

LACK OF KINETIC INTERACTION BETWEEN ZOLPIDEM AND DULOXETINE: RESULTS FROM A DRUG-DRUG INTERACTION STUDY IN HEALTHY VOLUNTEERS

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ABSTRACT. This open-label, non-randomized, two-period and sequential study aimed to evaluate a potential kinetic interaction between zolpidem ((N,N-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]acetamide), a widely known and used sedative-hypnotic and duloxetine ((3S)-N-methyl-3-naphthalen-1-yloxy-3-thiophen-2-ylpropan-1-amine), an antidepressant. A total of 23 healthy volunteers received the following medications: period 1 (Reference) - zolpidem 5 mg (single dose) and period 2 (Test) - zolpidem 5 mg and duloxetine 30 mg. Non-compartmental method was employed to determine the pharmacokinetic parameters of zolpidem and its main metabolite, zolpidem phenyl-4-carboxylic acid (Z4CA) while analysis of variance (ANOVA) was used to test the differences between study periods. Zolpidem exhibited similar pharmacokinetics with or without duloxetine (C_{max} : 59.64±27.64 ng/mL vs 53.28±22.77 ng/mL, AUC_{0-t} : 239.45±158.26 ng*h/mL vs 217.21±135.95 ng*h/mL, $AUC_{0-\infty}$: 245.87±161.84 ng*h/mL vs 224.61±138.86 ng*h/mL, $t_{1/2}$: 2.97±2.06 vs 3.12±1.86 h). Subsequently, no marked changes were observed for Z4CA. The statistical test confirmed that duloxetine had no significant influence on the exposure to zolpidem and Z4CA ($p < 0.05$ for all pharmacokinetic parameters). In conclusion, the study results excluded the possibility of a pharmacokinetic drug-drug interaction between these two drugs. Future investigations should focus on potential undesirable pharmacodynamic effects.

Keywords: zolpidem, duloxetine, kinetic interaction, healthy volunteers

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INTRODUCTION

A drug-drug interaction (DDI) usually represents the alteration of the expected drug response for a patient, which derives from the exposure of the same patient to another co-administered drug [1]. DDIs usually occur in the body after the drug molecules are absorbed in the systemic circulation and they can be either pharmacodynamic (PD) or pharmacokinetic (PK) [1]. Pharmacokinetic DDIs can emerge at each process (absorption, distribution, metabolism, and elimination) and entail the alteration of the PK profiles of drugs [1,2]

The most prevalent DDIs are those occurring at the level of drug metabolism [3]. The latter represents the process of converting one chemical species to another chemical species, called metabolite, which commonly possesses little or no pharmacological activity when compared to the parent compound [2]. DDIs that involve the inhibition or induction of the metabolism of one drug by another co-administered drug are best understood and evaluated by investigating the specific isoenzymes involved in that particular interaction [4]. This type of DDIs consists of CYP450 enzyme inhibition or induction, both processes involving an alteration in hepatic enzyme activity [5].

A drug acting as an enzymatic inhibitor decreases the metabolism rate of the simultaneously administered drug by several distinct mechanisms, either in a reversible or irreversible manner [1]. The reversible drug inhibition can occur as mutual competitive inhibition, noncompetitive and uncompetitive inhibition [2]. A competitive mechanism refers to a competition between the enzyme inhibitor and the substrate for the same binding site of the metabolizing enzyme. In this case, the two drugs involved seem to have structural similarities and for this reason, they are compatible with the same enzyme [1,6]. The mutual competitive inhibition occurs when the same isoenzyme is responsible for the metabolism of the two compounds, case in which the plasma levels of both inhibitor and substrate will be increased [6]. The noncompetitive inhibition was reported when the inhibitor and the drug behaving as a substrate bind to the same enzyme, but at different binding sites, leading to a conformational change in the proteic structure of the isoenzyme [1,3,6]. For the uncompetitive mechanism of inhibition, the inhibitor does not bind to the free enzyme, but to the complex formed between the enzyme and the substrate. Consequently, the inhibition is more marked when the concentration of the substrate is higher [1,6].

The irreversible inhibition is a consequence of the formation of complexes with the haem portion or the proteic part of the enzyme through covalent bonds [1,6]. Furthermore, the mechanism-based inactivation (also referred to as time-dependent inhibition) occurs more frequently than presumed, partly due to redox cycling-allied enzymatic action of CYPs, and leads to the inactivation of the target enzymes [3].

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It is important to evaluate the possibility of metabolic DDIs as their occurrence in the liver and/or gastro-intestinal tract can alter the PK profiles of concomitantly administered drugs and thus potentially leading to therapeutic failure or increased incidence and severity of side effects [3]. Moreover, depending on the localization of the inhibited/induced enzyme(s), an alteration of the bioavailability alongside decreased/increased hepatic clearance can be observed for orally administered drugs [1,3,5].

The degree of inhibition depends on the affinity of the substrate for the inhibited enzyme and on the half-life time ($t_{1/2}$) of the inhibitor [3]. The onset of inhibition and the disappearance of this effect are directly related to the $t_{1/2}$ and the time required to reach the steady-state concentration of the inhibitory drug [1,2]. Thus, metabolic DDIs emerge only after the process of inhibition is completed [1,2,3]. For drugs subjected to intensive first-pass metabolism, the co-administration of an enzyme inhibitor can significantly alter their bioavailability after oral administration [3].

Prior to systemic absorption, inhibition and DDIs can also take place in the gut wall, considering that some of the CYP450 isoforms can be found at this biological site as well [9].

The binding of the inhibitor to the enzyme can take place at the lipophilic domain of the active site, or by ionic bonds with the specific aminoacids from the active site or by hydrogen bonds [1]. Some reversible inhibitors act by binding the haem portion of the enzymes, but the most effective inhibitors are those who, in addition, bind to the hydrophobic site of the active part of the enzymes [2].

From the previously mentioned mechanisms of drug inhibition, the most commonly encountered DDIs are due to reversible inhibition and mechanism-based inactivation [3,10]. Moreover, because a large number of drugs are metabolized via isoenzymes CYP2D6 and CYP3A4, a special attention should be given whenever drug substrates for these isoenzymes are prescribed concomitantly with inhibitors/inducers of the same metabolic pathway [7,8].

Zolpidem (IUPAC name (N,N-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]acetamide) is a γ -aminobutyric acid (GABA)_A-receptor agonist, with an imidazopyridine structure, which exhibits high affinity for the benzodiazepine ω 1 receptor [11]. The drug is recommended worldwide for the short-term treatment (<4 weeks) of insomnia at typical dosages that consist of 5-10 mg/day at bedtime [12]. Several CYP450 isoenzymes are involved in the metabolism of this sedative-hypnotic: CYP3A4, CYP2C9, CYP1A2, CYP2D6 and CYP2C19 [11]. In the liver, zolpidem is converted to three pharmacologically inactive metabolites via oxidation and hydroxylation. The 4-carboxy-derivative (zolpidem phenyl-4-carboxylic acid – Z4CA) is the predominant metabolite and accounts for 72 up to 86% of the administered dose [13].

Duloxetine (IUPAC name (3S)-N-methyl-3-naphthalen-1-yloxy-3-thiophen-2-ylpropan-1-amine) is an antidepressant with a dual mechanism of action that acts like a potent norepinephrine and serotonin-reuptake inhibitor (SNRI) [14]. Besides major depressive disorder, it is also used to treat generalized anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia, and severe stress urinary incontinence [15,16]. This drug undergoes extensive metabolic degradation in the liver mainly via CYP1A2 and CYP2D6, to pharmacologically inactive metabolites that are excreted in the urine [14-16]. Previous studies confirmed that duloxetine is a moderate inhibitor of CYP2D6, thus a risk of drug interaction exists whenever this antidepressant is co-administered with other substances metabolized via the same isoenzyme [14-16], like zolpidem.

Due to a high prevalence of polymedication in patients with depression and sleep disorders, the probability of DDIs is consistent and should be taken into account when drugs belonging to different therapeutic classes are equally needed in clinical practice [17]. In this view, the aim of this study was to investigate whether a pharmacokinetic interaction does occur between zolpidem and duloxetine and, if that is the case, to elucidate the mechanism of the kinetic interaction.

RESULTS AND DISCUSSION

Subject demographics

The study enrolled 23 healthy volunteers (7 women and 16 men) and was completed without any dropouts. The mean age of the subjects was 25.7 ± 3.00 years old (range: 20-35) and they had a mean body mass index (BMI) of 24.00 ± 3.00 kg/m² (range: 19-25).

Pharmacokinetic analysis

The mean plasma concentration-time profiles of both zolpidem and its main metabolite, before and after pretreatment with duloxetine are practically similar (**Figure 1**).

In addition, the pharmacokinetics of both analytes (zolpidem and Z4CA) were not influenced by the co-administration of duloxetine (**Table 1** and **Table 2**) as none of the pharmacokinetic parameters presented statistically significant differences between the study periods.

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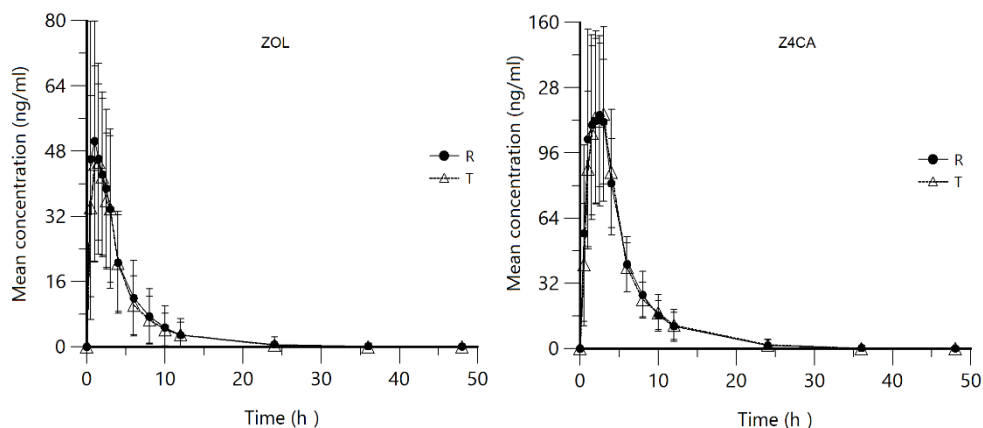


Figure 1. Mean plasma concentrations – time curves of **zolpidem 5 mg p.o. (left)** and **zolpidem's main metabolite (Z4CA, right)** during both study periods: Reference (**R**), zolpidem administered alone, Test (**T**) zolpidem co-administered with duloxetine, after pre-treatment with duloxetine for 4 days (30 mg/day for 2 days and 60 mg/day for other 2 days). Data are presented as mean \pm SD (n=23).

Table 1. Pharmacokinetic (PK) parameters of zolpidem (ZOL) in 23 healthy volunteers after a single oral dose of 5 mg zolpidem, before and after treatment with duloxetine and the statistical evaluation of the differences between treatments (ANOVA test)

ZOL	Study period						p* value (ANOVA)
	Reference			Test			
PK parameter	Mean	SD ^a	CV% ^b	Mean	SD ^a	CV% ^b	
C _{max} (ng/mL)	59.64	27.64	46.35	53.28	22.77	42.73	0.16
t _{max} (h)	1.00	0.69	69.08	1.28	0.77	59.73	0.10
AUC _{0-t} (ng*h/mL)	239.45	158.26	66.09	217.21	135.95	62.59	0.25
AUC _{0-∞} (ng*h/mL)	245.87	161.84	65.82	224.61	138.86	61.83	0.26
K _{el} (h ⁻¹)	0.32	0.16	50.64	0.32	0.25	76.91	0.57
t _{1/2} (h)	2.97	2.06	69.27	3.12	1.86	59.53	0.57
Cl _F (L/h)	32.03	30.37	94.81	31.97	20.16	63.06	0.26
Vd _F (L)	99.61	46.27	46.45	105.70	29.39	27.80	0.26

^aSD – standard deviation; ^bCV% - coefficient of variation; p* <0.05 statistically significant.

Table 2. Pharmacokinetic (PK) parameters of zolpidem's main metabolite (Z4CA) in 23 healthy volunteers after a single oral dose of 5 mg zolpidem, before and after treatment with duloxetine and the statistical evaluation of the differences between treatments (ANOVA test)

Z4CA PK parameter	Study period						p* value (ANOVA)
	Reference			Test			
	Mean	SD ^a	CV% ^b	Mean	SD ^a	CV% ^b	
C _{max} (ng/mL)	129.17	45.54	35.26	130.91	41.61	31.79	0.61
t _{max} (h)	2.17	0.86	39.60	2.37	0.79	33.19	0.36
AUC _{0-t} (ng*h/mL)	684.04	170.76	24.96	680.33	209.66	30.82	0.65
AUC _{0-∞} (ng*h/mL)	717.95	167.09	23.27	712.49	214.92	30.16	0.59
K _{el} (h ⁻¹)	0.24	0.12	48.11	0.22	0.10	46.57	0.16
t _{1/2} (h)	3.69	2.04	55.15	3.99	1.94	48.55	0.16
Cl _F (L/h)	7.48	2.51	33.52	7.83	3.00	38.28	0.59
Vd _F (L)	37.75	19.20	50.86	41.37	16.76	40.52	0.10

^aSD – standard deviation; ^bCV% - coefficient of variation; p* <0.05 statistically significant.

This lack of a pharmacokinetic interaction between zolpidem and duloxetine can be attributed to relatively different metabolic pathways. As mentioned before, only two minor correlations were found in the literature regarding their metabolic profiles: first, duloxetine is a moderate enzymatic inhibitor of CYP2D6 while the same isoenzyme has a minor contribution to the net intrinsic clearance of zolpidem and second, both drugs are metabolized, although not to the same extent, by CYP1A2 (duloxetine - extensively metabolized, zolpidem - 14%) [18,19,20]. In addition, duloxetine is highly plasma protein bound (>90%) and could displace zolpidem and increase the concentration of free drug [21,22]. Despite these potential causal factors, the present study results do not confirm the existence of an interaction between the two molecules. Other pharmacokinetic data supports the outcome of this study. Ruike *et al.* showed that duloxetine has the ability to inhibit the function of P-glycoprotein (P-gp) [23], but there is no evidence to suggest that zolpidem is a substrate of this transport system [24].

Unlike duloxetine, other antidepressants are capable of altering the pharmacokinetics of zolpidem. For example, experimental data demonstrated the existence of a pharmacokinetic interaction between fluvoxamine and the sedative-hypnotic drug [13,25]. These differences in the safety profile of

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antidepressants might be useful to clinicians when choosing the most appropriate drugs in patients that require medications from both pharmacological classes. However, even though the pharmacokinetics of zolpidem was unaltered by the combination with duloxetine (at steady-state concentration), a potential pharmacodynamic impact cannot be excluded, especially when a multiple dosing regimen is employed for both substances. Controlled clinical trials reported not only insomnia, but also somnolence during treatment with duloxetine [21,26] and various reports have described patients experiencing hallucinations when taking zolpidem and antidepressants concomitantly [22].

Safety evaluation

No serious adverse events associated with the study medication were reported throughout the clinical trial. Moreover, none of the subjects discontinued the study due to safety concerns.

CONCLUSIONS

To our knowledge, this study is the first to investigate whether duloxetine can influence the pharmacokinetics of zolpidem and its main metabolite. Based on the present findings, the antidepressant did not change the exposure to zolpidem in healthy volunteers which suggests that this drug combination can be considered in clinical practice. However, a pharmacodynamic interaction cannot be excluded and requires further investigation.

EXPERIMENTAL SECTION

Subjects: 23 Caucasian healthy volunteers were enrolled in the present study. The subjects' selection was thoroughly made based on precise inclusion and exclusion criteria. The volunteers were considered eligible for the study based on their medical history, physical examination, vital signs, and clinical laboratory tests. Prospective volunteers were excluded if any clinical abnormalities were identified during the physical examination. All volunteers gave their written informed consent prior to any study procedure. 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.

Study design: The study was designed as an open-label, single-center, non-randomized, sequential study that consisted of two periods. During the first study period (Reference, R), all volunteers were given a single dose of zolpidem 5 mg (p.o.). In the second period (Test, T), after a 4-day pretreatment regimen with duloxetine (a single daily dose of 30 mg for two days and 60 mg/day (30 mg/12 h) for another two days) in order to achieve steady-state plasma concentrations, the subjects received a combination of zolpidem 5 mg and duloxetine 30 mg. These doses represent a typical dosage regimen for clinical practice.

Study protocol/Drug administration: Each dose of the selected drugs was administered in the morning, after an overnight fast and with at least 150 mL of water.

The pharmaceutical products used were Stilnox® (10 mg film-coated tablets, Sanofi-Aventis, Romania) for zolpidem and Cymbalta® (30 mg hard gastro-resistant capsules, Lilly SA, Spain) for duloxetine, respectively.

Sample collection: On the first and last day of the study, venous blood (5 ml) was drawn into heparinized tubes, before zolpidem administration and after, at the following times: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36 and 48 hours. Blood samples were centrifuged at 5000 rpm for 10 min and the separated plasma was stored frozen (-20°C) until analysis.

Drug analysis from plasma samples: Zolpidem and Z4CA plasma concentrations were determined by using a validated high-throughput liquid chromatography (HPLC) tandem mass spectrometry analytical method. The HPLC system was an Agilent 1100 series (binary pump, autosampler, thermostat) (Agilent Technologies, USA), coupled with a Bruker Ion Trap SL (Bruker Daltonics GmbH, Germany). The chromatographic column used was a Zorbax SB-C18 (100 mm x 3.0 mm i.d., 3.5 µm) (Agilent Technologies). The same bioanalytical method was employed for quantification of zolpidem in other kinetic (PK) study and PK drug-drug interaction study [13,25,27].

Pharmacokinetic analysis: The standard non-compartmental method was employed to calculate the main PK parameters of zolpidem and its metabolite, Z4CA. The maximum plasma concentration (C_{max} , ng/mL) and the time to reach it (t_{max} , h) were directly obtained from the plasma concentration-time curves of each volunteer. The area under the concentration-time profile from time 0 to time of last quantifiable concentration (AUC_{0-t} , ng*h/mL) was calculated by applying the linear trapezoidal method. The total area under the curve ($AUC_{0-\infty}$, ng*h/mL) was obtained by adding C_t/K_{el} to AUC_{0-t} , where C_t (ng/mL) is the last quantifiable concentration of zolpidem and K_{el} (h^{-1}) is the

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rate constant of elimination process estimated from the terminal region of the semi-logarithmic curve of plasma concentration-time corresponding to 1st order kinetics of elimination. The half-life time ($t_{1/2}$, h) was determined as $0.693/K_{el}$. All PK calculations were performed with Phoenix WinNonlin 6.1 (Certara, USA) software.

Statistical analysis: Analysis of variance (ANOVA) was used in order to compare the main PK parameters of zolpidem between study periods. All calculations were performed with Phoenix WinNonlin 6.1 (Certara, USA) software. Statistical significance was defined for $p < 0.05$.

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