Pharmacokinetics of Paroxetine Tablets in healthy Arabic Subjects

Jaafar Jaber Ibraheem Al-Tamimi
Department of Pharmaceutics, College of Pharmacy, Baghdad University.
E-mail: drjaafarjaber@yahoo.com

Abstract:

A single oral dose of paroxetine 20 mg tablets (Seroxat®, GlaxoSmithKline, England) were administered to thirty six healthy male adult fasting subjects to study the pharmacokinetics of the drug in Arabic population.

Twenty blood samples were obtained from each subject up to 96 hours after dosing. The concentrations of paroxetine were monitored in plasma to calculate the pharmacokinetic parameters; C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, K_{el} & $T_{0.5}$; applying non-compartmental analysis.

The mean±SD for the abovementioned parameters were; 3.14±2.09 ng/ml, 5.1±1.28 hr, 48.6±45.9 ng.hr/ml, 59.5±42.3 ng.hr/ml, 0.066±0.022 hr^{-1} and 11.9±5.1 hrs, respectively. The present investigation demonstrated high inter individual variation particularly in the primary pharmacokinetic parameters C_{max} (CV=66.5%), AUC_{0-t} (CV=94.5%), and $AUC_{0-\infty}$ (CV=71%). Beside, comparing the results of the current investigation obtained from Arabic population with that published in other studies conducted in other nations indicating that there is clear population variability in the pharmacokinetic of paroxetine.

Therefore, it can be concluded from the present investigation that individualization and therapeutic drug monitoring are suggested for optimal therapy with paroxetine. However, further investigations are recommended to confirm this suggestion by studying the pharmacokinetics of the drug in Arabic patients and after multiple dosing.

Keywords: *Paroxetine, Pharmacokinetics, Healthy Arabic subjects.*

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حركية الباروكستين فى جسم أشخاص عرب أصحاء
جعفر جابر إبراهيم التميمي
فرع الصيدلانيات، كلية الصيدلة، جامعة بغداد

الخلاصة:

الباروكستين ذو الإسم التجارى سيروكزات 20 ملغم لشركة كلاكسوسمث كلاين نكليزيــــ 36 من الاشخاص البالغين الاصحاء الصائمين العرب لغرض دراسة حركية الدواء فى الجسم. 20 عينة دم من كل شخص لغاية 96 . تم حساب تراكيز عقار الباروكستين فى البلازما لغرض حساب معامل حركية الدواء وهى: Cmax, Tmax, AUC0-t, AUC0-∞, Kel , T0.5 التحليل غير الحجيرى وكان معدل معامل حركية الدواء وبالتعاقب كما يأتى: 3.14±2.09 ng/ml, 5.1±1.28 hr, 8.6±45.9 ng.hr/ml, 59.5±42.3 ng.hr/ml, 0.066±0.022 hr-1,11.9±5.1. البحث وجود فارق عالى لعامل حركية الدواء اللاساسيه وكما يأتى: Cmax (CV=71%). CV=66.5%), AUC0-t (CV=94.5%), and AUC0-∞ النتائج التى تم الحصول عليها من الحاليِ جرائها على قوميات من غير العرب تدل على وجود فارق واضح فى حركية الباروكستين فى الجسم راح من هذه الدراسة بحساب جرعة الدواء لكل شخص مع المناظرة الدوائية للحصول حسن علاج بعقار الباروكستين ولكن يجب عطاء جرع متعاقبه كيد النتائج الحاليِ .

الكلمات المفتاحية: باروكستين، حركية الدواء، الأشخاص العرب الأصحاء.

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Introduction:

Paroxetine hydrochloride is a brand product of GlaxoSmithKline, England. It is marketed as Seroxat® 10 mg, 20 mg and 30 mg tablets, in addition to 20 mg/ml oral suspension. Other brand is Paxil[TD] which contain paroxetine hydrochloride equivalent to paroxetine 10 mg, 20 mg, 30 mg

and 40 mg tablets, and also available as suspension for oral administration, each 5 ml contain paroxetine hydrochloride equivalent to paroxetine 10 mg. Paroxetine hydrochloride is chemically unrelated to the tricyclic, tetracyclic and other available antidepressants. The molecular weight is 374.8 (329.4 as free base). The structure of paroxetine hydrochloride is shown below[1]:
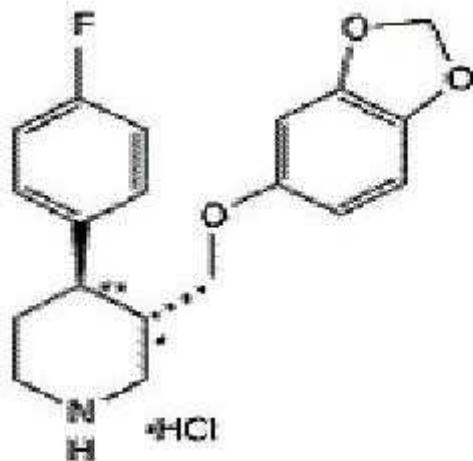
Paroxetine is a potent and selective inhibitor of 5-hydroxytryptamine (5-HT) uptake, and its antidepressant action and effectiveness is thought to be related to its specific inhibition of 5-HT uptake in brain neurons. Paroxetine is indicated for the treatment of social anxiety disorder/social phobia, general anxiety disorder, post-traumatic stress disorder, panic disorder and obsessive compulsive disorder[1]. Steady state systemic levels are attained by 7 to 14 days after starting treatment with immediate or controlled release formulations and pharmacokinetics do not appear to change during long-term therapy [1-3].

Paroxetine is extensively distributed into tissues and pharmacokinetic calculations indicate that only 1% of the paroxetine in the body resides in the plasma. At therapeutic concentrations, approximately 95% of paroxetine is protein bound. No correlation has been found between paroxetine plasma concentrations and clinical effect including adverse experiences and efficacy[1-3]. The principal

metabolites of paroxetine are polar and conjugated products of oxidation and methylation which are readily cleared. In view of their relative lack of pharmacological activity, it is most unlikely that they contribute to paroxetine's therapeutic effects. Metabolism does not compromise paroxetine's selective action on neuronal 5-HT uptake[1-3].

Urinary excretion of unchanged paroxetine is generally less than 2% of dose, whilst that of metabolites is about 64% of the dose. About 36% of the dose is excreted in stool, probably via the bile, of which unchanged paroxetine represents less than 1% of the dose. Thus, paroxetine is eliminated almost entirely by metabolism. Metabolite excretion is biphasic, being initially a result of first-pass metabolism and subsequently controlled by systemic elimination of paroxetine. The elimination half-life is variable but is generally about one day[1-3].

Paroxetine hydrochloride is well absorbed after tablet dosage form and is completely absorbed after oral dosing of a solution of the hydrochloride salt. Because of extensive first-pass metabolism of the drug in the liver, the amount of paroxetine available to the systemic circulation is less than that absorbed from the gastrointestinal tract [1-3]. Higher single doses or multiple dosing of paroxetine cause partial saturation of the first-pass effect and reduction in plasma clearance. These results in disproportional increases in plasma concentrations and pharmacokinetic parameters of paroxetine with doses, resulting in non-linear kinetics[3].The bioavailability of paroxetine is similar from oral suspension and tablets[4].

Administration of paroxetine to adult healthy subjects, adults patients, pediatric patients, elderly patients, and to different populations; showed clear differences in the primary pharmacokinetic parameters C_{max} and AUC. Beside, these studies demonstrated high inter-individual variation in the above mentioned

parameters[2-8]. Thus, a safety and efficacy concern is raised on paroxetine therapy. Therefore, the present investigation was aimed first by studying the pharmacokinetics of paroxetine in Arabic healthy subjects since up to date no pharmacokinetic data available for Arabic populations. Subsequent studies in Arabic patients and after multiple dosing need to conducted thereafter.

Materials and Methods:
Subjects:

The study was performed according to the ethical principles for clinical studies in human stipulated in the latest version of Helsinki declaration[9], and the International Conference on Harmonization (ICH) guidelines for good clinical practice (GCP)[10]. The study protocol and the informed consent form were approved by the principal investigator, clinical investigator, and the Institutional Review Board (IRB).The subjects who were willing to participate in the study provided with the informed consent forms. Each subject with two witnesses signed the informed consent from before enrolment in the study. For ethical considerations, the subjects were free to leave the study at any time for any reason. Beside, subject's withdrawal at any time during the study was also considered to protect the health of the subjects according to the clinical investigator decision.

Study design:

As per the protocol, the study was designed to recruit 36 Arabic healthy male adult subjects. The screening of eligible subjects was based on to the following inclusion criteria: age between 18-48 years, body mass index between 18-30, weight between 50-110 kg, no participation in drug research study and blood donation within a period of at least 2 months prior to receiving the investigational drug (paroxetine), non-smokers or light smokers (less than 10 cigarettes a day), no drugs or alcohol abuse, no history

of contraindication and/or hypersensitivity to paroxetine or any related compounds, not using any prescription drug therapy for at least 14 days of receiving the investigation drug, OTC drugs were permitted according to the clinical investigator decision, and finally no significant clinical abnormalities based on; physical examinations, medical history, clinical examinations (including ECG, vital signs, and temperature), and clinical laboratory tests (biochemistry, hematology, serology (-HIV, and -hepatitis B&C), liver and kidneys function tests and urine analysis).

The study was a single-center, open label, randomized, fasting, single dose design to determine the pharmacokinetics of 20 mg paroxetine hydrochloride tablets (Seroxat®, GlaxoSmithKline, UK) in Arabic population. The subjects admitted to the clinical site before about 14 hours of the investigational drug administration (about 20:00 pm) and remained confined at the clinical site until 24 hours after dosing. Alcohol abuse test and drug abuse tests (amphetamine, barbiturates, benzodiazepines, cocaine, methamphetamine, tetrahydrocannabinol, methadone, morphine, phenocyclidine, and tricyclic antidepressants) were performed during admission to exclude any positive result. Consumption of xanthine containing food and drinks were precluded 12 hours before dosing and until 24 hours after dosing. Consumption of grapefruit or grapefruit juice were prohibited within 7 days prior the study and until the completion of the whole study. A standard dinner was served to the subjects before 12 hours of dosing, thereafter, food intake prohibited until 4 hours after dosing. Water consumption was not allowed 2 hours before and 2 hours after dosing. The drug was administered with 240 ml of water. Mouth checks and hands checks were performed by the investigators to ensure that the drug was swallowed by the subjects as directed. Four hours after dosing, a standard lunch was served to the

subjects. The subjects remained sitting up-right with controlled and limited ambulation in the clinical site during the first four hours of drug dosing.

Serial blood samples (7 ml each) were obtained from each subjects via an Indwelling cannula placed into the forearm anticubital vein. The cannula was kept patent by pushing 1 ml of heparinized saline (2 IU per ml) after each blood sample withdrawal. Prior to each blood sampling, about 0.2 ml of blood was discarded from the cannula to get rid of residual blood from previous sampling. Blood was sampled from each subject before about 30 minutes of dosing (zero time), and then after 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 12.0, 24.0, 48, 72, and eventually after 96 hours post dosing. A total of 20 blood samples obtained from each subject.

The blood samples were placed into heparinized tubes and then directly centrifuged within 10 minutes at 4000 rpm to separate the plasma. The separated plasma samples were immediately trans-ferred to eppendorf tubes and then directly stored at −20°C until the analysis was performed for measurement of paroxetine concentrations for pharmacokinetic calculations. The tubes containing blood and plasma samples were labeled by confidential coding system as per in-house Standard Operating Procedures (SOP) of the research unit. Only the principal investigator and the quality assurance responsible have the excess to the labeling system.

The adverse events and serious adverse events if any, were reported by the clinical staff based on clinical obser-vations, direct questioning, and vital signs including blood pressure, pulse and temperature. The vital signs were monitored before about 30 minutes of drug dosing and then after 1, 2, 3, 6, 9, 12, 24 and eventually after the last blood sampling withdraw (96 hours post dosing), which is the time of subjects discharge.

Pharmacokinetic (PK) analysis:

The concentration of paroxetine in plasma was determined by a validated HPLC method as per FDA Bioanalytical Method Validation Guidance[11]. The method was developed in-house using MS/MS detector and paroxetine_d4 as internal standard. The lower limit of quantitation of the drug in plasma was 0.2 ng/ml and the upper limit of quantitation was 50 ng/ml.

The PK parameters; C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, K_{el} and $T_{0.5}$ were calculated for each subject by non-compartmental analysis[12] using Kinetica software. The parameters C_{max} which is the maximum (peak) concentration of the drug in plasma and the corresponding time T_{max} to reach C_{max} were determined visually from the plasma concentration versus time profile. The AUC_{0-t} which is the area under plasma concentration-time curve from time zero (t_0) to the time of last quantifiable concentration t_{last} was measured by trapezoidal rule. The $AUC_{t-\infty}$ which is the extrapolated (residual) area under plasma concentration-time curve from t_{last} to t_∞ was determined as C_{last}/K_{el}. The C_{last} is the last quantifiable concentration. The $AUC_{0-\infty}$ which is the total area under plasma concentration-time curve from t_0 to t_∞ was calculated from sum of $AUC_{0-t} + AUC_{t-\infty}$. The terminal elimination rate constant (K_{el}) was determined based on linear regression of the last concentrations in the terminal phase of the log concentration-time profile (at least three data points). The terminal elimination half-life ($T_{0.5}$) was estimated by $0.693/K_{el}$. The mean ± SD of paroxetine plasma concentrations versus time data and the log-mean values were plotted in regular and semilog graph types, respectively.
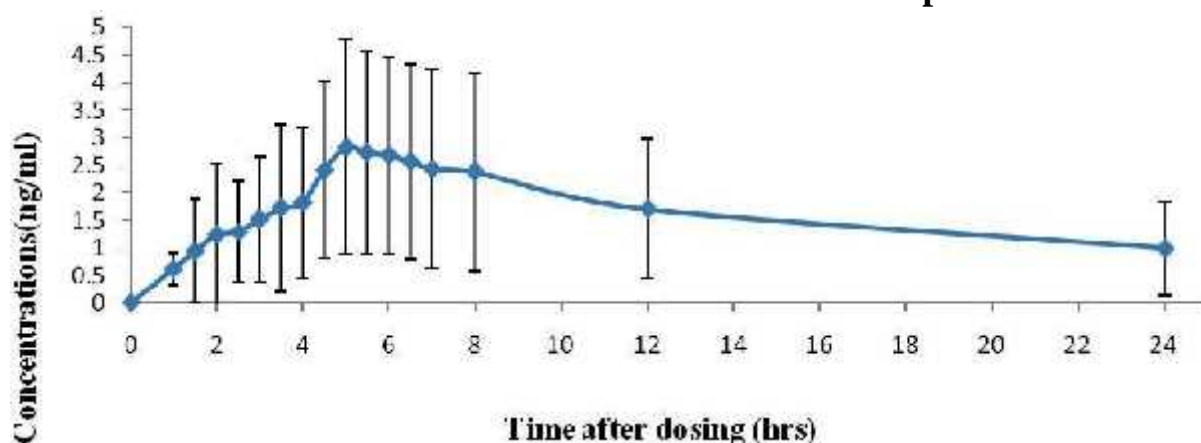
Figure-1: Paroxetine plasma concentrations - time profile after a single dose Seroxat® 20 mg tablets administered to thirty six healthy male adult fating Arabic subjects. Mean ± SD.
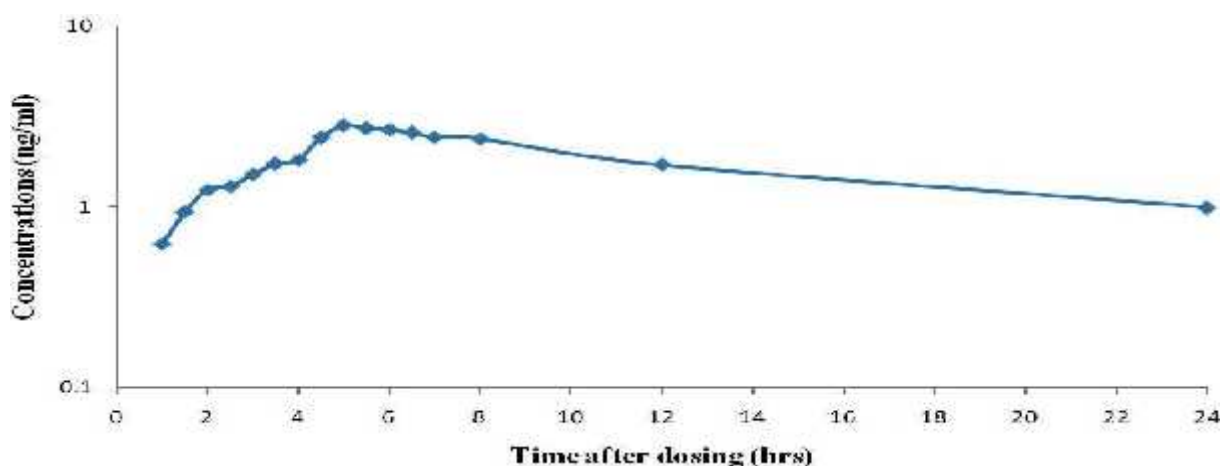

Figure-2: Paroxetine mean plasma concentrations - time profile (semilog scale) after a single dose Seroxat® 20 mg tablets administered to thirty six healthy male adult fating Arabic subjects.

Results:

Demographic data and safety assessments:

The demographic characteristics of the subjects were; mean age 25.6 years (range 18-41), mean weight 73.8 kg (range 54-105), mean height 1.75 meter (range 1.63-1.90), and mean BMI 24 (range 18.7-30.0). All the subjects participated in the study had successfully completed the investigation without any drop out or withdraw. The drug was generally safe and well tolerated by all subjects. Beside, no incidence of adverse events or serious adverse events were reported during the entire study. The subjects left the study without clinically significant changes in the safety parameters and the base line vital signs.

Drug pharmacokinetics:

Paroxetine was detected in plasma samples of all subjects after 1.0 hour of drug intake (the first sampling time). Although the sampling was up to 96 hours post dosing, the levels of paroxetine were not detected (below the lower limit of quantitation 0.2 ng/ml) in plasma samples of the subjects after 24 hours post dosing of the drug. Figures 1 and 2 shows mean plasma concentrations of paroxetine versus time profiles in regular and semilog graphs, respectively.

Table-1: Pharmacokinetic parameters of paroxetine after a single dose Seroxat® 20 mg tablets administered to thirty six healthy male adult fasting Arabic subjects. Mean ± SD.

Parameter	Mean	± SD	CV%
C_{max} (ng/ml)	3.14	2.09	66.5
T_{max} (hr)	5.1	1.28	25.0
AUC_{0-t} (ng.hr/ml)	48.6	45.9	94.5
$AUC_{0-\infty}$ (ng.hr/ml)	59.5	42.3	71.0
K_{el} (hr^{-1})	0.066	0.022	32.8
$T_{0.5}$ (hr)	11.9	5.1	42.9

Table-1 present the pharmaco-kinetic parameters C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, K_{el} & $T_{0.5}$ of paroxetine. The mean±SD for the above parameters were; 3.14±2.09 ng/ml, 5.1±1.28 hr, 48.6±45.9 ng.hr/ml, 59.5±42.3 ng.hr/ml, 0.066±0.022 hr^{-1} and 11.9±5.1 hrs, respectively. It is obvious from table-1 that considerable intersubjects variability was found in the primary pharmacokinetic parameters C_{max} and $AUC_{0-\infty}$ which reflect drug onset of effect, duration of effect, safety and efficacy, with coefficient of variation (CV) of 60-90%. The secondary parameters T_{max}, K_{el} & $T_{0.5}$ demonstrated lower CV of 25-40%.

Discussion:

Paroxetine is a selective serotonin reuptake inhibitor (SSRI). The drug is indicated for prevention and treatment of depression and anxiety disorders. These diseases impose great impact, distress and suffering for the patients, their friends and their families, in addition to major economic costs. Beside, relative to other diseases, depression is associated with high rates of recurrence and relapse, therefore, the need for long term therapy is recommended. Good knowledge of drug pharmacokinetics is the key for solving the above mentioned problems accompanied drugs therapy like paroxetine. In spite of

the wide spread of depression in Arabic population and the great use of paroxetine, up to date there is no reported data concerning the pharmacokinetics of paroxetine in Arabic population. Therefore, the present investigation was aimed to study the pharmacokinetic characteristics of paroxetine in Arabic healthy subjects to find out if there is any considerable difference with other healthy populations in one hand, and with patients on the other hand.

The current study involved the participation of 36 healthy male adult Arabic subjects with nearly similar age, weight and BMI in order to reduce the potential variability in drug pharmaco-kinetics raised by differences in subjects demographic data.

According to FDA bioanalytical method validation criteria[11], the method applied in the present investigation proved to be specific and sensitive enough for pharmacokinetic study of paroxetine in human plasma at therapeutic doses of the drug. Beside, a lower limit of quantification of 0.2 ng/ml and upper limit of quantification of 50 ng/ml applied are adequate enough for following the entire pharmacokinetic behavior of the drug in the body including drug absorption, distribution and elimination phases. The blood sampling strategy employed in the study protocol involved frequent blood sampling from 1.0 hour and up to 96 hours post dosing (20 blood samples were withdrawn from each subject) in order to distinguish and well recognize each phase and notice any fluctuation in the concentration-time profile, as shown in table-1, figures 1 and 2. The present investigation indicate that the drug is rapidly absorbed and appeared in general circulation, however it need relatively long time to peak with an average T_{max} of 5.1 hours (Table 1, Figures 1 and 2). Blood sampling for 96 hours applied in this study is extra enough for reliable estimation of the terminal elimination half-life of paroxetine in plasma since the average

extrapolated (residual) AUC was less than 20%, as shown in table-1 and figure-2.

As shown in table-1, the primary pharmacokinetics parameters which have direct impact on drug safety, onset of action, duration of effect and efficacy, namely C_{max} and AUC, demonstrated great intersubject variability with coefficient of variation (CV) ranged between 60-90 %. On the other hand, the secondary pharmacokinetic parameters, namely T_{max}, K_{el} & $T_{0.5}$ exhibited relatively lower CV of 25-40%.

The present investigation revealed that administration of a single dose of paroxetine 20 mg oral tablets to Arabic healthy adult subjects yielded a mean± SDC_{max} of 3.14±2.09 ng/ml (Table-1). This value is relatively lower that that published in other studies[2, 5-8]. A recent study showed that administration of a single dose paroxetine 40 mg oral tablets to healthy Chinese subjects yielded an average C_{max} of about 30 ng/ml[5]. However, surprisingly a previous study showed that administration of a single dose paroxetine 40 mg oral tablets to healthy Chinese subjects yielded an average C_{max} of about 60 ng/ml[6]. Other studies in Japan[7,8] indicated that administration of a single dose of paroxetine 20 mg oral tablets to healthy subjects produced mean C_{max} of about 6 ng/ml. Beside, administration of repeated doses of 20 mg oral tablets paroxetine to adult patients in a study conducted in USA revealed a mean steady state C_{max} of about 35 ng/ml with high CV of 70%[2]. The same study[2] elucidated a mean steady state C_{max} of about 50 ng/ml with large CV of 63% after administering repeated 20 mg oral tablets paroxetine to child patients. Interestingly, the same study[2] demonstrated clear dose dependent (nonlinear) pharmacokinetic of C_{max} when comparing 10 mg, 20 mg and 30 mg paroxetine oral tablets administered to both children and adult patients. It is obvious from the above reported results and the current finding that, in addition to the nonlinear kinetics in the primary

pharmacokinetic parameter of paroxetine C_{max}, there is apparent variability between populations, ages and the condition of the subjects.

Similarly, the same above mentioned variability in C_{max} is also observed for the other primary pharmacokinetic parameter which is AUC. The current finding showed an average total AUC ($AUC_{0-\infty}$) of 59.5±42.3 ng.hr/ml with considerable intersubject variation (CV=71%) as shown in Table 1. A mean total AUC of about 696 ng.hr/ml was reported recently after oral administration of a single dose of 40 mg paroxetine tablets to healthy adult Chinese subjects[5]. Other study on healthy adult Chinese subjects showed a mean total AUC of about 1086 ng.hr/ml following administration of a single oral dose of 40 mg paroxetine tablets[6]. Pharmacokinetic investigation on Japanese healthy adult subjects exhibited an average total AUC of approximately 137 ng.hr/ml with CV of 53% after single dose of 20 mg oral paroxetine tablets[7]. Other study on Japanese healthy adult subjects supported the above results with an average total AUC of about 127 ng.hr/ml and CV of 53% following a single oral dose of 20 mg paroxetine tablets[8]. Pharmacokinetic study performed in USA after multiple oral intakes of 20 mg paroxetine tablets on children and adult patients[2] showed average total AUC of about 570 ng.hr/ml with large CV of 82% on children[2], whereas, the average total AUC on adults patients was nearly 770 with big CV of 60%[2]. Other study demonstrated dose and time dependent pharmacokinetic of paroxetine including AUC and $T_{0.5}$[3]. The time dependency was found to be more pronounced after a single dose than after repeated dosing of oral 20 mg paroxetine tablets[3]. Surprisingly, the total AUC elevated dramatically from 191 ng.hr/ml to 1481 when comparing the single to repeated dosing[3]. Thus, from the above mentioned data, it is very apparent that AUC of paroxetine show interesting

pharmacokinetic behaviors including; nonlinear pharmacokinetics, variability among individuals, populations, ages, and the condition of the subject (i.e. healthy and patients).

Concerning the secondary pharmacokinetic parameters T_{max} and $T_{0.5}$, it seems that there is good agreement between the results published in many literature in one hand, and with the results found in the current investigation on the other hand. The mean T_{max} found in the present study was 5.1 ± 1.28 hr with CV 25%, and the mean $T_{0.5}$ was 11.9 ± 5.1 hrs with CV 42.9%. The published average T_{max} and $T_{0.5}$ were as follow; T_{max} 5.6 ± 1.84 hr with CV 33%, and $T_{0.5}$ 20.0 ± 5.33 hrs with CV 27%[6]; $T_{0.5}$ 16.1 ± 3.4 hrs with CV 21%[7]; $T_{0.5}$ 15.3 ± 2.4 hrs with CV 16%[8]. Besides, the investigations conducted in adult and pediatric patients after repeated doses of 10-30 mg paroxetine oral tablets revealed almost similar T_{max} values with an average of about 5.0 hours after 10 and 20 mg doses, and 3.3 hours after 30 mg doses[2]. However, interestingly the time and dose dependent variability in AUC mentioned in the above[3] was also found for the parameter $T_{0.5}$ which stated that after 15 days of therapy with 20 mg per day oral paroxetine tablets, $T_{0.5}$ elevated by 12% (elevation from 16.4 to 18.3 hrs). The increase in $T_{0.5}$ was more dramatic (more than double) after 15 days therapy with the drug (elevation from 9.8 to 21.0 hrs)[3]. The same investigation[3] also demonstrated elongation in $T_{0.5}$ in elderly patients. Therefore, according to the results found in the current investigation, and in all the above published articles, it seems that paroxetine should be administered with special and extra care taking into account all potential factors which may influence drug pharmacokinetics, and therefore therapeutic drug monitoring (TDM) is essential for safe and effective treatment with paroxetine.

Conclusion:

The current study introduce for the first time the pharmacokinetics of paroxetine 20 mg tablets administered under fasting state to healthy male adult Arabic subjects. High intersubject variability was found in the primary pharmacokinetic parameters C_{max} and AUC which arise safety and efficacy concern. Beside, Arabic population demonstrated clear differences in the primary pharmacokinetic parameters of paroxetine relative to other populations. Therefore, individualization of the administered dose and therapeutic drug monitoring (TDM) are recommended for optimal therapy with paroxetine. Further investigations need to be conducted in Arabic patients after repeated and different therapeutic doses of paroxetine to obtain more pharmacokinetic knowledge and consequently optimal therapy can be assured for Arabic patients treated with paroxetine.

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