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THE INFLUENCE OF PAROXETINE ON THE PHARMACOKINETICS OF ATOMOXETINE AND ITS MAIN METABOLITE

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Abstract

Background and aims. *To evaluate the effects of paroxetine on the pharmacokinetics of atomoxetine and its main metabolite, 4-hydroxyatomoxetine-O-glucuronide, after coadministration of atomoxetine and paroxetine in healthy volunteers.*

Methods. *22 healthy volunteers, extensive metabolizers, took part in this open-label, non-randomized, clinical trial. The study consisted of two periods: Reference, when a single oral dose of 25 mg atomoxetine was administrated to each subject and Test, when 25 mg atomoxetine and 20 mg paroxetine were coadministered. Between the two periods, the volunteers received an oral daily dose of 20-40 mg paroxetine, for 6 days. Atomoxetine and 4-hydroxyatomoxetine-O-glucuronide plasma concentrations were determined within the first 48 hours following drug administration. The pharmacokinetic parameters of both compounds were assessed using a non-compartmental method and the analysis of variance aimed at identifying any statistical significant differences between the pharmacokinetic parameters of atomoxetine and its main metabolite, corresponding to each study period.*

Results. *Paroxetine modified the pharmacokinetic parameters of atomoxetine. C_{max} increased from 221.26±94.93 to 372.53±128.28 ng/mL, while AUC_{0-t} and $AUC_{0-\infty}$ also increased from 1151.19±686.52 to 6452.37±3388.76 ng*h/mL, and from 1229.15±751.04 to 7111.74±4195.17 ng*h/mL respectively. The main metabolite pharmacokinetics was also influenced by paroxetine intake, namely $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty}$ decreased from 688.76±270.27 to 131.01±100.43 ng*h/mL, and from 4810.93±845.06 to 2606.04±923.88 and from 4928.55±853.25 to 3029.82 ±941.84 respectively.*

Conclusions. *Multiple-dose paroxetine intake significantly influenced atomoxetine and its active metabolite pharmacokinetics, causing a 5.8-fold increased exposure to atomoxetine and 1.6-fold reduced exposure to 4-hydroxyatomoxetine-O-glucuronide.*

Keywords: atomoxetine, 4-hydroxyatomoxetine , paroxetine, pharmacokinetics, drug interaction

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Background and aims

Atomoxetine (ATM) is a highly selective presynaptic norephinephrine reuptake inhibitor. The substance was approved in 2002 by the Food and Drug Administration (FDA) for the treatment of attention deficit hyperactivity disorder (ADHD) and is the first non-stimulant medication used for ADHD in children, adolescents and adults [1–5]. Although atomoxetine is not considered a first-line approach like stimulant medication, due to its milder side effect profile, it is preferred when ADHD is associated with psychiatric comorbidities such as tics, major depression, Tourette syndrome, psychosis, or anxiety [2,6]. Moreover, because of its negligible abuse potential or misuse risk, atomoxetine is recommended for patients who are at risk for substance abuse or for those who refuse to take a controlled substance [1,2,5,7].

Atomoxetine is well absorbed after oral administration, because of its high water solubility and membrane permeability. Oxidation via genetically polymorphic cytochrome P450 (CYP)2D6 is considered to be the primary metabolic pathway for this drug. As a consequence of its status as a substrate of CYP2D6 and due to the fact that CYP2D6 is characterized by genetic polymorphism, atomoxetine metabolism is a source of intersubject variability. Two subpopulations of metabolizers have been identified: extensive (EMs) and poor metabolizers (PMs) [3–5,8]. The absolute bioavailability after ingestion is 63% in EMs and 94% in PMs [4,5] and the half-life ($t_{1/2}$) of atomoxetine ranges from 5 hours in EMs to 20 hours in PMs. The main metabolite for both EMs and PMs is 4-hydroxyatomoxetine, an equipotent active metabolite which undergoes a glucuronidation process before renal excretion. CYP2D6 mediates only the biotransformation of atomoxetine to 4-hydroxyatomoxetine, while another metabolic process, N-demethylation via CYP2C19, occurs to a much lesser extent and is responsible for the forming of a minor metabolite, N-desmethylatomoxetine [1–4]. More than 80% of the parent drug is eliminated under its glucuronidated form via renal excretion, with approximately 1-2% and 13-22% fecal excretion for EMs and PMs respectively. Less than 3% of an oral dose is excreted unchanged [1,4,5].

Paroxetine is a selective and potent inhibitor of presynaptic serotonin reuptake, indicated for the treatment of major depressive disorder and anxiety disorders, including obsessive-compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, post- traumatic stress disorder and premenstrual dysphoric disorder, in the adult population [9,10].

The pharmacokinetic properties of paroxetine revealed a good absorption, almost complete, following oral administration. The steady-state plasma concentrations are achieved after 7 to 14 days in healthy volunteers [9,11]. Paroxetine is highly protein bound (about 95%) [11] and has an elimination half-life of approximately 21 hours. It is subjected to extensive hepatic metabolism primarily via CYP2D6 to inactive metabolites in EMs [9,11]. Most importantly, paroxetine is a potent inhibitor of CYP2D6 and as a result, it can alter the pharmacokinetics of coadministered drugs known as substrates of the same isoenzyme [12], like atomoxetine. Even though the existence of a pharmacokinetic interaction between atomoxetine and paroxetine was already revealed in another research [13], the objective of the present study was to confirm the previous results and to provide a deeper insight into the mechanism of this interaction by investigating its impact not only on atomoxetine pharmacokinetics, but also upon the pharmacokinetic parameters of its main active metabolite (4-hydroxyatomoxetine).

Patients and methods

Patients

Twenty-three volunteers were enrolled in the present study. All the subjects (Caucasian males and females, aged 20 to 30 years) were considered to be healthy on the basis of medical history, physical examination and clinical laboratory tests. They had no history of alcohol or substance abuse and did not take any regular medication.

The study was conducted in accordance with the principles of Helsinki (1964) and its amendments (Tokyo 1975, Venice 1983, Hong Kong 1989) and Good Clinical Practice (GCP) rules. The clinical protocol and informed consent documents were reviewed and approved by the Ethics Committee of the Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania. All participants provided informed written consent prior to the study enrollment.

Study design

An open-label, non-randomized, two-period sequential study was conducted. During the first period (Reference), a single oral dose of atomoxetine 25 mg was administered to each volunteer, while during the second period (Test) atomoxetine 25 mg was coadministered with paroxetine 20 mg. In order to obtain steady state concentrations for paroxetine, between the Reference and the Test period all the subjects received an oral dose of paroxetine 20 mg twice daily (12 h distance) for 2 days and continued with paroxetine 20 mg per day for another 4 days. The participants were in a fasted state prior to drug administration and all the doses were taken with at least 150 mL of water. Alcohol, smoking or any other medication (except the study drugs and oral contraceptives) were forbidden throughout the trial.

The pharmaceutical products used were Strattera® (atomoxetine hydrochloride, 25 mg hard capsules; Lilly SA, Hampshire, Great Britain) and Seroxat® (paroxetine hydrochloride, 20 mg film-coated tablets; SmithKline Beecham Limited, Great Britain).

Plasma samples collection and analysis

During both study periods 5 mL of venous blood was

drawn into heparinized tubes before drug administration as well as at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36 and 48 hours post- dose. The separated plasma was stored frozen (-20°C) until analysis. Atomoxetine and 4-hydroxyatomoxetine-*O*-glucuronide plasma concentrations were determined using a validated high-throughput liquid chromatography-mass spectrometry method. The HPLC system was an Agilent 1100 series (binary pump, autosampler, thermostat) (Agilent Technologies, USA) and was coupled with a Brucker Ion Trap SL (BruckerDaltonics GmbH, Germany). A Zorbax SB-C18 chromatographic column (100 mm x 3.0 mm i.d., 3.5 μm) (Agilent Technologies) was used. The mobile phase was a mixture of 2 mM ammonium formate solution and acetonitrile, elution in gradient: 11 % acetonitrile at start, 41% at 2 minutes. The flow rate was 1 mL/min and the thermostat temperature was set at 48°C. The mass spectrometry detection was in single ion monitoring mode, positive ions, using an electrospray ionization source. The ions monitored were m/z 256 for atomoxetine and m/z 448 for its metabolite, respectively. The retention times for atomoxetine and 4-hydroxyatomoxetine-*O*-glucuronide were 4.1 min and 2.2 min, respectively. The calibration curves for both atomoxetine and its metabolite were linear between 8-600 ng/mL.

Pharmacokinetic analysis

The pharmacokinetic parameters of atomoxetine and its glucuronidated active metabolite, 4-hydroxyatomoxetine-*O*-glucuronide, corresponding to both study periods (Reference and Test) were determined using a non-compartmental analysis. The maximum plasma concentration (Cmax, ng/mL) and the time to reach the peak concentration (t_{max}, h) were obtained directly by the visual inspection of each subject's plasma concentration-time profile. The elimination rate constant, $k_{el,}$ was estimated by the least-square regression of plasma concentration-time data points lying in the terminal region, by using semi-logarithmic dependence that corresponds to first-order kinetics. The terminal half-life ($t_{½}$) was calculated as 0.693/ k_{el}. The area under the concentration-time curve (AUC_{0-t}) was estimated by integration using the trapezoidal method, from time zero to the last measurable concentration at time t. The area was extrapolated to infinity ($AUC_{0-\infty}$) by addition of C_t/ k_{el} to AUC_{0-t}, where C_t is the last quantifiable drug concentration. Phoenix WinNonlin version 6.3 (Pharsight Co., Mountain View, CA, USA) software was used in order to determine the pharmacokinetic parameters.

Phenotype analysis

The AUC metabolic ratio of atomoxetine/ glucuronidated active metabolite was used to identify potential PMs and to further exclude them from the final analysis.

Statistical analysis

Statistical analysis was used in order to determine any statistical differences between the pharmacokinetic parameters of atomoxetine, as well as 4-hydroxyatomoxetine-*O*-glucuronide, calculated during the two study periods (Test versus Reference). Except for $t_{max,}$ the analysis of variance (ANOVA) was applied for the comparison of all parameters. General linear model procedures were used, in which sources of variation were subjects and study treatment.

The 90% confidence intervals (90% CIs) of the Test/Reference period ratios for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ (log transformed) were calculated using the Schuirmann's two one-sided *t* test, in order to estimate the existence of a possible clinical significance for this pharmacokinetic interaction. The bioequivalence for atomoxetine and 4-hydroxyatomoxetine-*O*-glucuronide between the two study periods was demonstrated if the 90% CIs for their corresponding pharmacokinetic parameters were within the range 0.8-1.25. Regarding the analysis of t_{max}, the equivalence range was expressed as untransformed data and significance was tested using the nonparametric Friedman test. Phoenix WinNonlin version 6.3 (Pharsight Co., Mountain View, CA, USA) software was used for the statistical analysis and the level of significance was considered to be $p<0.05$.

Results

Phenotype analysis

Based on the AUC metabolic ratio, 1 subject was identified as PM and was excluded from the final analysis (data not shown).

Demographics

The 22 EMs (15 males and 7 females) were aged 20-30 (mean ± SD, 25.27±2.31) years and with a body mass index (BMI) between 19-29.7 (24.09±3.09) kg/m^2. All the 22 EMs completed the study without protocol deviations and were included in the pharmacokinetic final analysis.

Pharmacokinetics

The mean concentration-time profiles of atomoxetine and its glucuronidated active metabolite, when administrated alone or in combination with paroxetine, after 6 days treatment with paroxetine, are shown in **Figure1** and **Figure 2**, respectively.

The mean pharmacokinetic parameters as well as their statistical interpretation, for both, atomoxetine and its metabolite, during the two study periods, are presented in **Table I** (atomoxetine) and **Table II (**4-hydroxyatomoxetine-*O*-glucuronide).

A bioequivalence evaluation for atomoxetine and its glucuronidated active metabolite was performed by using the main pharmacokinetic parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and t_{max}) determined during the two study periods (Reference and Test). The 90% CIs for atomoxetine and 4-hydroxyatomoxetine-*O*-glucuronide and the bioequivalence conclusion are presented in **Table III**.

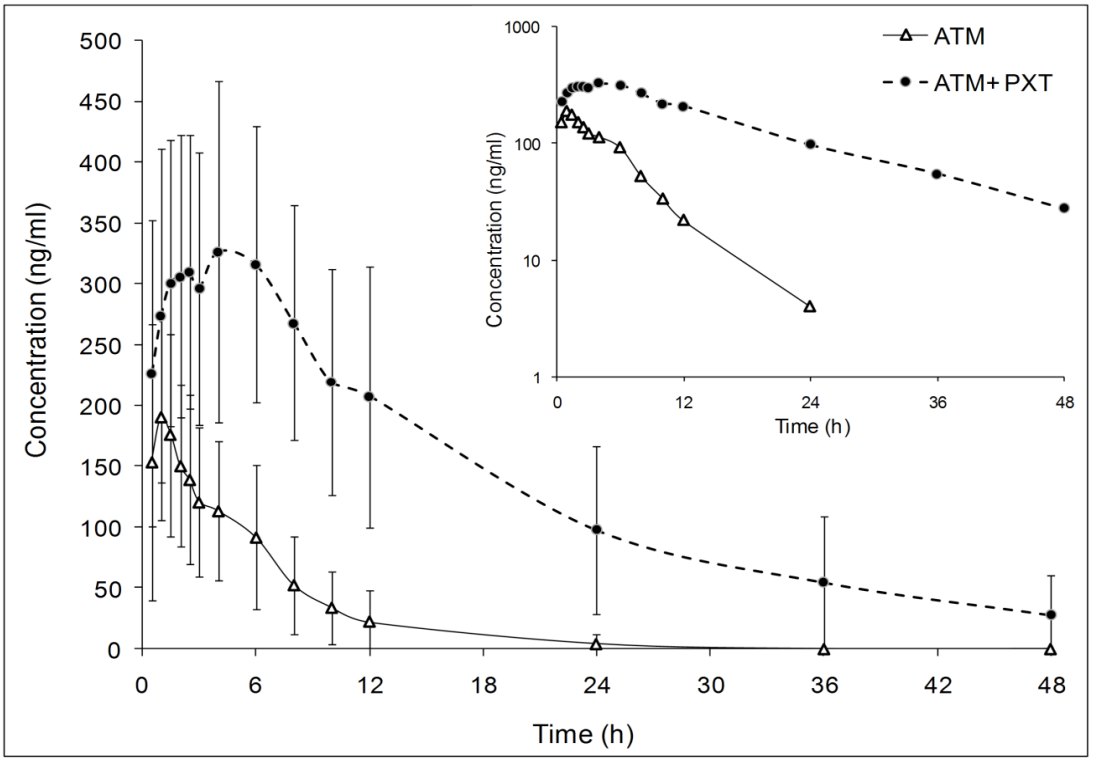

Figure 1. Mean (± SD) plasma levels of atomoxetine (ATM), after a single oral dose of atomoxetine 25 mg, before and after 6 days treatment with paroxetine (PXT) 20-40 mg/day, n=22. Insert: semilogarithmic presentation.

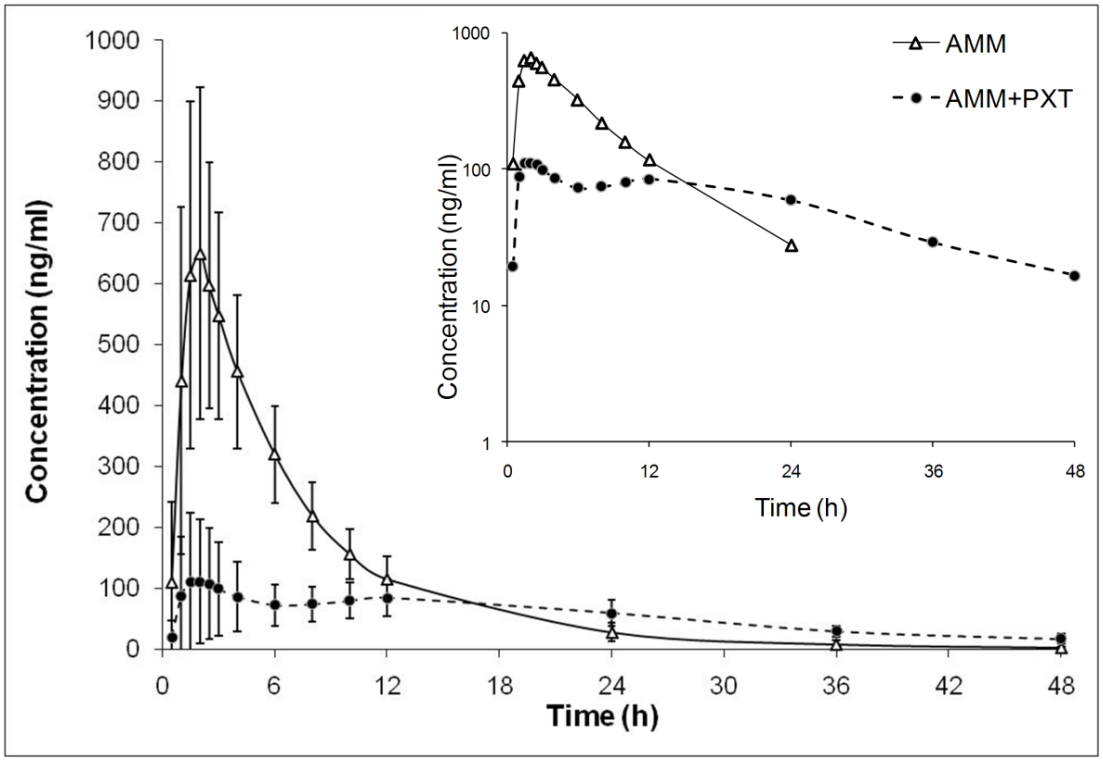

Figure 2. Mean (± SD) plasma levels of 4-hydroxyatomoxetine-*O*-glucuronide (AMM), after a single oral dose of atomoxetine 25 mg, before and after a 6 days treatment with paroxetine (PXT) 20-40 mg/day, n=22. Insert: semilogarithmic presentation.

Table I. Pharmacokinetic (Pk) parameters of atomoxetine (ATM), after a single oral dose of 25 mg atomoxetine, before and after a 6 days treatment with paroxetine (PXT) 20-40 mg/day, in 22 healthy volunteers (EMs) and the results of statistical analysis of variance (ANOVA) test used for comparison.

Pk parameter (mean ± SD)	ATM alone	ATM + PXT	P* value (ANOVA**)
C_{max} (ng/mL)	221.26±94.93	372.53±128.28	0.000000 S
AUC_{0-t} (ng*h/mL)	1151.19±686.52	6452.37±3388.76	0.000000 S
$AUC_{0-\infty}$ (ng*h/mL)	1229.15±751.04	7111.74±4195.17	0.000000 S
t_{max} (h)	1.30±1.20	3.05±2.18	Friedman, S
k_{el} (1/h)	0.23±0.08	0.07±0.02	0.000000 S
$t_{½}$ (h)	3.57±1.71	11.79±3.77	0.000000 S

*Statistically significant(S) for P<0.05; ** ANOVA except where stated otherwise

Table II. Pharmacokinetic (Pk) parameters of 4-hydroxyatomoxetine-*O*-glucuronide (AMM), after a single oral dose of 25 mg atomoxetine, before and after a 6 days treatment with paroxetine (PXT) 20-40 mg/day, in 22 healthy volunteers (EMs) and the results of statistical analysis of variance (ANOVA) test used for comparison.

Pk parameter (mean ± SD)	AMM alone	AMM + PXT	P* value (ANOVA**)
C_{max} (ng/mL)	688.76± 270.27	131.01± 100.43	0.000000 S
AUC_{0-t} (ng*h/mL)	4810.93± 845.06	2606.04± 923.88	0.000000 S
$AUC_{0-\infty}$ (ng*h/mL)	4928.55± 853.25	3029.82 ± 941.84	0.000000 S
t_{max} (h)	2.07± 0.73	7.77± 6.13	Friedman, S
k_{el} (1/h)	0.13±0.03	0.05±0.02	0.000000 S
$t_{½}$ (h)	5.71± 1.47	15.57± 6.17	0.000000 S

*Statistically significant(S) for P< 0.05; ** ANOVA except where stated otherwise

Table III. Bioequivalence evaluation of pharmacokinetic parameters of atomoxetine (ATM) and its glucuronidated active metabolite (AMM), before and after a 6 days treatment with paroxetine, in 22 healthy volunteers =(EMs).

ATM/ AMM	Pharmacokinetic parameter	90% CI	Bioequivalence conclusion
ATM	C_{max}	1.53±1.94	Bio-ineq
	AUC_{0-t}	4.79±7.47	Bio-ineq
	$AUC_{0-\infty}$	4.88±7.58	Bio-ineq
	t_{max}	Friedman	Bio-ineq
AMM	C_{max}	0.13±0.20	Bio-ineq
	AUC_{0-t}	0.45±0.58	Bio-ineq
	$AUC_{0-\infty}$	0.53±0.65	Bio-ineq
	t_{max}	Friedman	Bio-ineq

90% CI- 90% confidence intervals
Bioequivalent if 90% CI fall between: 0.8-1.25
Bio-ineq: Bio-inequivalent

Discussion

ADHD is a neurodevelopmental disorder characterized by excessive inattention, hyperactivity, and impulsivity [14]. Although it has a childhood onset, it can persist into adulthood [15] and approximately 60 to 70% of children diagnosed with this disorder grow into adulthood retaining at least some, if not all the specific manifestations of ADHD [16].

A large percent of adults with ADHD (75%) are associated with at least one psychiatric condition [17]. Mood, anxiety, sleep, personality disorders and substance use disorders are acknowledged as the most common comorbidities in adults with ADHD [18] and these comorbid diagnoses represent one of the reasons for using a combination of medications [19]. The Texas Children's Medication Algorithm Project (CMAP) concluded that in the case of ADHD associated with other disorders, like major depressive disorder (MDD), the first step includes an evaluation of the severity of both disorders, with the purpose of initiating a treatment for the most severe one first. In case the symptoms of MDD persist even though the symptoms of ADHD were resolved, the guidelines specify that antidepressant therapy should be considered alongside treatment for ADHD. Serotonin reuptake inhibitors can also be added to ADHD therapy for patients with ADHD and comorbid anxiety [20]. The treatment recommendations for managing adult ADHD and depression are similar to those for children [21] and acknowledge as a third-line treatment option the association of atomoxetine and antidepressants [22]. Moreover, a study conducted by Kratochvil *et al.* revealed that atomoxetine and fluoxetine, a selective serotonin reuptake inhibitor (SSRI), combination therapy was effective in improving symptoms of ADHD associated with depression and anxiety [23] .

Atomoxetine is considered an alternative treatment option for ADHD patients not responding to stimulant medications and for those unable to tolerate their side-effects [24]. Paroxetine is an antidepressant indicated for the treatment of MDD and anxiety disorders and is also a potent inhibitor of CYP2D6 [9], the same isoenzyme involved in atomoxetine metabolism. Therefore, the combination of atomoxetine and paroxetine could be encountered in clinical practice for treating ADHD associated with MDD or anxiety disorders, but precaution may be needed considering their relation to CYP2D6. Even though the existence of a phamacokinetic interaction between atomoxetine and paroxetine was already established in a previous study [13], the objective of this research was to reassess the influence of paroxetine on atomoxetine pharmacokinetics and to further investigate the interaction by also evaluating its impact upon 4-hydroxyatomoxetine, the main active metabolite.

Because CYP2D6 is the main metabolizing enzyme of atomoxetine, its genetic polymorphism influences its pharmacokinetics [25]. Therefore, in order to avoid any interference with the study results, the PMs were identified by using the AUC metabolic ratio (atomoxetine/metabolite) and subsequently were excluded from the final analysis.

The present study revealed that the coadministration of atomoxetine and paroxetine, after 6 days pretreatment with paroxetine, had a great influence upon atomoxetine metabolism. Figure 1 shows that the mean plasma concentrations of atomoxetine have increased after atomoxetine and paroxetine intake. Furthermore, the results presented in Table I and II, indicate a marked drug-drug interaction. The metabolic changes are clearly observed, as the exposure (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) to atomoxetine notably increased after the addition of paroxetine. A comparative analysis of the pharmacokinetic parameters of atomoxetine calculated during the two periods of the study revealed that C_{max} values were 1.7-fold higher (221.26±94.93 vs. 372.53±128.28 ng/mL) during the Test period when the two drugs were given together. Also, AUC_{0-t} and $AUC_{0-\infty}$ increased 5.6-fold, respectively 5.8-fold, after combined atomoxetine and paroxetine intake. The calculated values of these parameters varied from 1151.19±686.52 to 6452.37±3388.76 ng*h/mL, respectively from 1229.15±751.04 to 7111.74±4195.17 ng*h/mL, before and after paroxetine multiple-dose treatment. Both absorption and elimination processes were significantly altered, as t_{max}, $t_{½}$ and k_{el} underwent substantial changes between the two periods (Reference and Test). As displayed in Table I, $t_{½}$ increased by 3.3-fold, while k_{el} underwent a 3.3-fold reduction when atomoxetine was coadministered with paroxetine (Test) in comparison with atomoxetine alone (Reference), thus highlighting the presence of a metabolic drug-drug interaction between the two substances.

A previous study conducted by Belle *at al* investigated the pharmacokinetic interaction between paroxetine and atomoxetine in 22 healthy subjects characterized as EMs. The study concluded that paroxetine was responsible for approximately 3.5-, 6.5- and 2.5-fold increases in C_{max}, AUC_{0-t} and $t_{1/2}$ of atomoxetine. Although the pharmacokinetic interaction between atomoxetine and this antidepressant was clearly demonstrated, this study was unable to evaluate the impact of paroxetine intake on 4-hydroxyatomoxetine due to the fact that the main metabolite could not be quantified, as a significant number of subjects had undetectable levels. The present study was able to quantify the glucuronide form of 4-hydroxyatomoxetine, which provided a better understanding of the mechanisms involved in this drug interaction.

The pharmacokinetic profile of 4-hydroxyatomoxetine-*O*-glucuronide, before and after pretreatment with paroxetine, confirmed the strong interaction between atomoxetine and the enzymatic inhibitor of CYP2D6. Figure 2 reveals that in the presence of paroxetine, the mean plasma concentrations of 4-hydroxyatomoxetine-O-glucuronide

were drastically decreased. Significant changes for all the pharmacokinetic parameters are shown in Table II. More specifically, C_{max}, AUC_{0-t} and AUC_{0-} demonstrated a 5.2-fold (688.76±270.27 to 131.01±100.43 ng*h/mL), 1.8-fold (4810.93±845.06 to 2606.04±923.88) and 1.6-fold (4928.55±853.25 to 3029.82±941.84) reduction after paroxetine coadministration. $t_{½}$ increased 2.7 times, while k_{el} decreased 2.6 times. These results support the fact that CYP2D6 mediated the biotransformation of atomoxetine to 4-hydroxyatomoxetine, its main active metabolite. Therefore, by inhibiting CYP2D6, paroxetine alters the process of metabolism of atomoxetine, resulting in a decreased exposure to 4-hydroxyatomoxetine-*O*-glucuronide.

All the pharmacokinetic parameters of atomoxetine and its active metabolite demonstrated statistically significant differences ($p<0.05$ for each calculated parameter) between the two study periods, which represent another confirmation of the marked impact that paroxetine has upon atomoxetine and its main metabolite pharmacokinetics.

All the data presented above illustrate that the biotransformation of both parent drug and its active metabolite goes through a pronounced change between the two study periods. The 90% CIs for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ corresponding to atomoxetine and its active glucuronidated metabolite, were outside the acceptable limits of bioequivalence: 0.8-1.25 (Table III), hence suggesting that the pharmacokinetic interaction between atomoxetine and paroxetine may also have clinical relevance.

Even though the clinical consequences of this pharmacokinetic interaction were not investigated in the present study, precaution is needed during paroxetine and atomoxetine coadministration. Due to increased exposure to atomoxetine, this association could lead to atomoxetine-related side-effects especially after multiple-dose intake of this drug. The most common adverse events reported during atomoxetine treatment include dry mouth, insomnia, nausea, decreased appetite, constipation, dizziness, sweating, dysuria and sexual problems [5]. Atomoxetine treatment was also associated with small increases in blood pressure and heart rate in children, adolescents and adults [26]. In a previous study, the association of atomoxetine and paroxetine lead to episodes of tachycardia related to postural changes, thus suggesting a possible pharmacodynamic interaction between the two drugs that needs further investigation [13]. The association of atomoxetine and fluoxetine presented greater increases in blood pressure and heart rate in comparison to atomoxetine monotherapy and although the differences were not statistically different, these results emphasize the need to monitor cardiovascular parameters during atomoxetine and SSRIs combined pharmacotherapy [23].

Study limitations

Even though the AUC metabolic ratio (atomoxetine/metabolite) was performed in order to identify and further exclude PMs, a genotype analysis of CYP2D6 was not conducted, which we acknowledge as a limitation of the present study. Another limitation is the lack of information concerning the potential clinical consequences of the pharmacokinetic interaction between atomoxetine and paroxetine. Although a previous research included a clinical assessment of atomoxetine and paroxetine combination, additional studies are required in order to establish the clinical relevance of this association.

Conclusion

The present study demonstrated that paroxetine, due to the capacity of inhibiting CYP2D6, significantly influenced the pharmacokinetics of atomoxetine and its main glucuronidated active metabolite, 4-hydroxyatomoxetine-*O*-glucuronide . As a result of this interaction, the exposure to atomoxetine was increased by 5.8-fold, while the exposure to the active metabolite was reduced by 1.6-fold. Because this combination could be associated with clinical consequences, precaution is recommended during coadministration.

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