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Effect of Food on the Pharmacokinetics of Fluoxetine in Healthy Male Adult Volunteers(Conference Paper)#

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Abstract

Fluoxetine (FX) is an antidepressant drug administered only orally in humans. Despite the wide use of FX, until now, there is only limited number of literature concerning the pharmacokinetics (PK) of FX and the effect of food on its PK. The objective of this investigation was to study the PK of FX in Arabic healthy male adult volunteers under fasting and fed conditions. The study was designed as a single dose , two periods. For both conditions; FX 20 mg capsules (Prozac®, Eli Lilly, Canada) were administered to 41 volunteers. Blood samples were drown from each volunteer immediately before dosing (zero time) and then after different time intervals after dosing (one hr. interval for the first 12 hrs., then 12 hrs. interval from 12-72 hrs. and finally 24 hrs. interval from 72-144 hrs.). In fasting study, fasting was overnight for 12 hrs. While, the fed study was conducted after 90 days wash-out period following the completion of the fasting study. The same subjects who received FX in the fasting study were administered the drug directly after a fatty breakfast. The concentrations of FX were assessed in the plasma samples obtained from each volunteer by rapid, accurate, precise, sensitive, and specific method. The PK parameters were calculated according to standard methods using non-compartmental data analyses using Kinetica software. The mean ± SD values of Cmax, Tmax, AUC_{0-t}, $AUC_{0-\infty}$, K_{el}, $T_{0.5}$, MRT, Cl/F and Vd/F of fluoxetine 20 mg capsules under fasting conditions were 11.5 ± 3.0 ng/ mL, 5.4 ± 1.6 hr, 408.9 ± 177.1 ng.hr/ml, 453.8 ±192.2 ng.hr/ml, 0.022 ± 0.005 hr^{-1}, 33.5 ± 7.4 hr, 51.1 ± 11.2 hr, 58.3 ± 33.0 L/h and 2845 ± 1807 L, respectively. The corresponding values of these parameters for fluoxetine 20 mg capsules under fed conditions were 10.9 ± 3.3 ng/ mL, 6.7 ± 1.9 hr, 329.1 ± 181.0 ng.hr/ml, 417.6 ±192.2 ng.hr/ml, 0.022 ± 0.008 hr^{-1}, 35.5 ± 11.6 hr, 51.9 ± 10.8 hr, 58.8 ± 24.2 L/h and 2482.4 ± 1371 L respectively. The current investigation demonstrated no statistical differences in the FX pharmacokinetic parameters C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, K_{el}, $T_{1/2}$, MRT, Cl/F, and Vd/F after fasting compared to the fed conditions, whereas there was statistically significant elongation in the T_{max} values after food intake. Therefore, this study concludes the absence of food effect on the PK of FX (except T_{max}) in the Arabic population and confirms the method of administration mentioned in the product information but also concludes high interindividual variation in FX exposure (AUC), which suggest that therapeutic drug monitoring (TDM) might be advisable when feasible.

Keywords: Fluoxetine, Pharmacokinetics, Food effect, Arabic volunteers.

تأثير الغذاء على الحرائك الدوائية للفلوكستين في المتطوعين البالغين الأصحاء (بحث مؤتمر)#

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الخلاصة

الفلوكستين (FX) دواء مضاد للاكتئاب يتم تناوله عن طريق الفم فقط في البشر. على الرغم من الاستخدام الواسع لـ FX ، حتى الآن ، لا يوجد سوى عدد محدود من الأدبيات المتعلقة بحركية الدواء (PK) لـ FX وتأثير الطعام على حركية الدواء الخاصة به. كان الهدف من هذه الدراسة هو دراسة حركية الدواء لـ FX في متطوعين بالغين أصحاء عرب في ظل ظروف الصيام والتغذية. صممت الدراسة كجرعة وحيدة على فترتين. لكلا الظرفين تم إعطاء كبسولات(Prozac®, Eli Lilly, Canada) إلى ٤١ متطوعًا. تم سحب عينات الدم من كل متطوع مباشرة قبل تناول الجرعات (صفر مرة) ثم بعد فترات زمنية مختلفة بعد الجرعات (فترة ساعة واحدة لأول ١٢ ساعة ، ثم ١٢ ساعة ، من ١٢ إلى ٧٢ ساعة ، وأخيراً ٢٤ ساعة. فترة من ٧٢-١٤٤ ساعة). في دراسة الصيام ، كان الصيام بين عشية وضحاها لمدة ١٢ ساعة. بينما أجريت دراسة التغذية بعد ٩٠ يوم من فترة الغسل بعد الانتهاء من دراسة الصيام. نفس الأشخاص الذين تلقوا FX في دراسة الصيام تم إعطاؤهم الدواء مباشرة بعد وجبة إفطار دسمة. تم تقييم تركيزات FX في عينات البلازما التي تم الحصول عليها من كل متطوع بطريقة سريعة ودقيقة وحساسة ومحددة. تم حساب معلمات الحركية الدوائية وفقًا للطرق القياسية باستخدام تحليلات البيانات غير المقسمة باستخدام برنامج Kinetica كانت قيم المعدل± الانحراف المعياري لـ Cmax و Tmax و AUC0-t و AUC0-∞ و Kel و T0.5 و MRT و Cl / F و Vd / F لكبسولات فلوكستين ٢٠ مجم تحت ظروف الصيام ١١,٥ ± ٣,٠ نانوغرام / مل ، ٥,٤ ± ١,٦ ساعة ، ٤٠٨,٩ ± ١٧٧,١ نانوغرام / ساعة / مل ، ٤٥٣,٨ ± ١٩٢,٢ نانوغرام ساعة / مل ، ٠,٠٢٢ ± ٠,٠٠٥ ساعة -١ ، ٣٣,٥ ± ٧,٤ ساعة ، ٥١,١ ± ١١,٢ ساعة ، ٥٨,٣ ± ٣٣,٠ لتر / ساعة ، ٢٨٤٥ ± ١٨٠٧ لتر ، على التوالي.

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كانت القيم المقابلة لهذه المعلمات لكبسولات فلوكستين ٢٠ مجم تحت ظروف التغذية ١٠,٩ ± ٣,٣ نانوغرام / مل ، ٦,٧ ± ١,٩ ساعة ، ٣٢٩,١ ± ١٨١,٠ نانوغرام / ساعة / مل ، ٤١٧,٦ ± ١٩٢,٢ نانوغرام / ساعة / مل ، ٠,٠٢٢ ± ٠,٠٠٨ ساعة- ١ ، ٣٥,٥ ± ١١,٦ ساعة ، ٥١,٩ ± ١٠,٨ ساعة ، ٥٨,٨ ± ٢٤,٢ لتر / ساعة و ٢٤٨٢,٤ ± ١٣٧١ لتر على التوالي. أظهرت الدراسة الحالية عدم وجود فروق ذات دلالة إحصائية في معاملات الحرائك الدوائية لـ FX Cmax و AUC0 t و AUC0 و Kel و T1 / 2 و MRT و Cl / F و Vd / F بعد الصيام مقارنة بظروف التغذية ، بينما كان هناك إحصائيًا زيادة كبيرة في قيم Tmax بعد تناول الطعام. لذلك ، خلصت هذه الدراسة إلى عدم وجود تأثير غذائي على الحركية الدوائية لـ FX باستثناء Tmax في الاشخاص العرب وتؤكد طريقة الاعطاء المذكورة في معلومات المنتج ولكنها تستنتج أيضًا تباينًا كبيرًا بين الأفراد في التعرض لكمية دواء الـFX (AUC) ، مما يشير إلى أن قد يكون من المستحسن تطبيق المراقبة الدوائية (TDM) عندما يكون ذلك ممكنًا.

الكلمات المفتاحية: فلوكستين ، حركية الدواء ، تأثير الغذاء ، متطوعون عرب

Introduction

Fluoxetine is indicated in adults for the symptomatic relief of various types of depression involving major depressive disorder, obsessive-compulsive disorder and some eating disorders (bulimia nervosa). Moreover, FX should only be used in combination with psychological therapy when prescribed to children or young persons with moderate to severe major depressive disorder. The usual initial dosage is 20 mg, administered once daily in the morning. If the expected clinical improvement does not take place after a trial period of several weeks, a gradual dose increase is recommended and should not exceed a maximum of 60 mg daily [1, 2].

Chemically, fluoxetine base (FX) is unrelated to tricyclic, tetracyclic or other available antidepressant agents. Fluoxetine is the first highly specific phenylpropylamine derivative belonging to the selective serotonin reuptake inhibitors (SSRI) class [1]. It facilitates serotoninergic neurotransmission through potent and selective inhibition of presynaptic serotonin reuptake. Fluoxetine gained approval by USFDA in 1987. The molecular formula of FX is $C_{17}H_{18}F_3NO$, and its molecular weight is 309.33 g/mol while that of fluoxetine hydrochloride is $C_{17}H_{19}ClF_3NO$, and its molecular weight is 345.79 gm/mol. Fluoxetine base is very lipophilic with logP equal to 4.05. Each 20 mg Prozac® capsule contains 22.36 mg of FX hydrochloride which equivalent to a 20 mg FX-free base [1, 2].

Oral FX is well absorbed from Gastrointestinal tract (GIT) with bioavailability (BA) of less than 90% due to hepatic first-pass metabolism. Peak plasma levels (C_{max}) of 15-55 ng/ml were achieved after 6 to 8 hours of a single 40 mg dose. The C_{max} of the FX 20 mg capsule was 11.754 ng/ml. The FX capsule is bioequivalent to the oral solution; however, the FX tablet demonstrates lower BA than the capsule formulation making the capsule slightly more effective than the tablet dosage form. Fluoxetine exhibits a nonlinear PK profile; therefore, it should be used with caution in patients with hepatic dysfunction. The age does not affect the PK of FX. Besides, the drug exhibits a better tolerability profile than tricyclic antidepressants making FX particularly appropriate for elderly patients with depression. Moreover, the PK of FX is not influenced by renal impairment or obesity [3-5].

Fluoxetine is extensively metabolized by demethylation in the liver to the active metabolite norfluoxetine and other unidentified metabolites. The FX's terminal elimination half-life ($T_{1/2}$) is 4 to 6 days, and for its active metabolite, norfluoxetine is 4 to 16 days (3) . The pharmacological activity of norfluoxetine is similar to the parent drug FX, and it contributes to the long duration of action of FX. This unique property makes the drug provide an antidepressant effect by less frequent administration (once weekly) than the usual daily doses. The apparent volume of distribution (Vd) of FX and its metabolite are high and vary between 20-42 L/kg. The total body clearance (Cl) of FX is reported to be 0.576 L/hr/kg. Fluoxetine is highly plasma protein bound (about 94%), allowing FX and its active metabolite (norfluoxetine) to be distributed to the brain. The FX is mainly eliminated in the urine. About 60% of an oral FX dose is excreted in urine within 35 days, and about 12% of the dose is excreted in the feces within 28 days [3-5].

Fluoxetine (as the hydrochloride salt) is administered in oral dosage forms only and is available as 20 mg tablets, 20 mg capsules, delayed-release capsules (hard-shelled and soft gel), and as a solution containing 20 mg/5 ml. The tablet is presented as a quick-release, delayed-release, chewable, or orally dissolving tablet (ODT), which breaks down in saliva. The chewable and ODT dosage forms can be helpful for patients having trouble or difficulty swallowing [3-5]. Other dosage forms are under investigation, such as transdermal [6], fast dissolving film [7], and other drug delivery systems [8, 9].

Knowledge of drugs PK is essential to obtaining safe and effective drug products. Besides, the administration of medications with food may significantly impact the rate and/or extent of drugs' absorption and, consequently, their BA. Therefore, several PK/BA/BE investigations were conducted to elucidate the PK characteristics of different drugs and dosage forms in the Arabic population. Among these investigations are studies that have been published recently for antibacterial drugs such as azithromycin [10], cefixime [11], levofloxacin [12], cefuroxime [13], fluconazole tablet and capsule [14, 15]; immunosuppressant drugs as cyclosporine [16]; drugs indicated for benign prostatic hyperplasia like doxazocin [17]; drugs indicated for Ménière's disease primarily betahistine [18] and antihypertensive agents

such as amlodipine, valsartan, hydrochlorothiazide [19]. The current study was conducted to demonstrate the PK of FX in Arab healthy male adult volunteers under fasting and fed conditions to see whether there is a necessity to change the dosage regimen and method of administration of FX in the Arabic population.

Materials and Methods

Ethical commitments

A study protocol containing all the details of this research involving the informed consent form was issued by the principal investigator according to the International Council for Harmonization (ICH) guidelines for good clinical practice (GCP) and the recent version of the Helsinki declaration (20-22). The protocol was reviewed and approved by the clinical investigator and the institutional review board/ethical committee (IRB/EC) before conducting the research. Any alterations and/or amendments in any section of the protocol suggested by the clinical investigator and/or the IRB/EC which may have a remarkable impact on the study conduct were made by the principal investigator, followed by further approval by the clinical investigator and the IRB/EC; unless if the suggested alterations or amendments were regarded minor according to the principal investigator's decision such as logistical or administrative issues.

Informed consent

Each volunteer, together with two witnesses in addition to the clinical investigator, personally signed two original copies of the consent form, one copy was delivered to the volunteer, and the other copy was saved in the research file as part of the source documents.

According to the study protocol and based on the principal and/or clinical investigator's decision, any volunteer's participation was terminated at any time during the research according to certain criteria. These criteria include the following: violation and/or bad compliance of the volunteer with the protocol, and in the case continued participation may impact the volunteer's health such as illness, and abnormal vital signs were detected. Moreover, any volunteer was allowed to withdraw from the study due to any personal reason without undue delay.

Volunteers

Forty six Arabic adult male healthy volunteers were screened in the study based on the following inclusion criteria: ages between 18-50 years; body mass index of 18-30 Kg/m^2; nonsmokers or light smokers (consume less than 10 cigarettes per day); non-vegetarians, no previous allergic responses to FX and related compounds, no hospitalization, blood donation or participation in any clinical trials such as BA/BE/PK two months before the current study; the volunteers had normal physical and clinical examinations including electrocardiograms (ECG), vital signs (systolic/diastolic blood pressure, pulse and temperature), absence of cardiovascular, pulmonary, renal, hepatic, gastrointestinal, hematological, endocrinal, immunological, dermatological, neurological and psychiatric diseases; no evidence of poor motivation, antagonistic personality, emotional or intellectual problems that may impact the validity of the volunteer's consent to participate in the study or limit the ability to comply with requirements of the study protocol. Moreover, the volunteers had normal clinical laboratory tests involving complete hematological and biochemical profiles, routine urinalysis, negative virologic tests (HIV, hepatitis B and C) and no alcohol and drug abuse.

Clinical procedures and dose administered

The study was designed as a single dose , two periods, in which the same subject were given the drug under fasting and fed study separated for 90 days wash out interval between dosing.

In the fasting study, the volunteers were admitted to the clinical site the evening before FX administration day at about 6:00 p.m., and then a standard dinner was served at 8:00 p.m. The volunteers were confined to the clinical site for 24 hours post drug administration. After overnight fasting of 12 hours (at 8:00 a.m.), the volunteers were given a single dose of the investigational drug Prozac® capsules (Eli Lilly, Canada) containing 20 mg FX with 240 ml of potable water.

In the fed study, FX capsules were administered to the same volunteers who received the drug in the fasting study after a washout period of 90 days after ending the fasting study by applying the same clinical procedures mentioned above, except FX capsules, were administered to the volunteers directly after serving a fatty breakfast.

Food and drink were not allowed until 4 hours after dosing (other than water, which was allowed 2 hours after drug intake). Standard lunch and dinner were served after 4 and 8 hours of FX administration, respectively. Beverages containing caffeine were banned 12 hours before dosing and up to 24 hours post-dosing. Grapefruit-containing beverages were prohibited 48 hours pre-dosing and until the end of both the fasting and fed studies. The volunteers were allowed to sit or walk around, but they were forbidden from strenuous activity. Besides, the volunteers were not allowed to lay or sleep during the first 4 hours of FX intake.

Approximately 5 ml blood samples were drawn from each volunteer to determine FX concentration in plasma. Each blood sample was placed into an evacuated heparinized glass tube through an indwelling cannula inserted in the forearm vein. The sampling time table was as follow: 0 (immediately before FX administration), then at 1, 2, 3, 4, 5, 6, 7,

8, 9, 10, 12, 24, 36, 48, 60, 72, 96, 120 and finally at 144 hours after dosing. The blood samples were centrifuged at 3500 rpm for 10 min and the separated plasma was transferred directly into two plastic tubes in approximately equal aliquots and stored frozen at -25±5 ˚C pending measuring FX levels in the plasma. In-house procedure proved that the storage temperature (-20±5 ˚C) was adequate for saving FX stable for two months. The actual clock time for each blood sample was recorded. Directly after each blood sample withdrawal, normal saline (0.5 mL) containing 20 units of heparin per ml was injected into the cannula to push the residual blood and prevent blood clotting. About 0.2 ml of blood was discarded from the cannula before each blood sample withdrawal to eliminate any residual blood in the cannula. Twenty blood samples were sampled from each volunteer.

The whole blood volume withdrawn from each volunteer for the fasting study was approximately 120 ml, including the blood obtained for screening and clinical laboratory testing at the last blood sample taken at 144 hours post-dosing before the volunteer's discharged from the fasting study and the blood taken before one day of admission to the fed study. The same blood volume was withdrawn from each volunteer for the fed study. Since the volume of blood (120 ml) sampled during six days for each of the fasting and the fed studies and the washout interval between both studies is about three months, thus there is no physiological concern regarding the total volume of blood taken from each volunteer.

A confidential system for tube labeling was applied based on in-house standard operating procedure (SOP) referring to the drug name (FX), the volunteer's identification number, and a number indicating the time of each blood/plasma sample withdrawal.

Safety evaluation

The entire clinical phase of the fasting and fed studies, including volunteer admission, drug administration, blood sampling and safety evaluation of FX, was accomplished by a qualified medical crew and under the supervision of the clinical investigator. Also, the QA personnel monitored all clinical procedures to assure adherence to the study protocol. The vital signs (blood pressure, pulse, and temperature) were recorded for each volunteer almost one hour before FX administration and then at 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, 96, 120 and ultimately upon volunteer's discharge at 144 hours after dosing. Moreover, laboratory tests for hematology, biochemistry, and routine urinalysis were achieved at the end of both the fasting and the fed studies. The clinical investigator, together with the clinical team, handled and recorded any adverse events (AE), adverse drug reactions (ADR), and serious adverse effects (SAE). In addition to that, several safety measures were taken into consideration, such as the availability of clinical facilities to handle any urgent case beyond the capability of the clinical site.

Fluoxetine determination

The concentrations of FX were assessed in the plasma samples obtained from each volunteer by a previously described analytical method (23) following FDA bioanalytical method validation guidance (24, 25). The method was proved to be rapid, accurate, precise, sensitive, and specific to determine FX in plasma. The linearity of the method was established for FX concentrations ranges of 0.05-100 ng/ml with a lower limit of quantification of 0.05 ng/ml and a lower limit of detection of 0.03 ng/ml [(23)]. A standard calibration curve involving a blank matrix was generated for each bioanalytical run to assess FX concentrations in the unknown authentic plasma samples. No determination was done by extrapolation below or above FX concentrations ranges of 0.05-100 ng/ml established in the standard calibration curve.

Pharmacokinetic computations

Kinetica software was used for pharmacokinetic (PK) calculations and statistical analysis, including ANOVA tests and descriptive statistics. Microsoft Excel was applied for data plotting. From each volunteer's FX plasma concentration-time data, the PK parameters were calculated according to standard methods using non-compartmental data analyses [(26, 27)].

The following PK parameters were computed for each volunteer:

C_{max} = maximum or peak blood concentration. T_{max} = time at which C_{max} occurs. Both C_{max} and T_{max} were obtained directly from the concentration-time profile of each volunteer. K_{el} = terminal elimination rate constant estimated by linear regression of at least three points of log-plasma concentrations versus time in the last terminal elimination phase. $T_{1/2}$ = terminal elimination half-life calculated from 0.693/K. AUC_{0-t} = area under concentration-time curve measured by Trapezoidal rule from time zero to the last time (t_{last}) of blood sampling. C_{last} = last measurable FX concentration at t_{last} that meets or above the lower limit of quantification (0.05 ng/ml). $AUC_{t-\infty}$ = extrapolated area under plasma concentration-time curve from t_{last} to infinity calculated from C_{last}/K_{el}. This area is also termed $AUC_{extrapolated}$, $AUC_{residual}$ or AUC_{tail}. $AUC_{0-\infty}$ = area under the concentration versus time curve from t_0 to t_∞ equal to $AUC_{0-t} + AUC_{t-\infty}$. The % extrapolated AUC was calculated as 100 x ($AUC_{t-\infty}/AUC_{0-\infty}$). MRT = mean residence time equivalent to AUMC/AUC; AUMC is the area under the moment curve. Cl/F = total body clearance measured from FX dose (20 mg) divided by $AUC_{0-\infty}$ of each volunteer. F is the absolute bioavailability. Vd/F = apparent volume of distribution of FX calculated from Cl/K_{el} of each volunteer.

Results and Discussion

Volunteers

Due to the relatively slow absorption rate (T_{max} range from 2-9 hours) and long $T_{1/2}$ of FX, which was reported to be about two days (3-5, 28-30), this study was designed to sample the drug in blood frequently and for 144 hours after FX administration to obtain a reliable and clear description of the PK behavior of the drug in the body including the absorption and disposition phases. Forty-six volunteers were screened for the study; two of them were medically not eligible to be enrolled in this research, one volunteer did not come to admission the day before FX administration at the fasting study, one volunteer withdrew during the fasting study, and another withdrew during the fed study due to personal causes; thus, the remaining 41 volunteers completed both the fasting and the fed studies.

Clinical procedures

The current trial was executed according to a study protocol based on ICH guidelines for good clinical practice [20, 21], the declaration of Helsinki [22], FDA guidance on bioanalytical method validation [24, 25], and the standard methods for PK data analysis [26, 27]. No violation of the study protocol was reported throughout all study phases.

The usual initial therapeutic dose of the FX capsule is 20 mg, administered to patients once daily [1-5]. If no clear clinical improvement occurs after a trial period of several weeks, it is recommended to escalate the dose gradually, provided that it should not be more than 60 mg daily (1-5). Therefore, in the current research, the dose strength (20 mg FX capsule) was decided to be evaluated to balance FX blood concentrations for reliable determination of the PK parameters of the drug on the one hand and to expose the volunteers to a safe therapeutic dose on the other hand.

Fluoxetine pharmacokinetics

Figure 1 shows FX plasma concentration-time profiles after fasting and fed conditions (Each point is represented as a mean±SD). While figure 2 and figure 3 show a direct comparison in mean FX plasma concentrations versus time curves between fasting and fed studies. As can be seen in figure 1, FX demonstrates clear interindividual variabilities in its plasma concentrations at all data points of the absorption and disposition phases for fasting and fed conditions. Fluoxetine reveals a slow absorption phase, followed by relatively slow distribution and then a long terminal elimination phase under both fasting and fed states. The absorption rate of FX seems to be delayed when the FX capsule was given directly after a fatty breakfast (fed study) compared to the absorption rate seen when the drug was administered on an empty stomach.

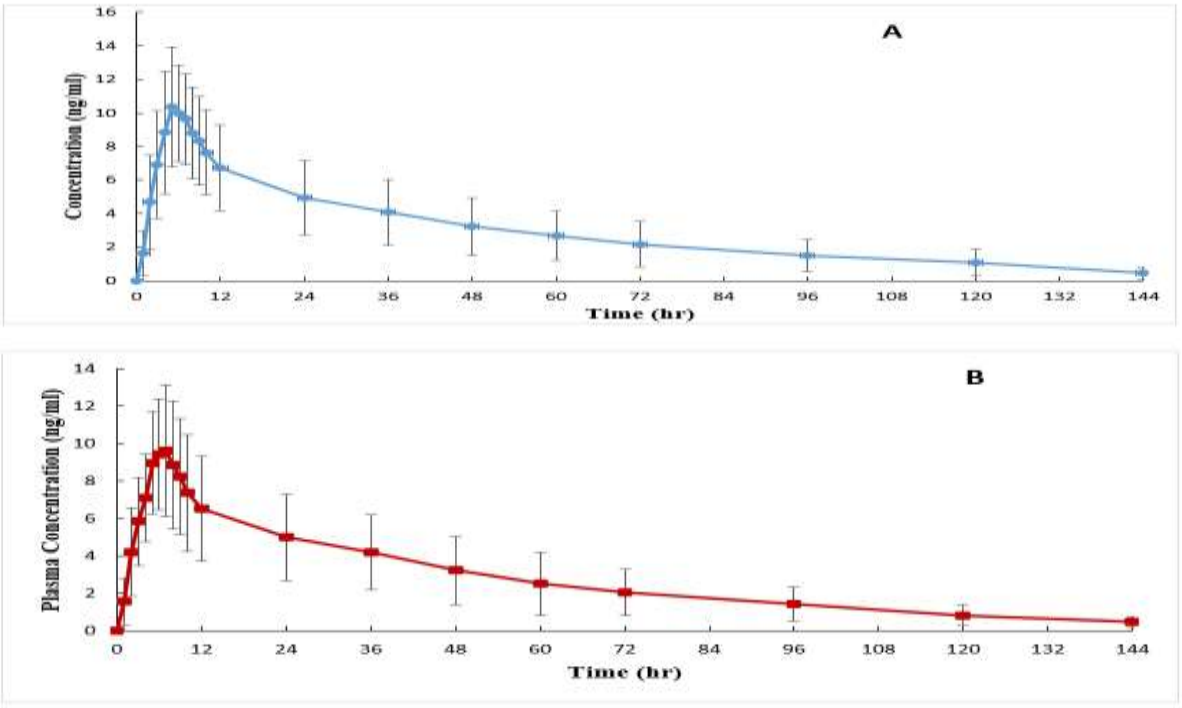

Figure 1. Plasma concentration-time profiles of fluoxetine after administering fluoxetine 20 mg capsules to healthy adult Arabic subjects under fasting (A) and fed (B) conditions (Each point is mean±SD , n=41 for each data points).

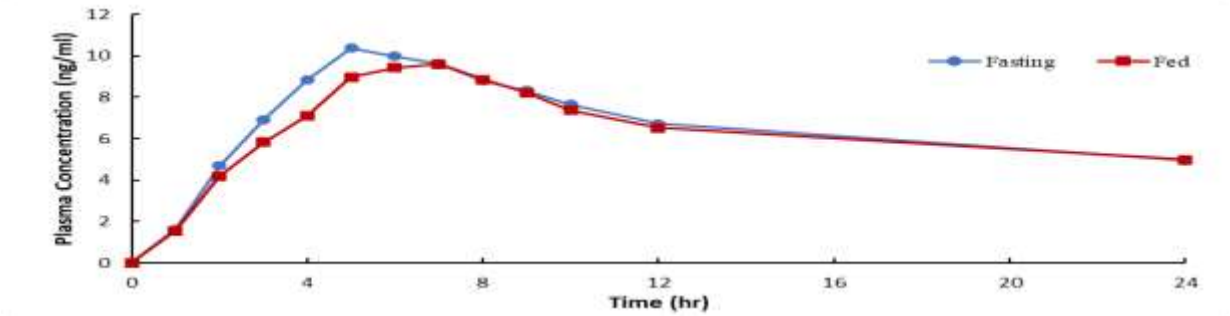

Figure 2 .Comparison of mean plasma concentration-time profiles (t=0-24 hr) of fluoxetine after administering fluoxetine 20 mg capsules to healthy adult Arabic subjects under fasting and fed states.

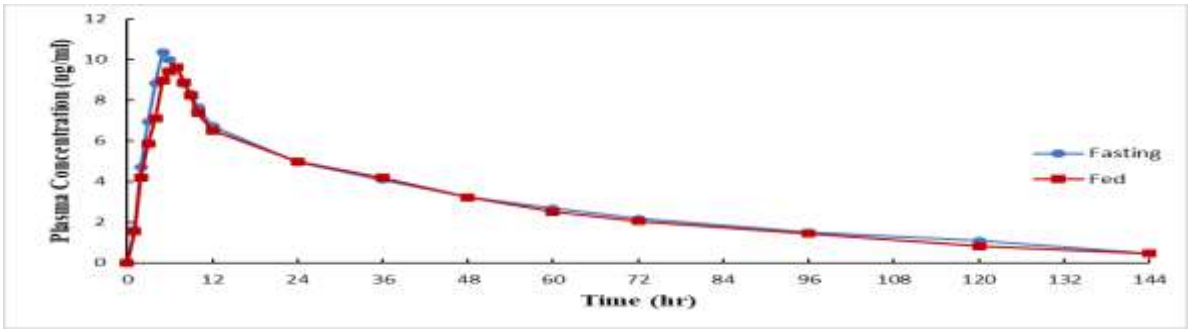

Figure 3. Comparison of mean plasma concentration-time profiles (t=0-144 hr) of fluoxetine after administering fluoxetine 20 mg capsules to healthy adult Arabic subjects under fasting and fed states.

The PK of FX resulting from the fasting and the fed studies are also enlisted in the given table below. The mean ± SD values of Cmax, Tmax, AUC_{0-t}, $AUC_{0-\infty}$, K_{el}, $T_{0.5}$, MRT, Cl/F and Vd/F of fluoxetine 20 mg capsules under fasting conditions were 11.5 ± 3.0 ng/ mL, 5.4 ± 1.6 hr, 408.9 ± 177.1 ng.hr/ml, 453.8 ±192.2 ng.hr/ml, 0.022 ± 0.005 hr^{-1}, 33.5 ± 7.4 hr, 51.1 ± 11.2 hr, 58.3 ± 33.0 L/h and 2845 ± 1807 L, respectively. The corresponding values of these parameters for fluoxetine 20 mg capsules under fed conditions were 10.9 ± 3.3 ng/ mL, 6.7 ± 1.9 hr, 329.1 ± 181.0 ng.hr/ml, 417.6 ±192.2 ng.hr/ml, 0.022 ± 0.008 hr^{-1}, 35.5 ± 11.6 hr, 51.9 ± 10.8 hr, 58.8 ± 24.2 L/h and 2482.4 ± 1371 L respectively.

Visual inspection of table 1 indicated that FX exhibit low interindividual differences in both fasting and fed conditions (CV% about 30%) for the PK parameters C_{max}, K_{el}, T_{max}, $T_{1/2}$, and MRT (Table 1). Higher intersubject variabilities (CV% ranges 42-64%) were found for the parameters AUC_{0-t} and $AUC_{0-\infty}$, Cl/F, and Vd/F. The same findings were reported in other literature [3-5, 28-30].

The current research demonstrated that the computed % extrapolated AUC had a small contribution to the total AUC (a mean = 5.7 ng.hr/ml, a range of 1.3-13.8 ng.hr/ml) in the fasting study and (a mean = 6.2 ng.hr/ml, range of 1.6-14.9 ng.hr/ml) in the fed study. These results indicated that 144 hours of blood sampling after FX administration and a lower limit of quantification of FX in plasma (0.05 ng/ml) were quite enough for a complete description of the concentrations versus time profiles of the drug and reliable determination of all PK characteristics of FX including the absorption and the terminal elimination phases for both fasting and fed studies.

Thus, due to the high interindividual differences in the total drug exposure (AUC) after fasting and fed states as shown in the table given later which may lead to high interindividual differences in the extent of drug effectiveness, the current investigation suggests that FXs therapeutic drug monitoring (TDM) can be useful in clinical practice to obtain safe and effective plasma concentrations.

The TDM of antidepressant agents has been declared as an important tool for demonstrating therapeutic and economic advantages. Recently, efforts have emphasized establishing more effective and safer regimens for antidepressants like FX by considering the individual PK properties of the patients. Accordingly, TDM of FX has been recommended for problems solving such as therapeutic failure and/or toxicity, dose titration, special populations (like children, pregnant women and elderly patients), a certain situation such as the high potential for clinically relevant drug interactions and pharmacokinetically important and special circumstances [31-37].

Statistical analysis

Applying ANOVA tests to compare the PK parameters of FX obtained after the fasting study in comparison to the corresponding parameters obtained after the fed study as shown in the table given below.The P values obtained from ANOVA tests for the PK parameters after fasting against the corresponding parameters obtained after the fed condition were 0.42853, 0.0020779, 0.69204, 0.68997, 0.99092, 0.39977 and 0.73251 for the parameters Cmax, Tmax, AUC0–t, AUC0–∞, Kel,

T1/2, and MRT, respectively. The results demonstrated no statistical difference ($P > 0.05$) for all the PK parameters C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, K_{el}, $T_{1/2}$, MRT, Cl/F and Vd/F except the parameter T_{max} which showed significant difference ($P < 0.05$) for the fasting versus the fed states due to delay in the absorption rate of FX after food intake. Thus, FX onset of action delay would be expected if FX capsules are taken with food.

Table1. Pharmacokinetic parameters of fluoxetine 20 mg capsules under fasting and fed conditions Fasting

Stat	C_{max} (ng/ml)	T_{max} (hr)	AUC_{0-t} (ng.hr/ml)	$AUC_{0-\infty}$ (ng.hr/ml)	K_{el} (hr^{-1})	$T_{0.5}$ (hr)	MRT (hr)	Cl/F (L/h)	Vd/F (L)
Mean	11.5	5.4*	408.9	453.8	0.022	33.5	51.1	58.3	2845
±SD	3.0	1.6	177.1	192.2	0.005	7.4	11.2	33.0	1807
%CV	26	30	43	42	25	22	22	57	64
Min	5.3	3	118.0	122.7	0.014	17.8	31.5	24.8	886
Max	16.4	10	775.6	807.5	0.039	49.4	72.7	163	7601

*** Median = 5**

Fed

Stat	C_{max} (ng/ml)	T_{max} (hr)	AUC_{0-t} (ng.hr/ml)	$AUC_{0-\infty}$ (ng.hr/ml)	Kel (hr^{-1})	T0.5 (hr)	MRT (hr)	Cl/F (L/h)	Vd/F (L)
Mean	10.9	6.7*	329.1	417.6	0.022	35.5	51.9	58.8	2482.4
±SD	3.3	1.9	181.0	192.2	0.008	11.6	10.8	24.2	1371
%CV	30	28	55	46	36	33	21	48	55
Min	3.5	2	94.9	107.9	0.012	17.3	35.6	23.6	820
Max	15.8	12	787.9	848.1	0.040	57.5	74.8	135.9	6630

*** Median = 7**

Safety and tolerability

For both fasting and fed studies, FX 20 mg capsules were tolerated well by all volunteers, and no AE, ADR, and SAE were noticed during each study period of 144 hours. Besides, the clinical examinations, including vital signs and laboratory tests, were not significantly altered after FX dosing compared to the baseline.

Conclusions

This article demonstrated the PK parameters of the therapeutic dose of FX 20 mg capsules administered to the Arabic population. No, statistically significant differences after the fasting versus the fed conditions were found in the primary and secondary PK parameters including C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, K_{el}, $T_{1/2}$, MRT, Cl/F and Vd/F. However, the absorption rate was slower, and consequently, the T_{max} was significantly longer after food intake. Thus, food intake with FX capsules may influence the onset rather than the intensity of the effect of FX. Interestingly, it was found in the current investigation that FX exhibited high interindividual differences in total drug exposure (AUC) when the drug was taken with or without food. Therefore, therapeutic drug monitoring of FX is preferable in therapy with FX capsules to obtain safe and effective drug levels in plasma.

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Conflict of interest

None

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