https://doi.org/10.31925/farmacia.2024.5.11 **ORIGINAL ARTICLE**

OLANZAPINE AND FLUOROQUINOLONES ANTIBIOTICS: A NON-CLINICAL STUDY OF DRUG-DRUG INTERACTIONS DUE TO CYP1A2 INHIBITION

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Abstract

This study aimed to investigate the pharmacokinetic interaction between olanzapine and two fluoroquinolone antibiotics, known for their inhibitory effects on CYP1A2. The obtained results demonstrated that the concomitant administration of ciprofloxacin or norfloxacin with olanzapine significantly altered the pharmacokinetic parameters of olanzapine and its active metabolite, N-des-methyl olanzapine. Specifically, the maximum plasma concentration of olanzapine (C_{max}) increased from 170.52 ± 107.27 ng/mL to 361.03 ± 186.96 ng/mL (after co-administration with ciprofloxacin) and 509.91 ± 259.80 ng/mL (after co-administration with norfloxacin). In addition, the total area under the curve ($AUC_{0-\infty}$) was significantly higher, increasing from 1601.60 ± 890.96 hr*ng/mL to 3589.32 ± 1334.15 hr*ng/mL (after co-administration with ciprofloxacin) and 5555.88 ± 2538.30 hr*ng/mL (after co-administration with norfloxacin). Similar trends were observed for its active metabolite, with a notable increase in C_{max} and significant changes in clearance (Cl_F) and volume of distribution (Vz_F). These results confirm that both ciprofloxacin and norfloxacin significantly inhibit CYP1A2, leading to reduced clearance and increased systemic exposure to olanzapine and its active metabolite. This is the first non-clinical study evaluating the impact of these antibiotics on olanzapine metabolism, providing important information on potential drug-drug interactions in clinical practice.

Rezumat

Acest studiu a avut drept obiectiv investigarea interacțiunii farmacocinetice dintre olanzapină și două antibiotice din clasa fluorochinolonelor, cunoscute pentru efectele lor inhibitoare asupra CYP1A2. Rezultatele obținute au demonstrat că administrarea concomitentă de ciprofloxacină sau norfloxacină cu olanzapină a modificat semnificativ parametrii farmacocinetici ai olanzapinei și ai metabolitului său activ, N-desmetil olanzapina. Mai precis, concentrația plasmatică maximă a olanzapinei (C_{max}) a crescut de la 170,52 ± 107,27 ng/mL la 361,03 ± 186,96 ng/mL (după co-administrarea cu ciprofloxacină) și 509,91 ± 259,80 ng/mL (după co-administrarea cu norfloxacină). În plus, aria totală sub curbă ($AUC_{0-\infty}$) a fost semnificativ mai mare, crescând de la 1601,60 ± 890,96 hr*ng/mL la 3589,32 ± 1334,15 hr*ng/mL (după co-administrarea cu ciprofloxacină) și 5555,88 ± 2538,30 hr*ng/mL (după co-administrarea cu norfloxacină). Tendințe similare au fost observate pentru metabolitul său activ, cu o creștere notabilă a C_{max} și modificări semnificative ale clearance-ului (Cl_F) și volumului de distribuție (Vz_F). Aceste rezultate confirmă faptul că atât ciprofloxacina, cât și norfloxacina inhibă semnificativ CYP1A2, ducând la reducerea clearance-ului și la creșterea expunerii sistemice la olanzapină și metabolitul său activ. Acesta este primul studiu non-clinic care evaluează impactul acestor antibiotice asupra metabolismului olanzapinei, oferind informații importante privind potențialele interacțiuni medicamentoase în practica clinică.

Keywords: olanzapine, fluoroquinolones, metabolic drug-drug interaction, enzyme inhibition

Introduction

Olanzapine is a second-generation antipsychotic drug commonly used in the treatment of schizophrenia and bipolar disorder. Its mechanism of action implies antagonizing dopamine (D2) and serotonin (5-HT2A and 5-HT2C) receptors. When administered orally, olanzapine is well absorbed and undergoes extensive hepatic metabolism primarily *via* the cytochrome P450 enzyme system, particularly CYP1A2 and CYP2D6 [5, 13]. Peak-plasma concentration is reached after 5 - 8 hours, with the half-life being 21 - 54 hours. Olanzapine's broad therapeutic efficacy, convenient dosing regimen and lower risk of extrapyramidal symptoms compared to first-generation antipsychotics have contributed to its widespread use in the treatment of psychotic disorders. Despite these advantages, careful monitoring remains essential throughout treatment due to the potential for adverse effects, ensuring both safety and optimal therapeutic outcomes [5].

Olanzapine is metabolised primarily through the CYP1A2 pathway into two major metabolites: N-

desmethyl olanzapine and 7-hydroxy olanzapine. While 7-hydroxy olanzapine is pharmacologically inactive, N-desmethyl olanzapine presents therapeutic activity, although with lower potency compared to the parent compound [13]. Consequently, when olanzapine is co-prescribed with antibiotics such as ciprofloxacin or norfloxacin, known inhibitors of the CYP1A2 enzyme, the potential for drug-drug interactions at the metabolic level must be carefully considered [7, 12]. Such interactions could significantly alter the pharmacokinetic profile of olanzapine and its main active metabolite, potentially affecting therapeutic efficacy and safety during coadministration with these antibiotics [9, 13].

Ciprofloxacin and norfloxacin, both fluoroquinolone antibiotics, are rapidly absorbed after oral administration, reaching peak plasma concentrations within 1 - 2 hours and presenting a half-life time of 3 - 5 hours [8]. These antibiotics exert their antibacterial effects by inhibiting bacterial DNA gyrase and topoisomerase IV, offering broad-spectrum activity against both Gram-positive and Gram-negative bacteria. Additionally, ciprofloxacin and norfloxacin are known inhibitors of the cytochrome P450 enzyme CYP1A2, which can result in increased plasma concentrations and prolonged effects of drugs metabolised by CYP1A2 when administered concomitantly [7].

In clinical practice, olanzapine is frequently co-administered with ciprofloxacin or norfloxacin in patients undergoing treatment for schizophrenia or bipolar disorder who develop bacterial infections [4, 8]. However, the potential pharmacokinetic interaction between these drugs has not been thoroughly investigated *in vivo*. As CYP1A2 is the primary enzyme involved in the metabolization of olanzapine to its active metabolite, N-des-methyl olanzapine, it plays a key role in determining the pharmacokinetic profile of olanzapine. Understanding how fluoroquinolones may influence CYP1A2 activity is essential for evaluating potential drug interactions.

This study aimed to evaluate whether such pharmaco-kinetic interactions occur using an animal model. The findings could provide valuable insights into the safety profile of olanzapine and highlight the need for further investigation in human studies to determine their clinical significance [3].

Materials and Methods

Chemicals and Reagents

Olanzapine was purchased from Actavis/Teva (Parsippany-Troy Hills, NJ, USA), olanzapine and N-desmethyl olanzapine analytical standards along with methanol analytical reagent were purchased from Sigma-Aldrich/ Merck Group (Darmstadt, Germany) and ciprofloxacin (Ciprinol®) and norfloxacin (Nolicin®) were obtained from KRKA (Novo Mesto, Slovenia). For the animal anaesthesia, ketamine (Vetased®) from Farmavet (Romania) and xylazine (XylazinBio®) from Bioveta (Czech Republic) along with diazepam (Terapia, Cluj-Napoca, Romania) were purchased. Heparin sodium 5000 UI/mL was obtained from Belmedpreparaty (Minsk, Belarus).

Study Design

This study was approved by the Institutional Ethics Committee of the "Iuliu Haţieganu" University of Medicine and Pharmacy from Cluj-Napoca, Romania, and the National Sanitary Veterinary and Food Safety Authority (Ethics Committee approval no. 313 from 20th May 2022). The protocol was in accordance with the 43/2014 law on the protection of animals used for scientific purposes published in "*Monitorul Oficial*", Romania which transposes Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes, published in the Official Journal of the European Union. The study was conducted at the Centre for Experimental Medicine and Practical Skills at "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania. It was designed as an open-label, sequential study with three periods. The non-clinical study was conducted on healthy adult male Wistar albino rats (*Rattus norvegicus*) obtained from the aforementioned Centre. The animals were housed individually in ventilated boxes under standard conditions specified by the previously mentioned directives and laws (22 ± 2°C, 50 ± 30% humidity, 12-hour light/dark cycles, standard food, *ad libitum* access to water and daily cleaning). To acclimatize the animals and minimize additional stress during the experiments, they were maintained under these conditions for at least 3 days prior to the start of the study.

Before surgery, each rat was anesthetised with a combination of ketamine, xylazine and diazepam (1:1:1) *via* intramuscular injection. Subsequently, cannulation of the left femoral vein was performed to facilitate connection to the BASi Culex ABC® system – Automatic Blood Collector from BASi (West Lafayette, IN, USA). This step was essential to facilitate the direct collection of venous blood samples through the ABS system, eliminating the need for additional human intervention. By doing so, we minimised variability in sample collection typically associated with human operators, ensuring greater consistency and reliability in the sampling process. This cannulation procedure was carried out one day prior to the administration of olanzapine. Blood samples (200 µL each) were collected at 5, 10, 15, 30 and 45 minutes, as well as 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 60 hours post-administration of olanzapine. The samples were stored at -20°C until further analysis.

The study consisted of three periods: a reference period and two test periods, each involving 14 rats with body weights ranging from 235 to 410 g. During the reference period, the rats received a single oral dose

of 12 mg/kg body weight (b.w.) of olanzapine. In the first test period, the rats were pretreated with an oral dose of 15 mg of ciprofloxacin for 5 consecutive days to achieve steady-state drug concentrations, thereby ensuring maximal inhibitory effects on the targeted enzyme, CYP1A2. On the 6th day, ciprofloxacin was co-administered with olanzapine (12 mg/kg b.w.). The second test period followed the same protocol, except ciprofloxacin was replaced by 30 mg of norfloxacin. Both olanzapine and norfloxacin were suspended in 1% carboxymethylcellulose and vortexed for 5 minutes before each administration. All oral doses were administered by oral gavage.

Sample preparation involved adding 180 µL of methanol to 60 µL of blood in an Eppendorf tube which was further vortexed for 10 seconds and then centrifuged for 8 minutes at 10,000 rpm. The supernatant was transferred into autosampler vials and injected into the HPLC-MS system.

Pharmacokinetic analysis

Pharmacokinetic (PK) parameters for olanzapine and its active metabolite, N-desmethyl olanzapine, were assessed both when olanzapine was administered alone and in combination with ciprofloxacin or norfloxacin. The PK analysis was performed using non-compartmental approach with the Phoenix WinNonlin 8.4 software (Pharsight Co., Mountain View, CA, USA). The peak plasma concentration (C_{max}, ng/mL) and the time to reach it (t_{max}, h) were determined by visually inspecting the plasma concentration-time profiles for each subject. The area under the concentration-time curve from zero to the last measurable concentration (AUC_{0-t}) was calculated using the linear trapezoidal method. To estimate the area under the curve extrapolated to infinity ($AUC_{0-\infty}$), the value of C_t/k_{el} was added to AUC_{0-t}, where C_t represents the last measurable plasma concentration and k_{el} is the elimination rate constant. The half-life ($t_{1/2}$) was subsequently calculated as $0.693/k_{el}$.

Statistical analysis

Statistical analysis was performed by using the above-mentioned software. The results are expressed as the mean value ± standard deviation (SD). PK parameters from all three study periods underwent comparison using a one-way analysis of variance test (ANOVA), with statistical significance determined at a *p* value less than 0.05.

HPLC-MS analysis

Olanzapine and its active metabolite plasma concentrations were concomitantly determined by a validated liquid chromatography tandem mass spectrometry method (LC-MS). The HPLC system was an Agilent 1100 series (equipped with binary pump, autosampler and thermostat from Agilent Technologies, Santa Clara, CA, USA) coupled with mass spectrometer from Agilent, the model with Ion Trap 1100 SL [18]. Chromatographic separation of the analytes was achieved with a Zorbax SB-C18 column (100 x 3.0 mm, 3.5 µm) (Agilent Technologies, USA). The mobile phase consisted of 0.3% formic acid in water (v/v) and methanol in an 89:11 ratio, with isocratic elution for 3.2 minutes. The injection volume was 4 µL, the flow rate was 1 mL/min and the thermostat temperature was set at 45°C. The MS detection was in multiple reaction monitoring mode (MRM) using an electrospray ionization source, in positive ion mode. The following mass transitions were used: olanzapine *m/z* 256 from *m/z* 313, olanzapine's metabolite *m/z* (230, 239) from *m/z* 299. The calibration curves of olanzapine and its metabolite were linear at a concentration range of 6 - 900 ng/mL.

Results and Discussion

Figure 1 and Figure 2 depict the mean plasma concentration-time profiles and standard deviation for both olanzapine and its active metabolite, N-desmethyl olanzapine.

Following non-compartmental analysis, the most important PK parameters for both compounds were determined across the three experimental groups. The obtained values, represented as mean values ± SD, are provided in Table I and Table II.

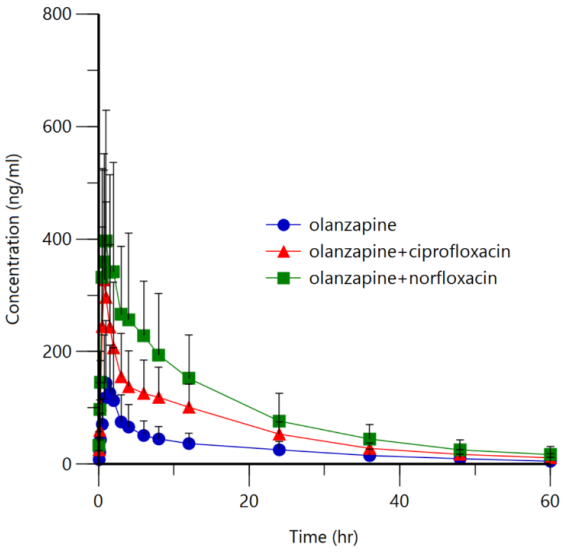

Figure 1.

Mean plasma concentrations *versus* time profile of olanzapine administered as a single dose (12 mg/kg b.w., *p.o.*) as monotherapy (○), after previous 6-day treatment with ciprofloxacin (15 mg) (Δ) and after previous 6-day treatment with norfloxacin (30 mg (□)

*data are presented as mean values + standard deviation

Table I

The main pharmacokinetic parameters of olanzapine (12 mg/kg, *p.o.*) administered as a single dose (Reference), with 6-day pretreatment with ciprofloxacin (Test 1) and with 6-day pretreatment with norfloxacin (Test 2)

Olanzapine	**Study group**		
PK parameter (U.M.)	**Olanzapine (Reference)**	**Olanzapine + Ciprofloxacin (Test 1)**	**Olanzapine + Norfloxacin (Test 2)**
C_{max} (ng/mL)	170.52 ± 107.27	361.03 ± 186.96*	509.91 ± 259.80*
T_{max} (hr)	1.20 ± 0.72	1.89 ± 3.02	1.41 ± 1.18
AUC_{0-60} (hr*ng/mL)	1587.38 ± 899.81	3574.52 ± 1349.82*	5519.93 ± 2561.86*
$AUC_{0-\infty}$ (hr*ng/mL)	1601.60 ± 890.96	3589.32 ± 1334.15*	5555.88 ± 2538.30*
k_{el} (1/hr)	0.05 ± 0.02	0.04 ± 0.01	0.04 ± 0.02
$t_{1/2}$ (hr)	17.86 ± 6.50	17.41 ± 5.23	17.32 ± 6.28
Cl_F (L/hr/kg)	8.81 ± 4.60	3.64 ± 1.79*	2.52 ± 1.40*
Vz_F (L/kg)	201.18 ± 80.46	85.65 ± 33.41*	63.46 ± 49.82*
MRT (hr)	23.26 ± 7.67	21.84 ± 4.17	20.87 ± 5.41

* $p < 0.05$, statistically significant difference compared to olanzapine administered alone.

Administering repeated doses of ciprofloxacin prior to a single dose of olanzapine resulted in a significant 111.66% increase in olanzapine's peak plasma concentration (C_{max}), with no significant change in the time at which this concentration is reached (T_{max}). Both the area under the concentration-time curve from zero to 60 hours (AUC_{0-60}) and the total area under the curve, from time zero to infinity ($AUC_{0-\infty}$), increased significantly by 2.25-fold and 2.24-fold, respectively. While the elimination rate constant (k_{el}) and terminal half-life slightly decreased (1.25-fold and 1.02-fold, respectively), these results were not statistically significant. Additionally, olanzapine's clearance and volume of distribution decreased by 2.42-fold and 2.34-fold, respectively.

Repeated doses of norfloxacin produced similar effects on single-dose olanzapine. C_{max} of olanzapine increased by 2.99-fold, while AUC_{0-60} and $AUC_{0-\infty}$ has risen by 3.47-fold and 3.46-fold, respectively. Additionally, olanzapine's clearance decreased by 3.49-fold, and its volume of distribution was reduced by 3.17-fold.

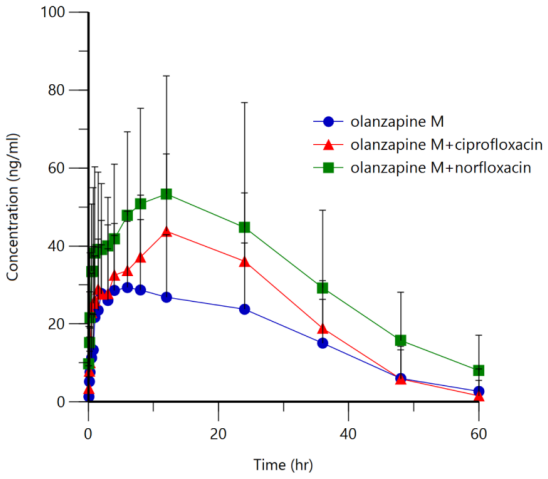

Figure 2.

Mean plasma concentrations *versus* time profile of N-desmethyl olanzapine corresponding to olanzapine single dose (12 mg/kg b.w., *p.o.*) as monotherapy (○), after previous 6-day treatment with ciprofloxacin (15 mg) (Δ) and after previous 6-day treatment with norfloxacin (30 mg (□)

* data are presented as mean values + standard deviation

Table II

The main pharmacokinetic parameters of N-desmethyl olanzapine formed after olanzapine (12 mg/kg b.w., *p.o.*) single dose (Reference), with 6-day pretreatment with ciprofloxacin (Test 1) and with 6-day pretreatment with norfloxacin (Test 2)

N-desmethyl olanzapine	**Study group**		
PK parameter (U.M)	**Olanzapine (Reference)**	**Olanzapine + Ciprofloxacin (Test 1)**	**Olanzapine + Norfloxacin (Test 2)**
C_{max} (ng/mL)	41.81 ± 18.63	51.24 ± 16.12	69.28 ± 29.17*
T_{max} (hr)	6.91 ± 9.47	8.59 ± 6.10	9.07 ± 8.89
AUC_{0-60} (hr*ng/mL)	986.81 ± 667.35	1331.11 ± 675.91	1968.79 ± 1102.58*
$AUC_{0-\infty}$ (hr*ng/mL)	1032.22 ± 671.77	1404.87 ± 652.23	1988.40 ± 1092.13*
k_{el} (1/hr)	0.05 ± 0.02	0.03 ± 0.02*	0.05 ± 0.03
$t_{1/2}$ (hr)	16.46 ± 7.18	43.57 ± 54.60*	16.80 ± 9.26
Cl_F (L/hr/kg)	24.20 ± 35.37	6.46 ± 4.06*	7.73 ± 5.69*
Vz_F (L/kg)	400.42 ± 340.00	256.29 ± 152.85	158.94 ± 95.49*
MRT (hr)	26.59 ± 10.11	65.56 ± 77.53*	29.66 ± 13.80

* $p < 0.05$, statistically significant difference compared to olanzapine administered alone.

For N-desmethyl olanzapine, the administration of ciprofloxacin resulted in a 40% reduction in the elimination rate constant (k_{el}), a 2.64-fold increase in half-life, a 3.74-fold reduction in clearance and a 59.44% increase in mean residence time (MRT). Although C_{max}, T_{max} and the AUCs were not significantly affected, these findings are important due to their impact on the pharmacokinetic profile of N-desmethyl olanzapine. Similarly, pretreatment with norfloxacin for 6 days prior to a single dose of olanzapine led to a 65.69% increase in C_{max}, a 99.49% increase in AUC_{0-60} and a 92.55% increase in $AUC_{0-\infty}$. It also caused a 3.13-fold reduction in clearance and a 2.51-fold decrease in volume of distribution. MRT was reduced by 1.11-fold, though this change was not statistically significant. These results suggest significant alterations in the pharmacokinetics of N-desmethyl olanzapine when co-administered with norfloxacin.

According to the Institute of Health Metrics and Evaluation, schizophrenia affects approximately 1 in 300 people, or 0.32% of the worldwide population [19]. Considering the relatively high incidence and the severity of the symptoms, this also makes schizophrenia one of the most common diagnoses among patients in psychiatric hospitals, with over 20% of all cases [1, 4, 14, 15]. More than 55% of the medications used to treat schizophrenia are newer anti-psychotics, with olanzapine being the most frequently prescribed, accounting for over 20% of prescriptions [10].

As previously mentioned, ciprofloxacin and norfloxacin are commonly prescribed fluoroquinolone antibiotics. In the United States of America (USA), fluoroquinolones ranked as the third most prescribed antibiotic class for outpatients. However, around 25% of these prescriptions were issued either when antibiotics were not necessary or when fluoroquinolones were not the recommended first-line treatment [7]. Considering their use as broad spectrum antibiotics and the overprescription, in the past decade the use of fluoroquinolones has been subject to scrutiny due to rising antibiotic resistance and adverse events, therefore the number of prescriptions has dropped by an approximate 10% in multiple areas of the world, including USA and Canada [17].

While the exact percentage of people concomitantly under treatment with olanzapine and ciprofloxacin or norfloxacin is not documented in the available literature, it is acknowledged that administering fluoroquinolones can lead to severe psychological side effects including delirium, acute psychosis and anxiety, which are also symptoms of schizophrenia [15, 17]. Therefore, fluoroquinolones may exacerbate symptoms of schizophrenia, potentially causing significant mental distress and interfere with the antipsychotic effects of olanzapine.

Given that olanzapine is also prescribed for the treatment of bipolar disorder, which affects approximately 2.4% of the global population, the risk of exacerbating mania, a common symptom of bipolar disorder and a known side effect of fluoroquinolones, should not be overlooked [4, 20].

Olanzapine is primarily metabolised by the cytochrome P450 isoenzyme CYP1A2, and to a lesser extent by CYP2D6 [6, 12]. Like other drugs metabolised by CYP1A2 to various extents, such as caffeine, clozapine, propranolol, nebivolol, zolpidem and several antibiotics that share the same metabolic pathway [2, 6, 11], there is a potential for significant drug-drug interactions during co-administration, which must be carefully managed to avoid adverse effects. Importantly, CYP1A2 is localised exclusively in the liver, meaning that interactions occur at a systemic level, during hepatic metabolism [5, 7]. In contrast, enzymes such as CYP3A4 are found both in the liver and the small intestine, broadening the potential for drug-drug or drug-food interactions [6].

N-desmethyl olanzapine, the active metabolite of olanzapine, exhibits therapeutic activity that contributes to the overall pharmacological profile of the parent compound. However, inhibition of CYP1A2 by ciprofloxacin and norfloxacin alters the pharmacokinetics of both olanzapine and N-desmethyl olanzapine. The changes in apparent clearance could also be partially due to altered bioavailability resulting from the concomitant administration of fluoroquinolones. Additionally, other factors such as gender, tobacco use, coffee consumption and dietary factors *(e.g.*, cruciferous vegetables) can further influence olanzapine metabolism, increasing the risk of interactions when combined with the aforementioned drugs [16]. Therefore, personalised medication strategies along with careful management of polypharmacy are crucial to avoid therapeutic failures and adverse events.

Conclusions

This study confirms the inhibitory effect of ciprofloxacin and norfloxacin on CYP1A2 when co-administered with olanzapine. Enzyme inhibition resulted in statistically significant changes in the pharmacokinetics of olanzapine and its active metabolite, N-des-methyl olanzapine. These results underscore the potential clinical implications of co-administration of fluoroquinolones with olanzapine, highlighting the importance of careful monitoring of patients receiving both drugs to avoid adverse effects or reduced treatment efficacy. Further studies are recommended to evaluate the clinical implications of this interaction in humans.

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Conflict of interest

The authors declare no conflict of interest.

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