

RESEARCH ARTICLE

Atomoxetine and Duloxetine: Evaluation of a Potential Pharmacokinetic Drug-Drug Interaction

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Objective: The present research aimed to investigate whether a pharmacokinetic drug interaction exists between atomoxetine, a substrate of CYP2D6 and duloxetine, an enzymatic inhibitor of the same metabolic pathway. **Methods:** Twenty-three healthy volunteers were enrolled in an open-label, non-randomized, sequential, 2-period clinical study. During the trial, they received a single dose of atomoxetine 25 mg (Period 1:Reference) followed by a combination of atomoxetine 25 mg and duloxetine 30 mg, after a pretreatment regimen with duloxetine 30-60 mg/day for 4 days (Period 2:Test). The pharmacokinetic parameters of atomoxetine and its main metabolite (4-hydroxyatomoxetine-O-glucuronide) were estimated using a non-compartmental approach and statistical tests were used to compare these parameters between study periods. **Results:** A total of 22 subjects, extensive metabolizers (EMs), were considered for the final report of the study findings. Duloxetine influenced the plasma concentration-time profile of both parent drug and its glucuronidated metabolite. The pharmacokinetic and statistical analysis revealed that pretreatment with the enzymatic inhibitor increased the mean atomoxetine AUC_{0-t} (from 1151.19 ± 686.52 to 1495.54 ± 812.40 [ng*h/mL]) and $AUC_{0-\infty}$ (from 1229.15 ± 751.04 to 1619.37 ± 955.01 [ng*h/mL]) while k_{el} was decreased and the mean $t_{1/2}$ was prolonged. With regard to 4-hydroxyatomoxetine-O-glucuronide, C_{max} was reduced from 688.76 ± 270.27 to 621.60 ± 248.82 [ng/mL] after coadministration of atomoxetine and duloxetine. **Conclusions:** Duloxetine had an impact on the pharmacokinetics of atomoxetine as it increased the exposure to the latter by ~30%. Although the magnitude of this pharmacokinetic interaction is rather small, a potential clinical relevance cannot be ruled out with certainty without further investigation.

Keywords: atomoxetine, 4-hydroxyatomoxetine-O-glucuronide, duloxetine, pharmacokinetic interaction

Received 27 May 2019 / Accepted 12 July 2019

Introduction

Atomoxetine, a selective and potent norepinephrine reuptake inhibitor, is the first nonstimulant agent indicated for the management of attention deficit hyperactivity disorder (ADHD) in pediatric and adult patients [1–3]. With a rapid absorption from the gastrointestinal tract, it reaches peak plasma concentrations (C_{max}) within 1-2 hours after oral intake [1,3]. The biotransformation process involves three metabolic pathways: aromatic ring-hydroxylation, benzylic hydroxylation and N-demethylation. The first one is the most important biotransformation step, is mainly mediated by CYP2D6 and leads to formation of 4-hydroxyatomoxetine. The latter is the primary and only active metabolite of atomoxetine and is equipotent to the parent drug as an inhibitor of the norepinephrine transporter. However, it is rapidly inactivated by glucuronidation and eliminated in the urine [3–5]. Given the genetic polymorphism of CYP2D6, the bioavailability of atomoxetine can vary between 63% in individuals considered extensive metabolizers (EMs) and 94% in those characterized as poor metabolizers (PMs); the mean plasma elimination half-life ($t_{1/2}$) ranges between 5.2 hours in EMs and 21.6 hours in

PMs [1,3]. Most of the oral dose (80-96%) is eliminated as glucuronidated metabolites *via* urinary excretion while less than 3% is excreted as unchanged drug [3,5].

Duloxetine, a serotonin-norepinephrine reuptake inhibitor, is widely recommended for the treatment of depression and generalized anxiety disorder. Apart from psychiatric conditions, it is also used to treat diabetic neuropathic pain, stress urinary incontinence and fibromyalgia [6,7]. Following oral administration, duloxetine reaches C_{max} in about 6 hours and has a bioavailability that ranges from 32% to 80% [8]. With a $t_{1/2}$ of approximately 10-12 hours, steady-state levels can be achieved within 3 days. This compound is not only a substrate, but also a moderate inhibitor of CYP2D6 [6,8].

Scientific sources report that a depressive disorder is 2 to 4 times more likely to appear for 30 to 60 % of adults diagnosed with ADHD [9]. Based on the recommendations of The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force, pharmacotherapeutic agents for ADHD, including atomoxetine, can be considered as add-ons to antidepressant agents in patients diagnosed with mood disorders and comorbid ADHD [10]. The 2019 European Consensus Statement regarding the diagnosis and treatment of adult ADHD also underlines the fact that combined psychopharmacology may be fre-

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quently needed due to a high rate of psychiatric comorbidity [11]. Duloxetine could be considered a viable option in these circumstances as some preliminary promising results reported that it can improve ADHD symptoms in children, adolescents and adults [12,13]. Therefore, as the data supports the hypothesis of a potential concomitant administration of atomoxetine and duloxetine in clinical practice and considering their common metabolic pathway, the objective of this study was to investigate whether the two drugs are involved in a metabolic drug interaction, in healthy subjects.

Methods

Participants

The study population comprised Caucasian, healthy, non-smoking men and women (age range: 18-55 years; body mass index (BMI) ≤ 25 kg/m²). Exclusion criteria included significant medical or medication history that can alter drug response and identification of any abnormal findings during various evaluation tests (clinical examination, electrocardiogram (ECG) and blood tests (hematology - complete blood count; biochemistry - sodium, potassium, calcium, transaminases (aspartate transaminase (AST) and alanine transaminase (ALT)), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), urea, glucose, uric acid, cholesterol and triglycerides, creatinine, total bilirubin and total serum protein levels, immunology and serology tests - screening for pregnancy, human immunodeficiency virus (HIV), syphilis, hepatitis B and C). Those with a history of alcohol or substance abuse and those unable to comply with the study requirements were also considered not eligible. Follow-up visits were performed approximately 30 days after the end of the trial.

Ethical approval

The clinical trial was carried out in accordance with the requirements of Good Clinical Practice (GCP) and the ethical standards included in the 1964 Declaration of Helsinki and its later amendments. Furthermore, an appropriate ethics committee (Ethics Committee of the University of Medicine and Pharmacy "Iuliu Hatieganu" from Cluj-Napoca, Romania) reviewed and approved the study protocol. Each volunteer provided a written informed consent before any study-related procedures were initiated.

Study design

The single-site study included 2 periods (Period 1:Reference and Period 2:Test) and used a prospective, open-label and sequential design, without randomization, to determine the effect of multiple-dose duloxetine on the pharmacokinetics of atomoxetine. During Period 1, subjects received a single oral dose of atomoxetine 25 mg (Strattera[®], atomoxetine hydrochloride 25 mg, capsules, manufactured by Lilly SA, Madrid, Spain). During Period 2, they were given a combination of duloxetine 30 mg (Cymbalta[®], duloxetine hydrochloride 30 mg, delayed-release capsules,

manufactured by Lilly SA, Madrid, Spain) and atomoxetine 25 mg, after a pretreatment regimen with duloxetine (Figure 1).

More specifically, before the concomitant administration of the two study drugs, a loading dose of duloxetine (60 mg/day) was given to all subjects, for 2 days, in order to speed up the process of reaching steady-state levels and thus ensuring a maximum inhibitory effect. Afterwards, the dose of the enzymatic inhibitor was reduced to 30 mg/day (2 days) to lower the risk of adverse effects. Overall, the chosen dosing regimen took into consideration the need to rapidly achieve steady-state concentrations for duloxetine while minimizing potential safety concerns and the importance of using dosing patterns usually encountered in clinical practice. The medicines were administered in the morning, under fasting conditions and only with water (≥ 150 mL). Volunteers were asked to abstain from consumption of methylxanthine-containing beverages for 2 days prior to the start of the clinical trial and throughout the entire study period. Intake of any other drug except the study medication and oral contraceptives was not permitted during the course of the trial. Alcohol consumption and smoking were also not allowed.

Blood sample collection and analysis

During both study periods, blood samples (5 ml) were collected on Day 1 (Reference) and Day 6 (Test) into sodium heparin-containing tubes, predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36 and 48 hours after oral administration of atomoxetine (Figure 1). Plasma samples were obtained by centrifugation at 9000 rotations per minute (rpm), for 6 minutes, and were stored at -20°C until their analysis.

High-performance liquid chromatography/tandem mass spectrometry assay (LC-MS) was used to determine the plasma concentrations of atomoxetine and its main metabolite. All LC-MS analyses were performed on an Agilent 1100 system equipped with a binary pump, autosampler and thermostat (Agilent Technologies, Santa Clara, CA, USA) and coupled with a Bruker Ion Trap SL (Bruker Daltonics GmbH, Bremen, Germany). Chromatographic separation was carried out on a Zorbax SB-C18, (Agilent Technologies) column, 100 mm x 3.0 mm i.d, 3.5 μl . The operating conditions included the following: mobile phase (2 mM ammonium formate solution/acetonitrile mixture), flow rate (1 mL/min), gradient program (at start \rightarrow 11% acetonitrile; after 2 minutes \rightarrow 41% acetonitrile), column temperature (48°C). Ionization was achieved by using electrospray in the positive ion mode; the ions monitored were m/z 256 for the parent drug (atomoxetine) and m/z 448 for its main metabolite (4-hydroxyatomoxetine-O-glucuronide). Atomoxetine retention time was 4.1 minutes while 2.2 minutes was the value corresponding to 4-hydroxyatomoxetine-O-glucuronide. The parameters used to validate the analytical method were linearity, specificity, intra- and inter-day precision, accuracy and analyte

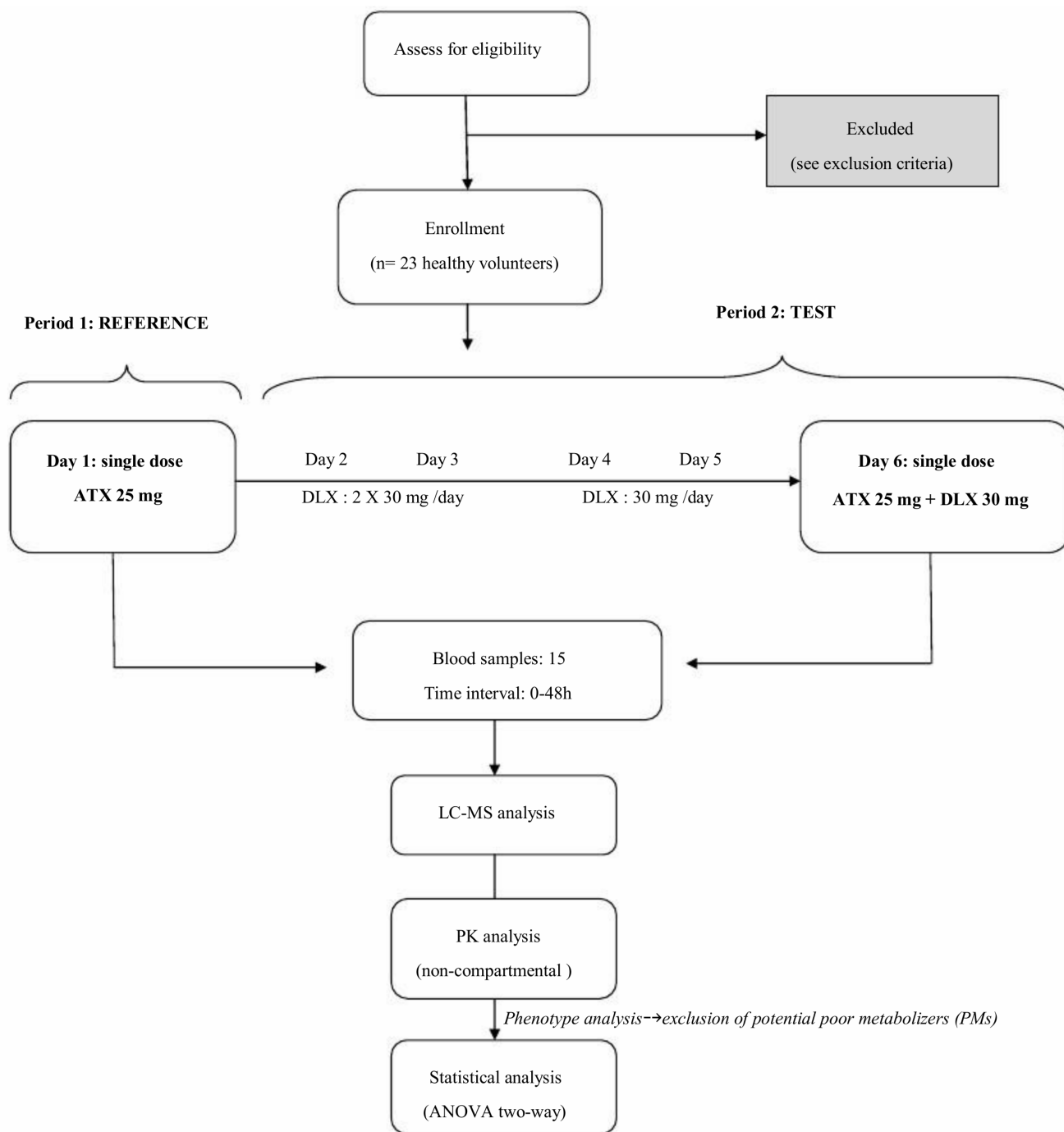


Fig. 1. Flowchart of the two study periods. Abbreviations: ANOVA - analysis of variance; ATX - atomoxetine; DLX - duloxetine; LC-MS - liquid chromatography–mass spectrometry; PK - pharmacokinetic.

recovery. The calibration curves were linear over a range of 8-600 ng/mL for both analytes; the correlation coefficients (mean ± standard deviation (SD), n = 5) were as follows: $r=0.9951\pm0.0016$ for atomoxetine, $r= 0.9982\pm0.0018$ for 4-hydroxyatomoxetine-*O*-glucuronide. The intra- and inter-day precision value was <8.2% for the parent drug and <10.7% for the glucuronidated active metabolite whereas the accuracy yielded a percentage of less than 11.5% and less than 9.3%, respectively. Their average recoveries were in the range of 89-103% for atomoxetine and between 91 and 105% for 4-hydroxyatomoxetine-*O*-glucuronide.

Pharmacokinetic analysis

The pharmacokinetic analysis was performed using Phoenix WinNonlin® software (Pharsight Co., Mountain View, CA, USA), version 6.3. The non-compartmental method was employed to determine the pharmacokinetic parameters of atomoxetine and 4-hydroxyatomoxetine-*O*-glucuronide, corresponding to both study periods (Reference/Test). The maximum plasma concentration (C_{max} , ng/ml) and time to reach C_{max} (t_{max} , h) were obtained directly from the plasma concentration-time curves. The elimination half-life ($t_{1/2}$, h) was calculated as $0.693/k_{el}$, where k_{el} (h^{-1}), the elimina-

tion rate constant, was the slope of log-linear regression of the terminal phase of the concentration-time curve. The area under the concentration-time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{0-t} , ng*h/mL) was obtained by using the linear trapezoidal method. Finally, the AUC extrapolated to infinity ($AUC_{0-\infty}$, ng*h/mL) was estimated as $AUC_{0-t} + C_t/k_{el}$, where C_t represents the last measurable concentration.

Phenotype analysis

CYP2D6 phenotype status was assessed for each subject by using the $AUC_{0-\infty}$ metabolic ratio ($MR_{AUC_{0-\infty}} = AUC_{0-\infty_atomoxetine} / AUC_{0-\infty_4\text{-hydroxyatomoxetine-O-glucuronide}}$). This calculus was done with the purpose of identifying all subjects characterized as potential PMs and subsequently ensuring their exclusion from the final analysis.

Statistical analysis

To compute the sample size for the differences between pharmacokinetic parameters, we used G*Power[®] (Germany), version 3.1.9.4 [14]. The simulations aimed for a power of 90%, with a level of significance of 0.05, for paired t-test, and a two-tailed p-value. We checked for different scenarios with correlation coefficients ranging from 0.01 to 0.99. We started the simulations with data from articles comparing atomoxetine 25 mg with different inhibitors like fluvoxamine [15], bupropion [16], and paroxetine [17]. From these articles, we used the average of the means of the $AUC_{0-\infty}$, the means of the standard deviations and the maximum of the standard deviations for worse scenarios. The majority of the simulations gave sample sizes ranged between 6 and 15, except the worse ones around 26. Thus, we aimed to enroll close to 25 subjects in our study.

Analysis of variance (ANOVA) with 2 sources of variation (subjects and study treatment) was conducted to detect differences between the pharmacokinetic parameters (except t_{max}) of atomoxetine and its active metabolite, in the presence and absence of duloxetine. (Test (vs) Reference). A second statistical method, the non-parametric assay known as the Friedman test, was used to compare the mean t_{max} values between study periods. The analyses were performed using Phoenix WinNonlin[®] software (Pharsight Co., Mountain View, CA, USA), version 6.3. Statistical significance was defined as $p < 0.05$.

Bioequivalence analysis

This methodology was used to obtain preliminary data regarding potential clinical consequences attributed to concomitant atomoxetine and duloxetine intake. Schuirman's two one-sided test procedure, an equivalence testing approach, was used to calculate the 90% confidence intervals (90% CIs) of the ratio (Test/Reference) for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ (log transformed). In order to fulfill the bioequivalence criteria, the 90% CI values

should be included within the acceptance interval of 0.80-1.25; for t_{max} , the range was expressed as untransformed data while the Friedman assay was used to establish significance level. The bioequivalence analysis followed the same protocol for both parent drug and glucuronidated active metabolite and was performed using Phoenix WinNonlin[®] software (Pharsight Co., Mountain View, CA, USA), version 6.3.

Results

Phenotypic assessment

An individual assessment of the $MR_{AUC_{0-\infty}}$ showed that the calculated values followed a normal distribution for 22 of the 23 volunteers initially included in the study (data not shown). Subsequently, the 22 subjects were considered to be EMs and were included in the final study sample. On the other hand, 1 subject proved to be an outlier and a potential PM which led to his exclusion from the final data analysis and interpretation.

Demographic data

The 22 Caucasian EMs included 15 men and 7 women with ages ranging between 20 and 30 years. Mean (\pm SD) BMI was 24.09 ± 3.09 kg/m².

Pharmacokinetic and statistical analysis

The mean plasma concentration-time profiles of atomoxetine [A] and its main metabolite, 4-hydroxyatomoxetine-O-glucuronide [B], when administered alone or in combination with the enzymatic inhibitor, duloxetine, are presented in *Figure 2*.

The following tables include the mean pharmacokinetic parameters of atomoxetine (*Table I*) and its glucuronidated active metabolite (*Table II*), for each treatment phase, and the main findings of the statistical tests used for comparison (Test vs Reference).

Bioequivalence analysis

The 90% CIs for both parent drug and active metabolite and the bioequivalence results are presented in *Table III*.

Safety evaluation

No clinically significant changes in vital signs, ECG and laboratory parameters were found when the health status of each subject was reassessed after the end of the trial. Special attention was given to the evaluation of the liver function before and after the administration of the study drugs. Thus, the following mean values (\pm SD) for ALT and AST were recorded: 14.94 ± 9.51 vs 13.30 ± 10.02 UI/l (ALT) and 16.75 ± 5.02 vs 16.53 ± 5.11 UI/l (AST) for female subjects (normal values: 5-33 UI/l (ALT), 5-32 UI/l (AST)), 21.95 ± 9.55 vs 16.20 ± 5.24 UI/l (ALT) and 22.97 ± 12.61 vs 17.86 ± 3.52 UI/l (AST) for male subjects (normal values: 5-41 UI/l (ALT), 5-40 UI/l (AST)).

No serious adverse events were reported and all the volunteers completed the study.

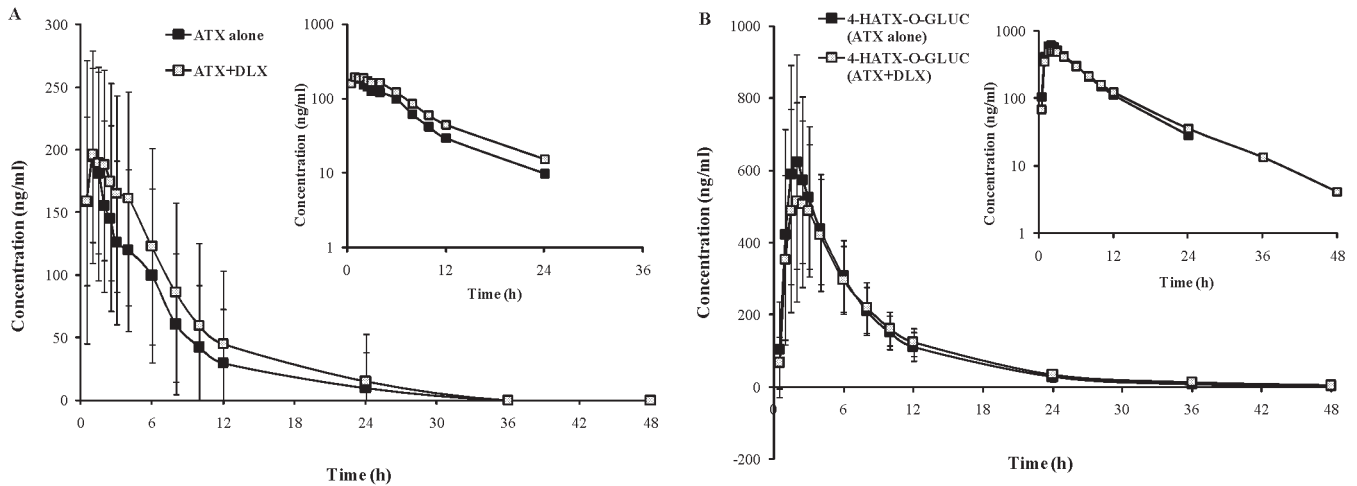


Fig. 2. Mean (\pm SD) plasma levels of atomoxetine (ATX; [A]) and its glucuronidated active metabolite, 4-hydroxyatomoxetine-O-glucuronide (4-HATX-O-GLUC; [B]), after a single oral dose of ATX 25 mg, before and after a 4-day pretreatment regimen with duloxetine (DLX: 30-60 mg/day), in 22 extensive metabolizers (EMs); Insert: semilogarithmic presentation.

Table I. Pharmacokinetic (PK) parameters for atomoxetine (ATX) after oral administration of 25-mg ATX alone (single dose) and following a 4-day pretreatment drug regimen with duloxetine (DLX) (30-60 mg/day), in 22 extensive metabolizers (EMs) and the statistical test results after interperiod comparison

PK parameters (mean \pm SD)	ATX (Period 1: ATX monotherapy)	ATX (Period 2: ATX+ DLX)	p* value (ANOVAa)
C _{max} (ng/mL)	221.26 \pm 94.93	226.07 \pm 57.83	0.411468, NS
t _{max} (h)	1.30 \pm 1.20	1.48 \pm 1.14	Friedman, NS
AUC _{0-t} (ng*h/mL)	1151.19 \pm 686.52	1495.54 \pm 812.40	0.000325, S
AUC _{0-∞} (ng*h/mL)	1229.15 \pm 751.04	1619.37 \pm 955.01	0.000158, S
k _{el} (1/h)	0.23 \pm 0.08	0.17 \pm 0.09	0.004857, S
t _{1/2} (h)	3.57 \pm 1.71	4.91 \pm 2.01	0.004857, S

*Statistically significant (S) at p< 0.05; statistically non-significant (NS); ^aANOVA except explicitly stated otherwise

Table II. Pharmacokinetic (PK) parameters of 4-hydroxyatomoxetine-O-glucuronide (4-HATX-O-GLUC) after oral administration of 25-mg ATX alone (single dose) and following a 4-day pretreatment drug regimen with duloxetine (DLX) (30-60 mg/day), in 22 extensive metabolizers (EMs) and the statistical test results after interperiod comparison

PK parameters (mean \pm SD)	4-HATX-O-GLUC (Period 1: ATX monotherapy)	4-HATX-O-GLUC (Period 2: ATX+ DLX)	p* value (ANOVAa)
C _{max} (ng/mL)	688.76 \pm 270.27	621.60 \pm 248.82	0.013971, S
t _{max} (h)	2.07 \pm 0.73	2.18 \pm 0.80	Friedman, NS
AUC _{0-t} (ng*h/mL)	4810.93 \pm 845.06	4842.92 \pm 958.21	0.931475, NS
AUC _{0-∞} (ng*h/mL)	4928.55 \pm 853.25	4958.99 \pm 944.73	0.895879, NS
k _{el} (1/h)	0.13 \pm 0.03	0.11 \pm 0.02	0.000900, S
t _{1/2} (h)	5.71 \pm 1.47	6.59 \pm 1.48	0.000900, S

*Statistically significant(S) at p< 0.05; statistically non-significant (NS); ^aANOVA except explicitly stated otherwise

Table III. Bioequivalence analysis of the pharmacokinetic (PK) parameters of atomoxetine (ATX) and its glucuronidated active metabolite (4-HATX-O-GLUC), before and after a 4-day pretreatment regimen with duloxetine (30-60 mg/day), in 22 extensive metabolizers (EMs)

Analyte	PK parameters	90% CIa	Bioequivalence conclusionb
ATX	C _{max}	0.93-1.21	Bio-eq
	AUC _{0-t}	1.21-1.56	Bio-ineq
	AUC _{0-∞}	1.22-1.56	Bio-ineq
	t _{max}	Friedman	Bio-ineq
4-HATX-O-GLUC	C _{max}	0.84-0.96	Bio-eq
	AUC _{0-t}	0.97-1.02	Bio-eq
	AUC _{0-∞}	0.97-1.02	Bio-eq
	t _{max}	Friedman	Bio-eq

^a90% CI- 90% confidence intervals; ^bBio-equivalent (Bio-eq) if 90% CI: 0.8-1.25; Bio-ineq; Bio-inequivalent

Discussion

ADHD is one of the most common childhood neurodevelopmental disorders, characterized by inattention, impulsivity and motor hyperactivity [18]. Nonetheless, the perception that this illness is restricted to children and adolescents is not accurate, as more than 50 % of those diagnosed with ADHD can experience part of the symptoms in adulthood [19,20]. A meta-analysis conducted by Willcutt *et al.* reported a prevalence of 5.9 -7.1 % for ADHD in children and adolescents [21] whereas for the adult population, The World Mental Health Survey Initiative established a prevalence rate ranging from 1.2 % to 7.3 % in a study that included ten countries across Americas, Europe and Middle East [22]. As atomoxetine is one of the main agents used to treat ADHD [1] and data regarding its pharmacokinetic

interactions are limited, the present study considered providing new information regarding its safety profile by investigating a potential drug interaction with duloxetine.

Since CYP2D6 is highly polymorphic and CYP2D6 inhibitors have little or no impact on atomoxetine pharmacokinetics in PMs [3], all data related to the subject identified as potential PM was removed from the final analysis in order to avoid any interference with the study outcomes. Besides the CYP2D6 PM status, two other potential confounding factors should be addressed. First, the use of hormonal steroid contraceptives can be problematic as the scientific literature provides evidence that compounds such as progesterone, pregnanolone, pregnenolone, 17 β -estradiol, and 17 β -hydroxyprogesterone are substrates and inhibitors of CYP2D6 [23]. However, even though the use of oral contraceptives was not considered exclusion criteria, none of the female subjects reported using this type of medication which disproves the hypothesis regarding a possible interference with the study results. Second, atomoxetine exposure can be increased when hepatic impairment is present [5] and, in some cases, duloxetine use was associated with hepatic injury [24]. However, in this study, no significant increases of liver transaminases were reported after treatment with the antidepressant and as a result, duloxetine-induced hepatotoxicity was also excluded as a potential interfering factor.

In the present research, the mean plasma concentration-time profile illustrated in *Figure 2 (A)* showed that a 4-day pretreatment with duloxetine produced a moderate increase in atomoxetine plasma concentrations. Contrarily, the mean plasma concentrations of the glucuronidated active metabolite suffered a slight decrease during the Test period (*Figure 2 (B)*) due to enzymatic inhibition, as the process slowed down the biotransformation of the substrate and the production of metabolite.

The pharmacokinetic analysis revealed that most of the calculated parameters for atomoxetine showed statistically significant changes between study periods (*Table I*). For example, the enzymatic inhibitor caused a 1.3-fold (~ 30%) increase in both AUC_{0-t} and $AUC_{0-\infty}$ for atomoxetine. The increased exposure can be interpreted as an indicator for the existence of a metabolic interaction between atomoxetine (CYP2D6 substrate) and duloxetine (CYP2D6 enzymatic inhibitor). Moreover, compared to Period 1, when atomoxetine was administered alone, during Period 2, after duloxetine pretreatment, a 26% decrease was reported for k_{cl} value while atomoxetine $t_{1/2}$ was prolonged by 37.5%. This suggests that, in this case, the clearance of the parent drug was reduced under the influence of the enzymatic inhibitor. As for C_{max} and t_{max} , no statistically significant differences were observed between study periods. In addition, the pharmacokinetic profile of the glucuronidated active metabolite (4-hydroxyatomoxetine-*O*-glucuronide) confirmed the drug-drug interaction. Duloxetine pretreatment significantly influenced three pharmacokinetic parameters of this compound as it decreased C_{max} and k_{cl} by

9.7% and 15.3%, and increased the mean $t_{1/2}$ value by ~ 15% (*Table II*).

Up until now, a relatively small number of studies provided information about the pharmacokinetic interactions of atomoxetine. Previous trials that evaluated the impact of other CYP2D6 inhibitors on atomoxetine pharmacokinetics concluded that paroxetine [25], bupropion [16] and fluvoxamine [15] increased the exposure to this agent by approximately 6.5-, 5.1- and 1.3-fold, respectively. In comparison with these antidepressants, duloxetine had only a modest impact on atomoxetine pharmacokinetics, comparable to fluvoxamine but much more reduced than paroxetine.

According to the bioequivalence analysis, the 90% CIs of t_{max} , AUC_{0-t} and $AUC_{0-\infty}$ corresponding to atomoxetine were not in the acceptable limit range (*Table III*), which could indicate a potential clinical relevance in this case. Even though bioequivalence was established for the rest of the pharmacokinetic parameters and the results revealed only a small magnitude for this pharmacokinetic interaction, any conclusion with regard to potential clinical outcomes cannot be drawn without additional investigations. Until then, caution is required whenever atomoxetine and duloxetine are concomitantly administered in clinical practice as the consequences of this pharmacokinetic interaction are not precisely known. In trials that included adult patients, the most frequently reported adverse events of atomoxetine were nausea, dry mouth and decreased appetite. Similar side effects (headache, abdominal pain and decreased appetite) were noted for children [26]. Several studies found slight increases in blood pressure and heart rate during treatment with atomoxetine which suggests that monitoring of cardiovascular parameters should be taken into consideration for safety purposes [27,28]. In a case report published in 2011, the addition of fluoxetine to the medication regimen of a 26 years patient who had been receiving atomoxetine for the past 6 years, led to an increased exposure to the ADHD agent, which caused the patient to experience cardiovascular side effects such as syncope, orthostatic hypotension and tachycardia [29]. Furthermore, whenever atomoxetine is coadministered with duloxetine, a potential pharmacodynamic interaction can also be present as the latter might cause additive increases in blood pressure [11].

Limitations

The absence of genotyping data that could have confirmed the phenotype analysis results can be considered as an important limitation of the present research. In addition, we acknowledge the fact that this study only focused on pharmacokinetic aspects and did not provide any useful information regarding the clinical relevance of this pharmacokinetic interaction.

Conclusion

Exposure to atomoxetine was increased after pretreatment with duloxetine. Thus, it can be concluded that the antide-

pressant has an impact on atomoxetine pharmacokinetics, but supplementary studies, preferably with a multiple-dose atomoxetine regimen, are needed in order to provide information with respect to any potential clinical consequences. Although the clinical relevance is not yet known, this research offers some insight that could be helpful to clinicians in the process of treatment selection in patients with ADHD and comorbid psychiatric disorders.

Conflicts of interest

None to declare.

Authors' contribution

Ioana Todor (Data curation; Writing – original draft)

Adina Popa (Methodology; Writing – review & editing)

Dana Muntean (Data curation)

Maria Neag (Investigation; Supervision)

Ana-Maria Gheldiu (Data curation; Writing – review & editing)

Corina Briciu (Data curation; Formal analysis; Writing – original draft)

Daniel Leucuta (Formal analysis; Methodology; Writing – review & editing)

Laurian Vlase (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – review & editing)

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