ORIGINAL ARTICLE

ASSESSMENT OF FLUVOXAMINE EFFECTS ON THE PHARMACOKINETICS OF ZOLPIDEM AND ITS METABOLITE IN HEALTHY VOLUNTEERS

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Abstract

The objective of this study was to investigate the effects of fluvoxamine on the pharmacokinetics of zolpidem and its main metabolite, zolpidem phenyl-4-carboxylic acid (Z4CA) in healthy volunteers. The study consisted of 2 periods: Period 1 (Reference), when the volunteers received a single dose of 5 mg zolpidem and Period 2 (Test), when a combination of 5 mg zolpidem and 100 mg fluvoxamine was administered, after a pre-treatment regimen with fluvoxamine for 6 days. The pharmacokinetic parameters of zolpidem and its metabolite were determined by using non-compartmental methods. Pre-treatment with fluvoxamine increased the mean peak plasma concentration (C_{max}) of zolpidem. Also, after concomitant intake of fluvoxamine, the total area under the curve ($AUC_{0-\infty}$) was significantly increased from 340.34 ± 249.02 to 725.05 ± 429.23 ng*h/mL. As for Z4CA, C_{max} was reduced from 117.08 ± 37.55 to 82.33 ± 25.71 ng/mL. After fluvoxamine intake, the clearance of Z4CA was to some extent impaired as suggested by reducing the elimination rate constant (k_{el}) and by prolonging its half-life ($t_{½}$).This study demonstrated that fluvoxamine was responsible for a 2.13-fold exposure to zolpidem and influenced Z4CA pharmacokinetics to a lesser degree. The clinical implications of this interaction need additional studies.

Rezumat

Acest studiu a urmărit evaluarea efectului fluvoxaminei asupra farmacocineticii zolpidemului și a metabolitului său principal, zolpidem 4-fenil-acid carboxilic (Z4CA) la voluntari sănătoși. Studiul a inclus 2 perioade: Perioada 1 (Referință) în care voluntarii au primit o doză unică de 5 mg zolpidem și Perioada 2 (Test) în care s-au administrat 5 mg zolpidem și 100 mg fluvoxamină, după un pretratament cu fluvoxamină timp de 6 zile. Parametrii farmacocinetici ai zolpidemului și ai Z4CA au fost determinați folosind analiza non-compartimentală. Tratamentul cu fluvoxamină a dus la creşterea concentrației plasmatice maxime (C_{max}) a zolpidemului și totodată, a determinat o creștere semnificativă a ariei de sub curbă totale ($AUC_{0-\infty}$) de la 340,34 ± 249,02 la 725,05 ± 429,23 ng*h/mL. Pentru Z4CA s-a înregistrat o scădere a C_{max} de la 117,08 ± 37,55 la 82,33 ± 25,71 ng/mL. Reducerea constantei de viteză a eliminării (k_{el}) și prelungirea timpului de înjumătățire ($t_{½}$) sugerează reducerea *clearance*-ului pentru Z4CA în urma tratamentului cu fluvoxamină. Fluvoxamina a crescut expunerea la zolpidem de 2,13 ori, în timp ce impactul asupra farmacocineticii metabolitului a fost mai puțin semnificativ. Sunt necesare studii suplimentare pentru stabilirea relevanței clinice a interacțiunii dintre zolpidem și fluvoxamină.

Keywords: zolpidem, fluvoxamine, zolpidem phenyl-4-carboxylic acid, pharmacokinetics

Introduction

Zolpidem is a non-benzodiazepine hypnotic agent of the imidazopyridine class recommended for the short-treatment of insomnia. This drug acts as an agonist at the benzodiazepine binding site of the gamma-aminobutyric acid type A (GABA-A) receptor [2, 3, 23]. It has very strong hypnotic properties and weak anxiolytic, myorelaxant and anticonvulsant properties [2, 23]. Zolpidem is rapidly absorbed following oral administration and has a bioavailability of approximately 70% [2, 4, 23]. The time required to achieve peak plasma concentration is about 1.6 h [2] and it displays linear pharmacokinetics in the 5-20 mg dose range [23]. The drug is highly bound to plasma proteins (approximately 92%). The mean elimination half-life ($t_{1/2}$) of zolpidem is 2.6 hours for a 5 mg dose and 2.5 hours for a 10 mg dose [9]. Zolpidem undergoes extensive hepatic metabolism *via* oxidation and hydroxylation to three metabolites,

principally by CYP3A4 and to a lesser extent by other isoenzymes [3, 4, 23]. *In vitro* studies demonstrated that three isoenzymes are responsible for the majority of zolpidem clearance and the relative contribution of each one is as follows: CYP3A (61%), CYP2C9 (22%) and CYP1A2 (14%) [6, 25]. Its major metabolites are zolpidem 6-carboxylic acid and zolpidem phenyl-4-carboxylic acid (Z4CA) [12, 20]. More precisely, the 4-carboxy-derivative is the predominant one and its fraction represents 72–86% of the administrated dose [12]. None of the metabolites of zolpidem appear to have any pharmacological activity [2, 6].

Fluvoxamine is a potent and selective inhibitor of serotonin reuptake (SSRI) [5, 8, 17] indicated in Europe for the treatment of major depressive episodes and obsessive-compulsive disorder [1], meanwhile in USA and Japan, it was also approved for the treatment of social anxiety disorders [1, 14].

It is almost completely absorbed (more than 90%) after oral administration Fluvoxamine undergoes a high first-pass metabolism and its bioavailability is approximately 50% [1, 5, 8]. The mean plasma half-life is about 13-15 h after a single dose and 17-22 h after repeated dosing [1]. Steady-state concentrations are achieved within approximately 10 days after the initiation of therapy. Fluvoxamine is characterized by nonlinear pharmacokinetics, with higher doses resulting in disproportionately higher concentrations [1, 5]. It is mainly metabolized in the liver by CYP450 isoenzymes (CYP1A2, CYP2D6) through demethylation and deamination [14, 17]. 11 metabolites have been identified for fluvoxamine and all are inactive [5, 8, 17].

Fluvoxamine is a potent inhibitor of CYP1A2 and CYP2C19 and a moderate inhibitor of CYP2C9 and CYP3A4 [15, 21]. In a small proportion, it also has an effect upon CYP2D6 activity [21]. As a consequence of its effect on the enzymatic activity of several CYP isoenzymes, fluvoxamine can be responsible for numerous pharmacokinetic interactions when combined with drugs that are substrates of the same isoenzymes [8], including zolpidem.

Although the existence of a pharmacokinetic interaction between zolpidem and fluvoxamine was already revealed in a previous research [24], the objective of this study was to confirm and support previous findings and to further investigate the impact of fluvoxamine on the pharmacokinetic parameters of Z4CA, a major metabolite of zolpidem, whose determination is of primary importance for toxicological investigations.

Materials and Methods

Subjects

The study was conducted according to the principles of Declaration of Helsinki (1964) and its amendments (Tokyo 1975, Venice 1983, Hong Kong 1989) and Good Clinical Practice (GCP) rules. The clinical protocol was reviewed and approved by the Ethics Committee of the University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania. All volunteers gave their written informed consent prior to study inclusion.

Twenty healthy, non-smoking volunteers were enrolled in the study. The health condition of each volunteer was determined based on medical history, a physical examination, a haematological test and electrocardiogram. They had no history of alcohol or drug abuse and did not take any regular medication.

Study design

The study was designed as an open-label, single-centre, non-randomized study that consisted of 2 periods: Period 1 (Reference), when volunteers received a single oral dose of 5 mg zolpidem and Period 2 (Test), when each volunteer received a combination of 5 mg zolpidem and 100 mg fluvoxamine. Between the two periods, the subjects were treated for 3 days with a daily dose of 50 mg fluvoxamine and for another 3 days with a single daily dose of 100 mg fluvoxamine in order to obtain steady-state at the end of this period, while representing doses typical of clinical practice. The consecutive doses of fluvoxamine were administered at the clinical site, under medical supervision.

The volunteers were confined in the study centre following an overnight fast of at least 12 hours. No consumption of alcohol or any beverages or foods containing methylxanthines (coffee, tea, cola etc.) was permitted from 48 hours prior to the first drug administration and until the collection of last blood sample of the respective study period. No fluid was allowed one hour prior to study drug administration. Following drug administration with at least 150 mL tap water, the volunteers were allowed to drink water starting two hours after dosing. During each in-house day, volunteers were provided with standardized meals (breakfast, lunch and dinner) scheduled at the same time in each period of the study, respectively after the 3-h, 6-h and 10-h post dose blood samples had been collected.

All medications were given in the morning, in fasted state. The pharmaceutical products used were Stilnox® (10 mg film-coated tablets, Sanofi-Aventis - Romania) and Fevarin® (50 and 100 mg film-coated tablets, Abbott Healthcare Products B.V - The Netherlands).

Analysis of plasma samples

Venous blood (5 mL) was drawn into heparinized tubes before dosing and at the following times: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36 and 48 hours after drug administration. The separated plasma was stored frozen (-20°C) until analysis. Zolpidem and Z4CA 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 (Brucker Daltonic s 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 multiple reactions monitoring mode, positive ions, using an electro-spray ionization source. The ion transitions monitored for zolpidem were m/z (235.5; 263.2) from 308 and for its metabolite m/z (265.1; 266.1; 293.1) from 338, respectively. The calibration curves for both zolpidem and its metabolite were linear between 2-400 ng/mL.

Pharmacokinetic analysis

The pharmacokinetic parameters of zolpidem and its metabolite (Z4CA) were analysed by using standard non-compartmental methods. The maximum plasma concentration (C_{max}, ng/mL) and the time to reach the peak plasma concentration (t_{max}, h) were observed directly from the plasma concentration-time profile of each participant. The area under the concentration-time curve from time 0 to time of last quantifiable concentration (AUC_{0-t}) was obtained using the linear trapezoidal method. $AUC_{0-\infty}$ from time 0 to infinity was calculated by addition of C_t/ k_{el} to AUC_{0-t} where C_t is the last quantifiable drug concentration and k_{el} is the elimination rate constant. 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 half-life ($t_{½}$) was calculated as $0.693/k_{el}$. Pharmacokinetic analyses were carried out using Phoenix WinNonlin 6.1 (Pharsight, SUA) software.

Statistical analysis

Analysis of variance (ANOVA) was used to compare the calculated pharmacokinetic parameters of zolpidem and its metabolite for the two periods, using general linear model procedures, in which sources of variation were the subject and the period.

A bioequivalence analysis was performed in order to identify possibly clinically significant differences in pharmacokinetic parameters. For estimation of bioequivalence, Schuirmann's two one-sided t test was conducted for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ (log transformed) with a 90% confidence interval (CI) [16]. The bioequivalence between zolpidem administered alone or in combination with fluvoxamine, as well as for Z4CA, was concluded if the 90% confidence intervals for pharmacokinetic parameters were within the range 0.8-1.25. For t_{max}, the bioequivalence range was expressed as untransformed data, and significance was tested using the nonparametric Friedman test.

Statistical analysis was performed using Phoenix WinNonlin 6.1 (Pharsight, SUA) software. Statistical significance was defined as $p < 0.05$.

Safety Evaluation

Safety evaluation was conducted throughout the study and included any change in the patient's condition throughout the study. The intensity of daytime sleepiness was evaluated using an empirical scale, respectively 1 (mild), 2 (moderate) and 3 (severe).

Results and Discussion

Demographics

Twenty healthy non-smoking caucasian volunteers were enrolled for the study (12 males and 8 females). The mean age of the subjects was 25.05 ± 4.01 years old, 68.77 ± 12.58 their weight and 1.73 ± 0.08 their height (mean ± SD). All the subjects completed the study and were included in the pharmacokinetic analysis.

Pharmacokinetic analysis

The mean plasma concentration-time profiles for zolpidem and its metabolite following administration of zolpidem alone or in combination with fluvoxamine are shown in Figure 1 (zolpidem) and Figure 2 (Z4CA), respectively.

Co-administration of zolpidem and fluvoxamine, after pre-treatment with fluvoxamine for 6 days produced a marked increase in zolpidem mean plasma concentrations and in the same time, a decrease in Z4CA mean plasma concentrations. The elevated concentration of zolpidem was particularly noticeable in the initial 2 hours after zolpidem and fluvoxamine intake.

The mean pharmacokinetic parameters of zolpidem, when administered alone or in combination with fluvoxamine, as well as the statistical test results, are presented in Table I (zolpidem).

The combination with fluvoxamine increased the mean C_{max} of zolpidem by 27%, from 65.48 to 83.19 ng/mL, the mean AUC_{0-t} by 115 %, from 327.06 to 702.29 ng*h/mL and the mean $AUC_{0-\infty}$ by 113%, from 340.34 to 725.05 ng*h/mL. Fluvoxamine significantly increased t_{max} from 1.28 h to 1.90 h and extended the $t_{½}$ of zolpidem by 75%, from 3.55 h to 6.20 h. The statistical analysis concluded that fluvoxamine had a significant influence upon zolpidem pharmacokinetics. These results are consistent with previous findings which demonstrated that concomitant intake of fluvoxamine increased exposure to zolpidem by 150% and that fluvoxamine influences zolpidem metabolism in both pre-systemic and systemic

manner [24]. More specifically, in the present study the co-administered zolpidem exhibited a significantly higher C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ indicating a pre-systemic metabolic drug-drug interaction, meanwhile the increase in the half-life of zolpidem as well as its decrease in clearance, as a result of impaired hepatic drug metabolism, suggested an effect of systemic drug-drug interaction.

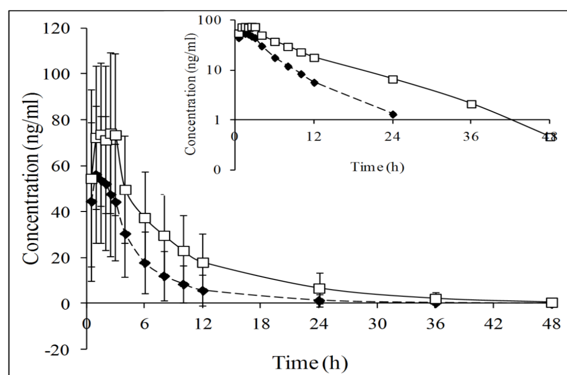

Figure 1.
Mean ± SD plasma concentration - time curves of zolpidem (5 mg, p.o.) administered alone (dotted line) or in combination(continuous line) with fluvoxamine (100 mg, p.o.) after pre-treatment with fluvoxamine for 6 days (50 mg/day for 3 days and 100 mg/day for 3 days), n = 20. inset: semi-logarithmic presentation.

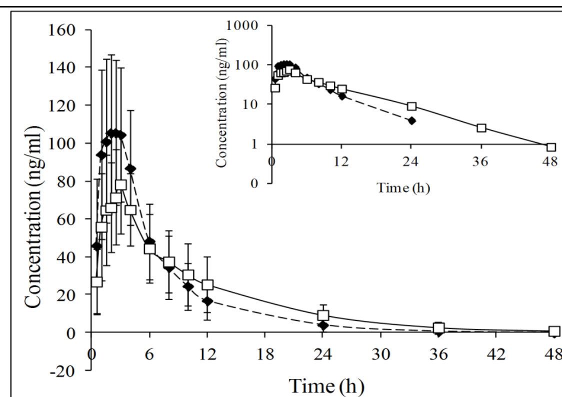

Figure 2.
Mean ± SD plasma concentration–time curves of zolpidem phenyl-4-carboxilic acid (Z4CA, zolpidem main metabolite) corresponding to zolpidem (5 mg, p.o.) administered alone (dotted line) or in combination (continuous line) with fluvoxamine (100 mg, p.o.), after pre-treatment with fluvoxamine for 6 days (50 mg/day for 3 days and 100 mg/day for 3 days), n = 20. inset: semi-logarithmic presentation.

The increase of zolpidem t_{max} when administered with fluvoxamine is a consequence of the decrease of its k_{el}, as

$$t_{max}=1/(k_a-k_{el})*Ln(k_a/k_{el}).$$

Table I

Pharmacokinetic (PK) parameters of zolpidem in 20 healthy volunteers after a single oral dose of 5 mg zolpidem, before and after treatment with fluvoxamine and the results of statistical test used for comparison

PK parameter (mean ±SD)	Zolpidem	Zolpidem + fluvoxamine	*p** value, ANOVA
C_{max} (ng/mL)	65.48 ±28.49	83.19 ± 32.72	0.00055, S
t_{max}(h)	1.28 ± 0.9	1.90 ± 0.93	0.01805,S
AUC_{0-t} (ng*h/mL)	327.06 ± 241.11	702.29 ± 422.75	0.00000, S
$AUC_{0-\infty}$ (ng*h/mL)	340.34 ± 249.02	725.05 ± 429.23	0.00000, S
k_{el}(1/h)	0.27 ± 0.19	0.15 ± 0.10	0.00016,S
$t_{½}$ (h)	3.55 ± 1.94	6.20 ± 2.53	0.00016,S

Statistically significant (S) when $p < 0.05$; NS – non-significant

Fluvoxamine is known to inhibit several cytochrome P450 isoenzymes, like CYP1A2, CYP2C19, CYP3A4, CYP2C9 and CYP2D6 [21]. Also, zolpidem is metabolised by CYP3A4 (~61%), CYP2C9 (~22%), CYP1A2 (~14%) and CYP2D6 (~3%) [25]. Until now, fluvoxamine demonstrated the greatest impact upon zolpidem pharmacokinetics according to the present study and previous researches [24]. Co-administration of zolpidem and this antidepressant was associated with a 2.55-fold increase in zolpidem $AUC_{0-\infty}$ in the first study [24], while in the present study fluvoxamine co-treatment resulted in 2.13-fold increased exposure to zolpidem. These results can be explained by the capability of fluvoxamine to strongly inhibit CYP1A2 and moderately inhibit CYP3A and CYP2C9, three isoenzymes majorly involved in zolpidem metabolism [6]. Strong and relatively selective CYP3A inhibitors, like ketoconazole, itraconazole and ritonavir were responsible for only a small increase in the AUC ratio (1.67-, 1-32- and 1.28-fold) of zolpidem [6, 7]. The explanation for this result resides in the fact that the metabolic clearance of zolpidem is not solely CYP3A-dependent. Other drugs, such as triazolam and midazolam were associated with greater AUC ratios when associated with the same CYP3A inhibitors because their clearance is completely dependent on CYP3A [6].

A summary of the pharmacokinetic parameters of zolpidem main metabolite, Z4CA, before and after pre-treatment with fluvoxamine, is illustrated in Table II.

Table II

Pharmacokinetic (PK) parameters of zolpidem phenyl-4-carboxilic acid (Z4CA, zolpidem main metabolite) in 20 healthy volunteers after a single oral dose of 5 mg zolpidem, before and after treatment with fluvoxamine and the results of statistical test used for comparison

PK parameter (mean ±SD)	Z4CA	Z4CA + fluvoxamine	p* value, ANOVA
C_{max} (ng/mL)	117.08± 37.55	82.33 ± 25.71	0.00060, S
t_{max}(h)	2.23 ± 0.88	3.05 ± 1.09	0.03054, S
AUC_{0-t} (ng*h/mL)	803.5± 283.52	829.40± 305.38	0.71390, NS
$AUC_{0-\infty}$ (ng*h/mL)	827.19±287.45	872.38 ±304.10	0.44063, NS
k_{el}(L/h)	0.18 ± 0.13	0.12 ± 0.09	0.00059, S
$t_{½}$ (h)	4.90 ± 2.13	7.41 ± 2.83	0.00059, S

Statistically significant (S) when $p < 0.05$; NS – non-significant

In comparison to the previous research, the present study also analysed the effect of the pharmacokinetic interaction upon zolpidem major metabolite (Z4CA), which can bring a deeper approach on the mechanism and magnitude of the interaction. The design of the trial was similar for both studies, as far as the dosing regimen of zolpidem is concerned. For the present study, between the two periods, the subjects were treated for 3 days with a single daily dose of 50 mg fluvoxamine and for the next 3 days with a single daily dose of 100 mg fluvoxamine whereas in the former study the subjects were treated for 6 consecutive days with a single daily dose of 100 mg fluvoxamine. The pharmacokinetic parameters varied in a similar manner for both studies, but a slight difference between the values was observed (they were higher for the present study by almost 10-15%). The overall magnitude of the interaction was also similar, an increase by approximately 150% of zolpidem's concentration being observed.

As a consequence of fluvoxamine and zolpidem metabolic interaction, C_{max} of Z4CA exhibited a decrease by 30%, from 117.08 to 82.33 ng/mL. As for the other pharmacokinetic parameters, the elimination of Z4CA was significantly reduced as k_{el} decreased by 33%, from 0.18 to 0.12 L/h and $t_{½}$ of the elimination process increased by 52%, from 4.90 to 7.41 h, thus suggesting that zolpidem metabolite is, to some extent, metabolized *via* the same metabolic pathway as the parent drug. AUC_{0-t} and $AUC_{0-\infty}$ of Z4CA did not present a statistically significant increase after co-administration of zolpidem and fluvoxamine. Hence, the systemic exposure to Z4CA was not majorly modified after co-administration with fluvoxamine. Considering that Z4CA is devoid of any degree of pharmacodynamic activity [2, 6], even a marked effect of fluvoxamine upon Z4CA pharmacokinetic parameters would not be associated with any alteration regarding the pharmacological effect of zolpidem. Nonetheless, the analysis of Z4CA pharmacokinetic parameters following administration of fluvoxamine furthermore supports the notion of a systemic drug-drug interaction between zolpidem and this antidepressant. Additionally, although Z4CA, the main metabolite of zolpidem is pharmacologically inactive [2, 6], several studies concentrated in proposing new methods of detection considering its utility in clinical and forensic settings [12, 13, 18]. Zolpidem has been implicated in drug-facilitated sexual assault (DFSA) and driving under the influence of drugs (DUID) cases and zolpidem metabolite can provide evidence for zolpidem intake. In a study that investigated the applicability of using zolpidem metabolite in determining zolpidem compliance in chronic pain patients demonstrated that metabolite testing identified 99 % of zolpidem use [19]. Hence, there are several studies that propose different rapid and accurate methods for the simultaneous determination of zolpidem and its major metabolites in human blood or urine, emphasizing that metabolite analysis is a solution to prolonging the window of detection for zolpidem [20, 22]. The increased incidence of polypharmacy and the fact that zolpidem metabolite analysis can be useful in toxicological determinations underlines the importance of the present study whose objective is to investigate fluvoxamine influence not only upon zolpidem pharmacokinetics, but also upon its main metabolite (Z4CA) pharmacokinetic parameters.

There was no bioequivalence between zolpidem alone and in combination with fluvoxamine, as evidenced by the fact that the 90% CI for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ did not fall in the 0.8-1.25 range (Table III). As for Z4CA, although C_{max} and t_{max} did not pass the bioequivalence test, this has no clinical relevance since the metabolite is not active.

Because the present study clearly demonstrated that fluvoxamine significantly altered zolpidem pharmacokinetics, co-administration of these drugs might lead to zolpidem-related adverse effects. The most common side effects reported for zolpidem in post-marketing studies include drowsiness, dizziness, headache and/or gastrointestinal symptoms (nausea, vomiting) [9, 23]. Zolpidem has also been associated with the development of adverse psychiatric reactions like vivid nightmares, visual and auditory hallucinations, confusion, sensory

distortion, delirium, amnesia, visual perception distortion, compulsive behaviour, nocturnal eating and sleepwalking. There are various cases of adverse reactions, particularly hallucinations, reported after concurrent use of zolpidem and SSRIs. Furthermore, a case of visual hallucinations and amnesia reported in the literature was attributed to a possible zolpidem-fluvoxamine interaction. Also, a 15-year-old high school girl experienced an episode of sleepwalking after co-administration of the two drugs [11]. The pharmacists also have an important role in monitoring the safety of medications [10]. In our country, the reporting of adverse drug reactions (ADRs) to the National Authority needs improvement [10], but it would be helpful in identifying different cases of ADRs, potentially even after zolpidem and fluvoxamine co-administration. Although fluvoxamine seems to be a mild inhibitor of efflux transporter systems [26], zolpidem is very unlikely to cause clinical drug interactions attributable to impairment of CYP activity or P-gp mediated transport [27]. For this reason we did not considerate necessary to suggest a second mechanism that could explain this interaction apart from CYP inhibition induced by fluvoxamine.

Table III

Bioequivalence (bioeq) evaluation of pharmacokinetic (PK) parameters of zolpidem and zolpidem phenyl-4-carboxilic acid (Z4CA, zolpidem main metabolite), after co-administration of zolpidem and fluvoxamine

Parent drug/Metabolite	PK parameter	90 % CI	Bioeq. conclusion
zolpidem	C_{max}	1.17-1.47	Bio-ineq
	AUC_{0-t}	1.90-2.67	Bio-ineq
	$AUC_{0-\infty}$	1.89-2.64	Bio-ineq
	t_{max}	Friedman	Bio-ineq
Z4CA	C_{max}	0.60-0.81	Bio-ineq
	AUC_{0-t}	0.90-1.16	Bio-eq
	$AUC_{0-\infty}$	0.93-1.18	Bio-eq
	t_{max}	Friedman	Bio-ineq

90% CI – 90% confidence intervals; Bioequivalent (Bio-eq) if 90% CI: 0.8–1.25.

One possible limitation of the study was its non-randomized character, leading to a probable period effect. However, this effect was minimized by carefully controlling the most important parameter influencing it, the food intake (both qualitative, quantitative and the delivery time reported to drug administration).

Safety Evaluation

All enrolled subjects completed the study. During this clinical trial, the volunteers accused moderate dizziness and daily sleepy mood and experienced some difficulties in focusing on certain activities and discussing with the researchers and medical staff involved in the study. Seven zolpidem-treated subjects experienced mild sleepiness (3 females, 4 males), 8 subjects reported moderate intensity (3 females, 5 males) and 1 experienced severe intensity (1 female), while after association of zolpidem and fluvoxamine, a number of 4 subjects described a severe sleepiness (3 males, 1 female), 9 subjects perceived the intensity of the effect as moderate (6 males, 3 females) and 3 experienced mild intensity (1 male, 2 females). More importantly, the analysis revealed that 8 subjects (2 females - 25% of all female volunteers and 6 males - 50% of all male volunteers) experienced an increase intensity of the potential adverse effect after fluvoxamine and zolpidem concomitant intake, as follows: no effect to severe (1 male), no effect to moderate (1 male), mild to moderate (2 males, 2 females) and moderate to severe (2 males). Therefore, this assessment did not confirm that female gender is more prone to develop adverse events after zolpidem intake, as mentioned in the scientific literature [6], but we emphasize that a more complex analysis is required in order to correlate the pharmacokinetic results and the incidence and intensity of zolpidem adverse effects, before and after fluvoxamine administration.

Conclusions

Co-administration of zolpidem and fluvoxamine resulted in a 2.13-fold increased exposure to zolpidem. The present study may have implications for clinical therapeutics. Further investigations are required to assess the clinical consequences of a long-term therapy with zolpidem and fluvoxamine, but until then, caution is recommended when zolpidem is co-administered with fluvoxamine.

Zolpidem metabolite (Z4CA) pharmacokinetics was also modified, but to a lesser extent than that of the parent compound. Nonetheless, the results of the present study could provide helpful information for toxicological and forensic investigations.

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