± 3.9 kg. All of them were within 20% of their ideal body weight. Medical histories were carefully evaluated; there were no volunteers with hypersensitivity to any drug or with allergy requiring treatment. Renal, hepatic, gastrointestinal, cardiovascular, haematological, respiratory, endocrine and central nervous system diseases were excluded. Nobody had drug, alcohol, caffeine or smoking abuse. All the volunteers had complete physical examinations before and after the study, including assessment of blood pressure and heart rate. Routinary laboratory tests, including a pregnancy test for women, were performed before administration of fluoxetine and 14 days after the last treatment. The subjects were taking no other medication and abstained from taking any other drug for two weeks before the study.

Experimental design

The study was performed according to a single dose, two treatment periods, crossover, randomised design. All subjects received Fluoxetine drops (1 ml = 20 drops = 20 mg) or 1 capsule of 20 mg. All drug preparations were given between 7.00 and 9.00 AM, after 12 hours fasting, with 150 ml of natural water. Four hours after the morning dose, a standard lunch was offered to all volunteers. There was a wash-out of at least 14 days and not longer than 21 days between treatments.

Products

Fluoxetine drops[1]
Fluoxetine capsules[2]

Blood sample collections

Five ml venous blood samples were taken before drug administration, and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24 hours after drug administration. All blood samples were drawn into vacutainer tubes.

Each plasma sample was immediately put in test tubes labelled with the protocol number, initials of the subject and hour of the drawing of blood and was stored at –20°C until tested. Determination of Fluoxetine was performed double blind after assignment of the code number according to a pre-set randomization list.

Analytical procedures

A sensitive reverse-phase high performance liquid chromatographic assay (HPLC) was used to determine the amount of Fluoxetine in human plasma samples. According to Wong et al[6], the drug was extracted with a mixture of hexane and isoamyl alcohol from the plasma sample. The organic layer was separated, back-extracted with diluted phosphoric acid and the extracts were analyzed in a Hitachi L Chromatograph. Clomipramine was used as internal standard. The method was linear between 5 and 800 ng/ml.

Pharmacokinetic parameters

The following pharmacokinetic parameters were measured:

AUC_{0-t}: area under the blood concentration-time curve from time 0 to time t, calculated by the trapezoidal rule, where t is the last concentration estimated.

$AUC_{0-\infty}$: area under the blood concentration-time curve calculated according to the formula:
$AUC_{0-t} + Ct/\beta$, where :
Ct: last concentration estimated
β : slope of the phase of elimination.

C_{max}: peak drug concentration, obtained directly from the data.

T_{max}: time to peak drug concentration, obtained directly from the data.

Statistical analysis

Results were expressed as mean values ± S.D. Analysis of variance (ANOVA) was performed on pharmacokinetic parameters AUCs and C_{max}, after logarithmic transformation, using the "general linear model" procedure. The 90% confidence intervals for the ratio between the test and the reference averages of AUC and C_{max} were calculated according to Westlake[7]. For bioequivalence they should lie within the ratio 0.8-1.25. The level of significance of the test was $\alpha = 0.05$.

The following sources of variation were considered: sequence, periods and treatments.

The plasma concentrations and T_{max} were evaluated by a non parametric procedure, the Wilcoxon matched-pair rank test. A p value < 0.05 was considered significant.

Results

The mean plasma Fluoxetine levels following administration of reference (capsules) and test preparation (drops) are shown in Table I and in Figure 1.

After the administration of fluoxetine drops, significant fluoxetine plasma concentrations were found after 30 min as like as after administration of the reference drug (capsules) but significant differences ($p < 0.01$) between the two groups were evident from 1 to 5 hours, with higher levels after fluoxetine drops. C_{max} was the same for two preparations (50.25 ± 4.43 vs 47.55

[1] (Daforin from Sigma Pharma, Brazil) 20 mg/ml.
[2] (Prozac from Eli Lilly, Italy) 1 capsule = 20 mg.

Table I. Plasma concentration (ng/ml) of fluoxetine in healthy volunteers after treatments with 20 mg of fluoxetine (capsules and drops). Mean values ± SD.

Hours	Test drug (drops)	Reference drug (capsules)
0	0	0
0.5	2.10 ± 2.71	1.02 ± 2.34
1	10.55 ± 3.52	5.35 ± 3.81
1.5	14.40 ± 4.66	9.71 ± 2.99
2	20.32 ± 7.04	12.73 ± 3.45
3	27.59 ± 10.30	18.43 ± 4.20
4	43.31 ± 9.64	26.62 ± 5.10
5	46.73 ± 4.74	38.36 ± 8.46
6	45.83 ± 5.45	44.87 ± 6.45
8	44.15 ± 5.50	43.89 ± 7.34
12	31.11 ± 3.99	27.61 ± 5.03
24	19.91 ± 3.83	20.36 ± 4.59

Table II. Pharmacokinetic parameters. Mean values ± SD.

Parameters	Test drug (drops)	Reference drug (capsules)
$AUC_{(0-t)}$ ng/ml/h	717.27 ± 71.29	644.91 ± 78.91
$AUC_{(0-inf)}$ ng/ml/h	1169.12 ± 246.53	1506.82 ± 615.62
C_{max} ng/ml	50.25 ± 4.43	47.55 ± 5.29
T_{max} h	4.61 ± 0.85	6.72 ± 1.23

± 5.29), the time needed to reach the peak drug concentration was significantly lower for fluoxetine drops (4.61 ± 0.85 vs 6.72 ± 1.23 h).

AUC_{0-t} (717.27 ± 71.29 vs 644.91 ± 78.91) and $AUC_{0-\infty}$ (1169.12 ± 246.53 vs 1506.82 ± 615.62) were significantly different between the two treatment groups (Tables II-III).

After log transformation 90% C.I. ratio for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were 1.05, 1.11, 0.82 ranging between values considered for bioequivalence (Table IV).

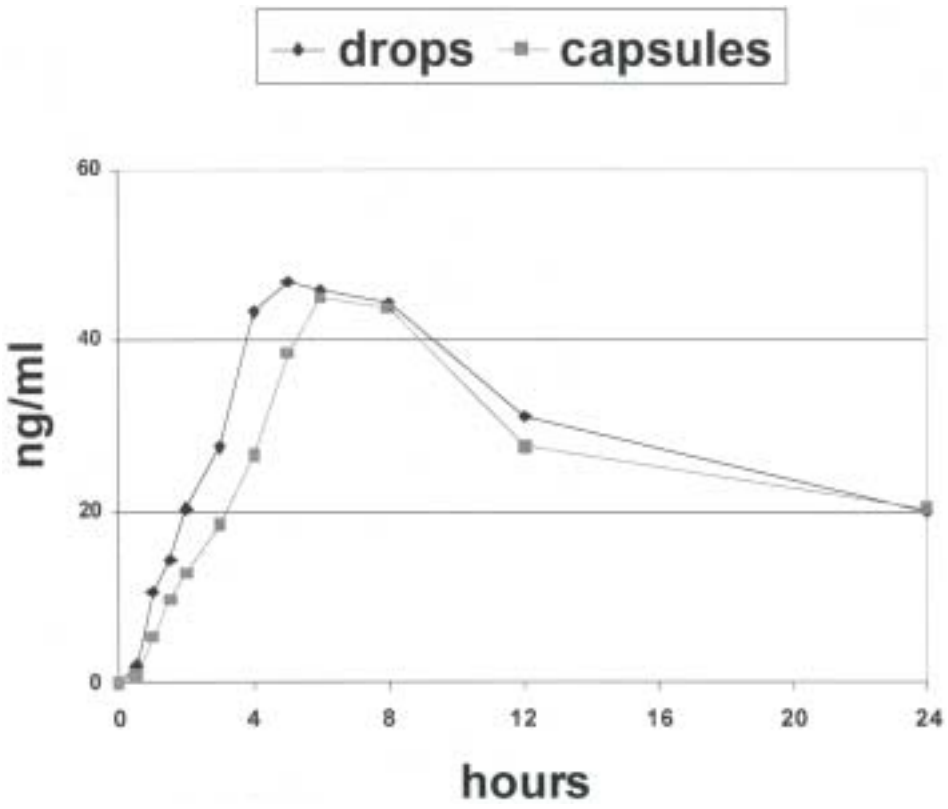

Figure 1. Plasma concentration (ng/ml) of fluoxetine in healthy volunteers after treatments with 20 mg of fluoxetine (capsules and drops).

Table III. Statistical evaluation (ANOVA) after log transformation.

	LOG $AUC_{(0-T)}$	LOG $AUC_{(0-INF)}$	LOG C_{MAX}
Sequence	0.386	0.386	0.247
Treatments	< 0.01*	0.08	0.054
Periods	0.014	0.611	0.066

*Significant.

All volunteers accomplished their participation in the study in good healthy. No side effects were observed. Physical examinations and clinical laboratory tests were unchanged.

Discussion

The use of Fluoxetine for treating patients affected by a great array of disorders primarily or secondarily linked to a significant reduction of cerebral serotonin levels such as depression, bulimia, PMS, headache, depression anxiety, chronic pain, etc. is strictly related to its pharmacokinetic characteristics. The drug is well absorbed by the gastrointestinal tract after oral administration, with a peak plasma concentration between 15 and 55 ng/ml and a time to achieve C_{max} between 6 and 8 hours (1-4,8). Fluoxetine is metabolized in the liver to nor-fluoxetine, which is also effective as antidepressant. Both the compounds have a large volume of distribution and are strongly concentrated in the brain tissue with a 2.6 ratio to the plasma concentrations[9]. The pharmacokinetics of Fluoxetine was found to be non-linear both in healthy volunteers and depressed patients[10]. Disproportionately higher plasma concentrations of the drug are found after administration of increasing doses of Fluoxetine. Furthermore, multiple dose administration allows a higher half-life and a lower clearance of Fluoxetine. Steady-state plasma concentrations of Fluoxetine are reached after 4-6 weeks and do not change later. Our results demonstrate that different Fluoxetine preparations, i.e. drops and capsule, show substantial differences in their pharmacokinetics. 20 mg fluoxetine drops and capsules are not to be considered bioequivalent on the basis of the statistical analysis proposed by Westlake[7]. The drops preparation were characterised by a faster absorption from the gastrointestinal tract with an earlier T_{max} and a higher AUC_{0-t} comparison to the reference drug preparation.

These pharmacokinetic characteristics of fluoxetine drops may be useful to reach best therapeutic results. Infact no clear relationship between therapeutic effects and drug plasma concentrations was found, with a strong evidence for a therapeutic window[1]. Combined plasma concentrations of Fluoxetine and Nor-fluoxetine above 500 ng/ml seem to be associated with a reduced therapeutic effects in comparison to lower concentrations[2]. This observation can explain the higher therapeutic effect of low doses of fluoxetine (20 mg) in comparison to high doses (40-60 mg)[12]. Also the high rate of side effects recorded after treatment with 40-60 mg fluoxetine as like as the relapse of depressive symptoms, when treatment is performed for a long time[13], could be caused by the accumulation of the drug. This finding suggests that the therapy should be individualized on the basis of clinical outcome and drug plasma

Table IV. Statistical evaluation – Westlake limits.

Variable	Mean capsules	Mean drops	Means square error	Lower limit	Ratio drops/capsules	Upper limit
Log $AUC_{(0-t)}$	2.806	2.854	0.0018	1.0539	111.51	1.1797
Log (AUC_{0-inf})	3.145	3.059	0.0199	0.6803	82.19	0.9929
Log C_{max}	1.674	1.699	0.0012	1.0090	105.88	1.1109

levels. The pharmacokinetic profile of fluoxetine drops suggests it can be very useful to reach this goal, because of the reduced T_{max}, the high AUC_{0-t}, that minimise the possibility of the drug accumulation. Finally the possibility of tailoring the therapy on the basis of the body weight and the clinical outcome plays in favour of the fluoxetine drop preparation. The clinical advantage of the new fluoxetine formulation allowing for tailored individual dosages could be examined in further studies.

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