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RESEARCH ARTICLE

The influence of multiple-dose oxcarbazepine on the metabolism of single-dose quetiapine. In vivo experiment in rats

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Objective: Psychiatric and neurologic disorders are susceptible to polypharmacy having a higher risk of developing drug-drug interactions. Quetiapine, a frequently used atypical antipsychotic, is extensively metabolized by cytochrome P450 3A4 isoenzyme, while oxcarbazepine, an antiepileptic drug, analog of carbamazepine, is a mild-to-moderate inducer of the same isoenzyme. This study aimed to evaluate the pharmacokinetic interaction between a single dose of quetiapine and multiple doses of oxcarbazepine, as pretreatment, compared to quetiapine single-dose alone in rats.

Methods: The in vivo experiment was carried out on two groups consisting of 12 Wistar albino rats each. The control group was given a single oral dose of quetiapine 85 mg/kg. The test group received oxcarbazepine 80 mg/kg/day orally, for 5 days followed by a single dose of quetiapine 85 mg/kg. A validated liquid chromatography with tandem mass spectrometry method was employed to simultaneously measure the plasma concentrations of quetiapine and its active metabolite, norquetiapine. Non-compartmental analysis was used to determine the pharmacokinetic parameters of both quetiapine and norquetiapine.

Results: Short-term administration of oxcarbazepine determined a significant increase in the systemic exposure of norquetiapine by increasing its peak plasma concentration and the total area under the concentration-time curve by 88.85% and 5.29-fold. The expected enzyme-inducing properties of oxcarbazepine were not visible on the quetiapine's pharmacokinetic profile, producing, although statistically insignificant, an increase in its exposure.

Conclusions: The present experiment showed that the administration of oxcarbazepine can determine some changes in the pharmacokinetics of quetiapine and norquetiapine in vivo.

Keywords: pharmacokinetics, metabolism, quetiapine, norquetiapine, oxcarbazepine

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Introduction

Quetiapine (QUE) is an atypical antipsychotic prescribed for schizophrenia, bipolar disorder, and as an adjunct treatment for major depressive disorder [1]. It is quickly absorbed following oral administration and undergoes extensive first-pass metabolism. The absolute bioavailability is unknown and it is approximately 83% bound to plasma proteins [2, 3]. It goes through extensive phase I metabolism mediated by the cytochrome P450 (CYP) system and undergoes phase II metabolism using uridine 5′-diphospho-glucuronosyltransferases (UGTs) conjugating enzymes [1, 4]. Hepatic CYP3A4 isoenzyme eliminates 89% of the dose, through sulfoxidation and N-dealkylation, the latter being responsible for the formation of the most important and its active metabolite N-desalkyl-quetiapine, also named norquetiapine (NQ). Secondarily, CYP2D6 and CYP3A5 are involved in the metabolism of the remaining dose of QUE, while CYP2D6 is known to further metabolize NQ [1]. The CYP3A4 isoenzyme, highly expressed in the adult human liver and intestine, has a major role in drug metabolism that makes it particularly susceptible to drug-drug interactions which may lead to changes in the pharmacokinetic (PK) profile of its substrates [5]**.** The putative mechanism of action of QUE involves the antagonism of serotonin 5-HT_{2A} receptors and dopamine D_2 receptors, associated with antipsychotic efficacy. The serotonin 5-HT_{1A} partial agonism is one of the proposed mechanisms for QUE's antidepressant effect together with NQ's selective inhibition on the noradrenaline reuptake. The adrenergic α_1 antagonism can cause orthostatic hypotension, associated with dizziness and tachycardia, while H_1 histamine receptor antagonism is linked to sedative effects and weight gain [6].

Oxcarbazepine (OXC), a second-generation antiepileptic drug (AED) is approved for the treatment of partial-onset seizures with or without secondary generalized tonic-clonic seizures [7]. Moreover, OXC is used off-label as a mood stabilizer in bipolar disorders, for neuropathic pain like trigeminal neuralgia or diabetic neuropathy and as an add-on for drug-resistant epilepsy. OXC, the 10-keto analog of carbamazepine, is a prodrug that is quickly and almost completely converted by cytosolic aryl-ketone reductase into its clinically active metabolite, licarbazepine, which is a racemic mixture of eslicarbazepine and (R)-licarbazepine [8-9]. The active metabolite is responsible for the pharmacological activity of OXC, based on the ability

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to block the voltage-gated sodium channels and inhibit the high-frequency repetitive neuronal firing [10]. Being considered a mild-to-moderate CYP3A4 inducer, OXC can mildly induce UGTs and inhibit CYP2C19 isoenzymes as well [3, 11, 12]. Dose-dependent induction of CYP3A4 by OXC was documented before [11], such that high doses of OXC (1200 mg/day or above) present clinically relevant risk of induction, for instance, by accelerating the clearance of certain psychotropic drugs, thereby reducing their effectiveness [7].

In vitro studies showed that both OXC and QUE are substrates for the membrane active transporter P-glycoprotein (P-gp) [13, 14], even though *in vivo* studies failed to show the transporter relevance in the disposition of the drugs. No transporters are known to influence the disposition of NQ [15]. P-gp is an ATP-dependent efflux pump encoded by the ABCB1 gene which exports substances outside the cells. At the small intestine level, P-gp is located at the luminal surface of enterocytes, influencing the bioavailability of orally administered drugs [16].

Based on the involvement of CYP3A4 in the metabolism of some atypical antipsychotics, including QUE, and the concomitant long-term use of AEDs, like OXC, in psychiatric and neurologic disorders, the risk of this PK interaction needs to be investigated. A lower plasma concentration of QUE can lead to a possible decrease in its pharmacological activity with patients displaying acute symptoms of the disorder intended to be treated. Dose correction factors have been suggested before for QUE when administered with inducers of inhibitors of CYP3A4 [3]. It is recommended that the therapeutic reference ranges for QUE are 100-500 ng/mL and for NQ are 100-250 ng/mL. Although there are differences between individuals regarding drug plasma concentrations and individual therapeutic response, subtherapeutic drug concentrations are believed to carry a risk of suboptimal response, which can be mitigated through therapeutic drug monitoring (TDM) [17]. While searching for an AED safer than the old, strong enzyme-inducing ones, the potential of other drugs to interact with the second-generation AEDs, like OXC, is often overlooked. The effectiveness of OXC and carbamazepine is comparable, with better tolerability and fewer drug-drug interactions for OXC. Still, OXC may produce PK interactions with other drugs at the metabolic site [7, 9]. The concomitant administration of OXC and QUE is possible since the frequency of epilepsy is 4-5 times higher in people with schizophrenia than in the general population. That may be due to a bidirectionality between psychosis and epilepsy [18]. Both drugs are used as mood stabilizers in bipolar disorders and agitation or they can be administered for different co-occurring psychiatric and neurologic disorders. Nearly 50% of epilepsy patients experience some form of psychiatric or neurologic comorbidity such as mood disorders, anxiety disorders and autistic spectrum disorders, all of which can use QUE and OXC as concomitant treatment [7].

This *in vivo* experiment aimed to evaluate the possible PK interaction between QUE single-dose and the antiepileptic OXC, given as a five-day pretreatment, compared to QUE single-dose alone, in an animal model.

Methods

The two-period preclinical study received approval from the local Ethics Committee of the "Iuliu Haţieganu" University of Medicine and Pharmacy and the relevant national authority. Ethics Committee approval number: 322/02.08.2022.

Chemicals and apparatus. Quetiapine fumarate substance was purchased from Menadiona (Barcelona, Spain), norquetiapine analytical standard (97.0% purity), methanol analytical reagent, 98% formic acid, and haloperidol pharmaceutical primary standard were purchased from Merck (Darmstadt, Germany). Oxcarbazepine was utilized from Trileptal® 600 mg immediate-release tablets, provided by Novartis (Nürnberg, Germany). Heparin sodium 5000 IU/mL was sourced from Belmedpreparaty (Minsk, Belarus). For rat anesthesia, ketamine (Vetased® 10%, Farmavet, Bucharest, Romania) and xylazine (XylazinBio® 2%, Bioveta, Ivanovice na Hané, Czech Republic) were procured. Blood samples were automatically collected at exact times after QUE single-dose administration using BASi Culex ABC®-Automatic Blood Collector device (BASi, Indiana, USA). The blood volume was sampled with accuracy, avoiding fluid depletion in animals. QUE and NQ were quantified using the Agilent 1100 series HPLC system equipped with a binary pump, autosampler, and thermostat (Agilent Technologies, USA). Detection was performed using a Bruker Ion Trap SL (Bruker Daltonics GmbH, Germany). The chromatographic separation of the analytes was accomplished with a Zorbax SB-C18 column (100 x 3.0 mm, 3.5 μm) (Agilent Technologies, USA).

Animals. Adult *Wistar albino* male rats, 250 ± 25 g, were purchased from the Experimental Medicine Centre and Practical Skills (Cluj-Napoca, Romania). Standard conditions like a constant temperature of 21-22°C, humidity of 50 ± 30% and 12 hours of light-dark cycles were assured. Animals were given access to tap water and standard laboratory pellet diet.

Study design and sample processing. For this *in vivo* study, 24 rats were randomly assigned to two groups, including QUE combined with OXC, representing the test group, and QUE alone, representing the reference group. Each rat in the reference group was administered QUE 85 mg/kg as an oral, single dose. For the test group, each rat received daily doses of oral OXC 80 mg/kg, for 5 days, then, on the fifth day, 30 minutes after the last dose of OXC, an oral, single dose of QUE 85 mg/kg was administered. The rats in both study groups were fasted for 12 hours prior to the administration of the single dose of QUE. The dose of QUE of 85 mg/kg was selected by considering 600 mg a mean maintenance dose in humans, which was multiplied

by 10, per rat body weight, taking into account the sensitivity of the analytical method developed for the quantitation of QUE and NQ, but also the rat's higher metabolic rate and proportion of CYP enzymes due to larger liver relative to body size, compared to humans [19]. A conversion factor of 6.2 between humans and rats (mg/kg) has been previously reported in the literature [20]. However, for our study, we had to increase this factor to 10 due to the sensitivity of the quantification method. A similar determination was made for rats' dose of OXC, considering 8 mg/kg as a standard dose in humans.

For oral gavage administration, quetiapine fumarate substance was dissolved in a mixture of distilled water, propyleneglycol as cosolvent and lactic acid for pH correction, 3:1:1 (v/v/v). OXC suspension was prepared from 600 mg Trileptal® tablets in carboxymethylcellulose 1%. The suspension was vortex-mixed before each administration.

The day prior to blood sampling, rats underwent femoral vein cannulation, an operation described before, that allowed the BASi Culex ABC® device to have access to the rats' bloodstream [21]. Eighteen blood samples, 100 µL each, were drawn automatically at times between 10 minutes and 30 hours after QUE single-dose administration.

Sample processing consisted of precipitating plasma proteins from 0.1 mL blood samples by adding 0.3 mL methanol, vortex-mixing for 10 seconds, and centrifuging at 10000 rpm for 5 minutes.

Analytical assay. A validated reverse-phase high-performance liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) method, using haloperidol as internal standard (IS), was used for the concomitant quantification of QUE and NQ. The mobile phase used was 0.3% (m/v) formic acid and acetonitrile eluted in a linear gradient, starting with 10% acetonitrile, increasing to 33% acetonitrile up to 3.5 minutes and keeping 33% acetonitrile until 4.1 minutes, then a re-equilibration with 10% acetonitrile for 2 minutes was made.

Pharmacokinetic and statistical analysis. Non-compartmental analysis (NCA) was employed to determine the PK parameters of QUE and NQ. The C_{max} and the T_{max} were determined by direct inspection of the data. Other parameters like the area under the curve (AUC) from QUE administration to the last measured concentration (AUC_{0-30}), the total AUC ($AUC_{0-\infty}$), the apparent elimination rate constant (k_{el}), the half-life ($t_{1/2}$), the mean residence time (MRT), the apparent volume of distribution (Vz_F) and the apparent total body clearance (Cl_F) were calculated. A metabolite-to-parent ratio was determined for each rat as the $AUC_{0-\infty}$ of NQ over the $AUC_{0-\infty}$ of QUE. The mean metabolite-to-parent ratios ± SD were determined in both groups.

NCA was performed using Phoenix Win Nonlin 8.4 software (Pharsight Company, Mountain View, CA, USA). The statistical analysis was performed using IBM SPSS Statistics 30.0.0.0 (Chicago, IL, USA). Data was tested for normal distribution, applying a two-tailed independent T-test for normally distributed values. For data that did not assume normality, the nonparametric Mann-Whitney U test was used. Statistical significance was set at $p < 0.05$.

Results

The mean QUE and NQ plasma profiles after a single dose of QUE 85 mg/kg alone (reference) and with a five-day OXC pretreatment (test) are presented in Figures 1 and 2, along with the respective semi-logarithmic representations. The PK parameters calculated for QUE and NQ after a single oral dose of QUE 85 mg/kg, alone or with OXC five-day pretreatment are presented as mean values ± SD in Table I and Table II.

The mean metabolite-to-parent ratio for the QUE single-dose group was 1.26 ± 0.44, while for the test group it increased to 2.32 ± 1.34.

Discussions

The concomitant administration of antipsychotic medication and AEDs, used as mood stabilizers, like QUE and OXC, respectively, is a common treatment approach in psychiatric patients. The importance of studying this interaction lies in the fact that QUE is known to be sensitive to CYP3A4 induction. It is also known that QUE should not be administered with potent inducers which would require a dose correction factor ≥5 for the antipsychotic [3]. Carbamazepine, phenobarbital or phenytoin can alter the efficacy of QUE by increasing the clearance to the point that QUE plasma concentrations are undetectable [22]. A PK study in 18 psychiatric patients titrated to steady-state QUE levels, with 300 mg QUE twice daily, revealed carbamazepine 600 mg/day decreased the steady-state mean plasma C_{max} and AUC in a dosing interval by 80 and 87% respectively and increased the apparent oral clearance 7.4-fold compared to QUE steady-state alone [23], while administration of carbamazepine 400-800 mg/day with QUE 700 mg/day determined undetectable levels of the antipsychotic (less than 25 µg/mL) in 3 patients showing on-going psychotic symptoms under treatment [24]. Ten-day administration of phenytoin 100 mg t.i.d to steady-state QUE 250 mg t.i.d increased the clearance of QUE 5.5-fold compared to QUE administered alone [25].

The effect of OXC on the pharmacokinetics of QUE hasn't been investigated so far. However, Leon et al. (2018) and Spina et al. (2016) recommended the combination should be administered only if TDM is available [3, 11]. We identified a single published case report discussing the QUE and OXC specifically. An 8-year-old patient with autism spectrum disorder experienced a reduction in QUE's efficacy evidenced by agitation after 14 days of treatment with OXC 450 mg twice daily. OXC reduced the concentration-to-dose ratio of QUE by more than 70%. Behavior improvement was noted with concomitant QUE dose increase and OXC tapering-off [26].

Our experiment showed that the short-term, five-day administration of OXC did not accelerate the metabolism

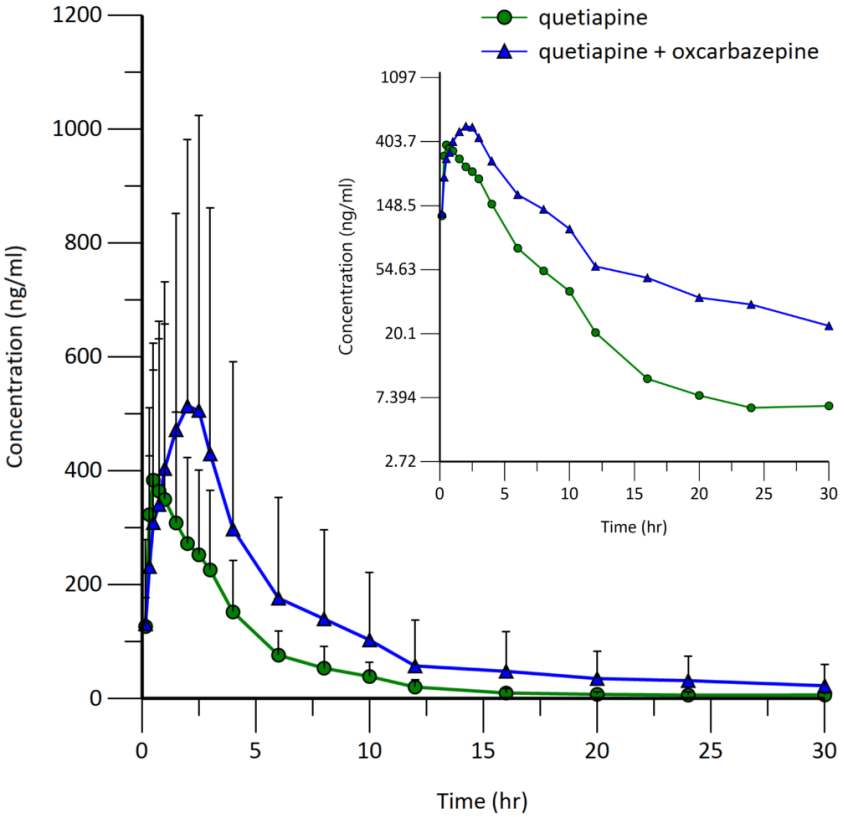

Fig. 1. The mean pharmacokinetic profile of quetiapine after an oral dose of 85 mg/kg with (Δ) (n=12 rats) and without (o) (n=12 rats) a five-day previous treatment with oxcarbazepine 80 mg/kg. Insert: Semi-logarithmic representation

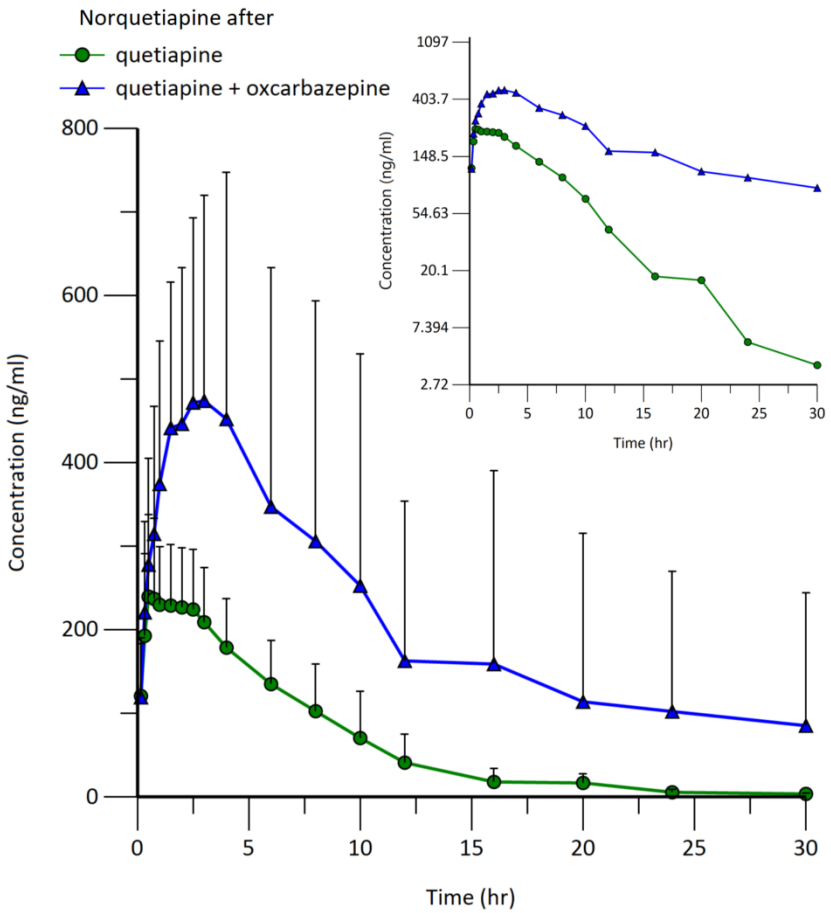

Fig. 2. The mean pharmacokinetic profile of norquetiapine after an oral dose of quetiapine 85 mg/kg with (Δ) (n=12 rats) and without (o) (n=12 rats) a five-day previous treatment with oxcarbazepine 80 mg/kg (n=12). Insert: Semi-logarithmic representation

Table I. The mean values ± SD of the pharmacokinetic parameters of quetiapine after a single oral dose of 85 mg/kg, alone (Reference, n=12) or in combination with a 5-day pretreatment with oxcarbazepine 80 mg/kg (Test, n=12)

PK parameters	Quetiapine (Reference)	Quetiapine + Oxcarbazepine (Test)	p-value
C_{max} (ng/mL)	497.65 ± 291.82	599.53 ± 503.92	0.980[a]
T_{max} (hr)	1.07 ± 0.90	1.81 ± 0.78	0.022[a*]
AUC_{0-30} (hr·ng/mL)	1742.74 ± 794.05	3496.78 ± 3093.08	0.204[a]
$AUC_{0-\infty}$ (hr·ng/mL)	1783.37 ± 806.72	3953.46 ± 3602.54	0.186[a]
kel (1/hr)	0.17 ± 0.11	0.09 ± 0.04	0.004[a*]
$t_{1/2}$ (hr)	5.44 ± 2.85	9.74 ± 4.92	0.006[a*]
MRT (hr)	5.90 ± 3.14	9.93 ± 7.26	0.029[a*]
Cl_F (L/hr/kg)	58.22 ± 28.78	43.60 ± 33.21	0.242[b]
Vz_F (L/kg)	442.20 ± 324.42	603.13 ± 551.54	0.724[a]

[a] p-values calculated using the Mann-Whitney U test, [b] p-values calculated using the two-tailed independent t-test, * statistically significant, p<0.05, C_{max} peak plasma concentration, T_{max} time to reach the maximum plasma concentration, AUC_{0-30} area under the plasma concentration-time curve from time zero to 30 hours, $AUC_{0-\infty}$ total area under the curve, k_{el} elimination rate constant, $t_{1/2}$ half-life, MRT mean residence time, Cl_F apparent systemic clearance, Vz_F apparent volume of distribution.

Table II. The mean values ± SD of the pharmacokinetic parameters of norquetiapine after an oral dose of 85 mg/kg, alone (Reference, n=12) or in combination with a 5-day pretreatment with oxcarbazepine 80 mg/kg (Test, n=12)

PK parameters	Quetiapine (Reference)	Quetiapine + Oxcarbazepine (Test)	p-value
C_{max} (ng/mL)	294.64 ± 76.72	556.43 ± 245.54	0.002[b*]
T_{max} (hr)	1.32 ± 1.05	2.46 ± 0.9	0.010[a*]
AUC_{0-30} (hr·ng/mL)	1933.57 ± 551.18	6399.66 ± 5861.34	<0.001[a]
$AUC_{0-\infty}$ (hr·ng/mL)	1964.28 ± 540.78	10402.08 ± 16502.5	<0.001[a*]
kel (1/hr)	0.26 ± 0.11	0.12 ± 0.08	0.002[b*]
$t_{1/2}$ (hr)	3.03 ± 1.07	11.24 ± 14.04	0.001[a*]
MRT (hr)	5.91 ± 2.12	15.65 ± 20.4	0.003[a*]
Cl_F (L/hr/kg)	46.42 ± 14.27	22.56 ± 15.44	<0.001[b*]
Vz_F (L/kg)	201.91 ± 100.98	216.19 ± 157.30	0.650[a]

[a] p-values calculated using the Mann-Whitney U test, [b] p-values calculated using the two-tailed independent t-test, * statistically significant, p<0.05, C_{max} peak plasma concentration, T_{max} time to reach the maximum plasma concentration, AUC_{0-30} area under the plasma concentration-time curve from time zero to 30 hours, $AUC_{0-\infty}$ total area under the curve, k_{el} elimination rate constant, $t_{1/2}$ half-life, MRT mean residence time, Cl_F apparent systemic clearance, Vz_F apparent volume of distribution.

of QUE, as initially expected. On the contrary, the changes in the mean PK parameters suggest an increased exposure of QUE after OXC administration by the slight increase in the mean C_{max} and AUCs. The mean C_{max} value did not suffer statistically significant changes for QUE, but it was delayed by 69.16%. The variation in the mean AUCs is statistically insignificant, however a twofold and 2.22-fold increase in the mean values of AUC_{0-30} and $AUC_{0-\infty}$ were noticed. The inductive effect of OXC should have led to a decrease in the exposure of QUE. However, another mechanism involving the concurrent use of OXC and QUE might have contributed to the observed results for QUE. The average Vz_F of QUE increased for the test group, although not significantly, by 36.39%. This suggests that active transporters may be involved in the mechanism of the interaction and change the disposition of QUE. Knowing that both QUE, OXC and metabolites of OXC proved *in vitro* studies to be substrates for P-gp, a mechanism at active transporter levels cannot be ruled out. Two transporter substrates can act as P-gp competitive inhibitors for one another. In this case, P-gp inhibition possibly determined by OXC, at the pre-systemic level could explain the slight increase in the bioavailability, thus increasing the exposure for QUE. The decrease in the Cl_F could have resulted from a decrease in the actual clearance or an increase in the bioavailability of QUE. Having no intravenous formulation for QUE, it is difficult to tell the bioavailability and the clearance apart in NCA. Since QUE has a high extraction ratio, it is expected that the decrease of 25.11% in the mean Cl_F is also attributed to an increase in bioavailability. The increase in the average half-life of QUE suggests that the reduction in the mean Cl_F is, at least partly, the result of a decrease in the clearance. The changes in the mean Cl_F led to a reduction in the mean k_{el} by 1.88-fold, which further contributed to an increase in the mean half-life of QUE by 1.79-fold. The decrease in the k_{el} may partially explain the increase in the mean T_{max} of QUE. The plasma concentrations of the antipsychotic drugs present great inter-individual variability and it seems that OXC pretreatment increased the variability even more, based on the high SD values, especially for the mean AUC, C_{max} and Vz_F of QUE in the test group.

The anticipated inductive effect of OXC on the metabolism of QUE may be observable from the exposure to its active metabolite, NQ. An OXC-induced CYP3A4-mediated metabolism for QUE may explain the significantly increased production of the NQ. The average Vz_F remained relatively unchanged (1.07-fold increase, 201.91 ± 100.98 vs. 216.19 ± 157.30 L/kg), suggesting that no transporters were involved in the disposition of the metabolite, which is in line with the current literature. The increased exposure of NQ is illustrated by its mean C_{max}

increase of 88.85%, while the mean AUC_{0-30} increased significantly by 3.31-fold (1933.57 ± 551.18 vs. 6399.66 ± 5861.34 hr·ng/mL) and the mean $AUC_{0-\infty}$ increased by 5.29-fold (1964.28 ± 540.78 vs. 10402.08 ± 16502.5 hr·ng/mL) for the test group. The SD of the mean AUC for NQ is notable, suggesting the high inter-individual variability in the size of the exposure to NQ. The mean Cl_F of NQ decreased 2.05-fold (from 46.42 ± 14.27 to 22.56 ± 15.44 L/hr/kg), which might have been determined by the increased production of the NQ. The mean k_{el} of NQ decreased 2.16-fold which determined the increase in the mean $t_{1/2}$ by 3.71-fold. The antipsychotic effect is not expected to be altered since the exposure to QUE did not change significantly. Given the consistent increase in NQ's AUCs, C_{max} and $t_{1/2}$, and its different pharmacological activity compared to its parent compound, the antidepressant effect is expected to increase. However, the increase may also lead to adverse reactions such as dizziness, drowsiness, and orthostatic hypotension, based on the pharmacodynamic profile of the metabolite [6].

The administration of OXC determined a significant increase in the exposure of the active metabolite, NQ. The metabolite-to-parent ratio is considered an *in vivo* estimate of metabolizing enzymes activity. A normal range of 0.54–3.10 for this ratio was determined before in individuals without genetic abnormalities in drug-metabolizing enzymes or co-medication with inhibitors or inducers of drug-metabolizing enzymes [17]. Our results showed a change in the metabolite-to-parent ratio from 1.258 ± 0.44 in the reference group to 2.324 ± 1.34 for the test group, which can be explained through the inductive properties of OXC, although visible only on the mean PK parameters of NQ fraction.

We considered the rat model appropriate as a starting point for investigating the effect of OXC on the systemic metabolism of QUE. Rats and humans share cytochrome P450 orthologous genes, including the CYP3A family. The most metabolically relevant isoforms in rats, CYP3A1 [27] and CYP3A9 [28] are considered the rat orthologous of human CYP3A4. As usual, the results from animal studies need to be interpreted with caution and need confirmation in human studies.

The results reported above suggest that short-term administration of OXC had less influence on the pharmacokinetics of QUE *in vivo* and a significant effect on the exposure of its active metabolite. The changes in the profiles of QUE could be attributed to several mechanisms, yet to be more in-depth investigated, such as the changes in drug disposition due to P-gp involvement and CYP3A4 enzyme induction. On account of the pharmacokinetic and dose-response variability between individuals, the application of TDM remains a good option for monitoring concomitant QUE and OXC administration, especially on a long-term and whether a lack or decrease in antipsychotic efficacy is suspected.

Conclusion

The five-day pretreatment with OXC 80 mg/kg to a single dose of QUE 85 mg/kg determined a significant increase in the systemic exposure of NQ. The expected inductive activity of OXC on the CYP3A4 metabolism was not observed on the pharmacokinetic profile of QUE. Its mean AUCs and C_{max}, although not statistically significant, registered a slight increase. Based solely on the results from the presented *in vivo* experiment in rats, the concomitant administration of OXC is not expected to have a notable effect, from a pharmacokinetic perspective, in decreasing the efficacy of the antipsychotic. Still, to ensure the efficacy of the concomitant QUE and OXC treatment it is important that this drug interaction is further studied in human subjects.

Authors' contribution

IMC (Conceptualization; Methodology; Validation; Formal analysis; Investigation; Resources; Data curation; Software; Writing – original draft; Writing – review & editing; Visualization; Project administration; Funding acquisition)

DMM (Conceptualization; Methodology; Validation; Formal analysis; Investigation; Resources; Data curation; Writing – review & editing; Visualization; Supervision; Funding acquisition)

LMG (Methodology; Investigation; Resources; Visualization)

LV (Conceptualization; Methodology; Validation; Formal analysis; Software; Data curation; Writing – review & editing, Visualization; Supervision, Funding acquisition)

Conflict of interest

None to declare.

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