Arabian Journal of Chemistry (2021) 14, 103136

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Arabian Journal of Chemistry

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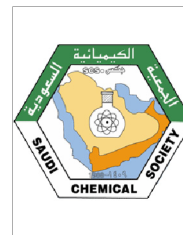

ORIGINAL ARTICLE

Inhibitory effect of propafenone on vortioxetine metabolism in vitro and in vivo

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Received 25 January 2021; accepted 18 March 2021
Available online 24 March 2021

KEYWORDS

Vortioxetine;
Propafenone;
Liver microsomes;
Pharmacokinetics

Abstract Vortioxetine, as a new therapeutic drug of major depressive disorder (MDD), was approved for MDD in the USA. The significance of our study in this paper was to explore the inhibitory effect of propafenone on the metabolism of vortioxetine through the in vivo and in vitro experiments. In the vitro experiments, we added a series of concentrations of propafenone into an incubation system as the inhibitors and calculated the half-maximal inhibitory concentration (IC_{50}) of propafenone on vortioxetine metabolism in human liver microsomes (HLMs) and rat liver microsomes (RLMs). Twelve male Sprague-Dawley (SD) rats were included in the vivo experiments. We randomly divided them into Group A (control group) and Group B (90 mg/kg propafenone). 30 min later, a single oral dose of 4.0 mg/kg vortioxetine was administrated to each rat. Then, we used ultra performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) to determine the concentrations of vortioxetine and its metabolite Lu AA34443. From our results, it indicated that propafenone inhibited the metabolic rate of vortioxetine in the vitro studies with the IC_{50} of 0.48 μM and 16.5 μM for HLMs and RLMs, respectively. And, propafenone could competitively inhibit vortioxetine in both HLMs and RLMs for the inhibitory mechanisms. Moreover, a single oral dose of 90 mg/kg propafenone obviously enchanced the exposure of vortioxetine in rats, but not Lu AA34443. Combined with the vitro and vivo data, propafenone showed the inhibitory effect on vortioxetine metabolism. Thus, more attention to the safety of vortioxetine in clinic should be paid when taking it with propafenone in combination for the therapy.
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Peer review under responsibility of King Saud University.

https://doi.org/10.1016/j.arabjc.2021.103136
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1. Introduction

As the new antidepressant drug, vortioxetine (Fig. 1A) is superior to other drugs for its multimodal activity, and is approved as a new antidepressant agent which can be used to treat major depressive disorder (MDD) in the worldwide recently (Gibb and Deeks, 2014). After orally administered, it is primarily metabolized by CYP2D6 and subsequently produced Lu AA34443 (Fig. 1B), which is the major metabolite but pharmacologically inactive (Hvenegaard et al., 2012). It was observed that the pharmacokinetic profiles of vortioxetine in subjects were dose proportional and linear (Chen et al., 2018). In addition, factors, such as food (Mayer et al., 2012; Wang et al., 2009), hepatic or renal function, sex, race, age, and body weight (Areberg et al., 2014), have no clinically effect on the exposure of vortioxetine. However, a reported drug-drug interaction study had showed that bupropion, a strong CYP2D6 inhibitor, and rifampin, a broad CYP450 inducer, significantly changed the concentrations of vortioxetine in subjects, and then influenced the safety profile in the clinically meaningful way (Chen et al., 2013).

Propafenone, a potent and well-accepted antiarrhythmic agent, is already widely used in the clinical therapy (Connolly et al., 1983). The antiarrhythmic agent propafenone is mainly metabolized by CYP2D6, CYP1A2 and CYP3A4 (Botsch et al., 1993; Zhou et al., 2003). It is also an inhibitor of CYP2D6 activity (Zhou et al., 2009). There were several studies about the interactions between propafenone and other drugs, such as metoprolol and venlafaxine (Duricova et al., 2013; Gareri et al., 2008).

Available data demonstrated that MDD is an reliable marker of risk assessment of cardiovascular disease (CVD), including arrhythmia (Hare et al., 2014). In patients with MDD, the risk of developing heart diseases may be even twice as high as in people without depressive symptoms (Rugulies, 2002). It has been reported that a number of biological mechanisms may be responsible for coexistence of MDD and CVD (Woron et al., 2019). Thus, polypharmacy is a common concern both in psychiatry and cardiology (Woron et al., 2019). It is significant to recognize the potential drug-drug interaction between medications as the simultaneous application of drugs for MDD and heart diseases. Both propafenone and vortioxetine are metabolized via CYP2D6, and propafenone is a CYP2D6 inhibitor. Thus, potential drug-drug interactions are considered to be clinical significance. However, until now, there is no literature related whether propafenone could influence the metabolism of vortioxetine.

In the present study, in order to ensure the effectiveness and safety of vortioxetine when combination with propafenone, we aimed to investigate the influence of propafenone on the pharmacokinetic profiles of vortioxetine in rats. In addition, the influence of propafenone on vortioxetine metabolism in rat liver microsomes (RLMs) and human liver microsomes (HLMs) were also evaluated.

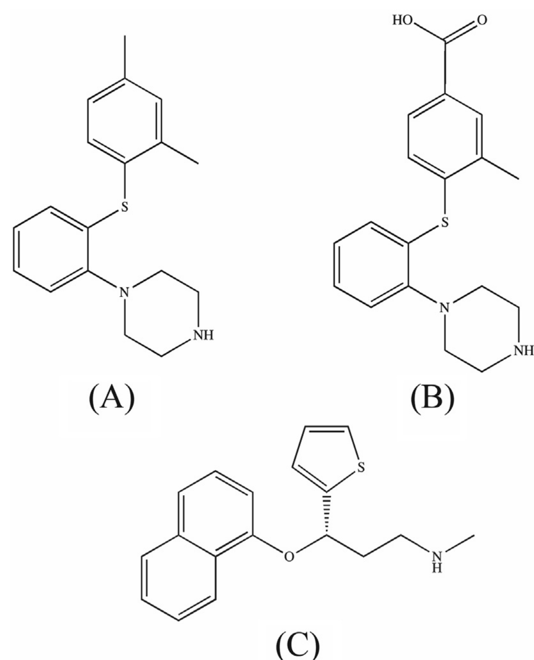

Fig. 1 Chemical structures of vortioxetine (A), Lu AA34443 (B) and duloxetine (IS, C) in this experiment.

2. Methods

2.1. Enzymes and chemicals

The reduced nicotinamide adenine dinucleotide phosphate (NADPH) was supplied by Roche Pharmaceutical Ltd (Basel, Switzerland). Cytochrome b5 was presented by Beijing Hospital (Beijing, China). Pooled HLMs provided by donors were obtained from Gentest (Woburn, MA, USA). Vortioxetine (purity > 98%), propafenone (purity > 98%), and duloxetine (Internal Standard, IS, purity > 98%, Fig. 1C) were provided by Beijing Sunflower and Technology Development CO., LTD (Beijing, China). Lu AA34443 was presented by Jiangsu Giebell Pharmaceuticals CO., LTD (Jiangsu, Chian). Liquid chromatography (LC) grade of formic acid (purity > 98%) was offered from Beijing Sunflower and Technology Development CO., LTD (Beijing, China). LC grade acetonitrile was supplied by Merck (Darmstadt, Germany). Ultrapure water was offered by a Milli-Q A10 System (Milli-pore, Billerica, MA, USA).

2.2. Instrumentation and conditions

A Waters ACQUITY UPLC system (Milford, MA, USA) combined with a Waters XEVO TQS triple quadrupole tandem mass spectrometer (Milford, MA, USA), which has an electrospray ionization (ESI) source, were employed to the quantification of the concentration levels of vortioxetine and its metabolite Lu AA34443 in plasma as described previously (Gu et al., 2020). Vortioxetine and Lu AA34443 were separated by an ACQUITY BEH C18 column (2.1 mm × 50 mm, 1.7 μm) with a C18 inline 0.2 μm stainless steel frit filter. Acetonitrile (A) and 0.1% formic acid (B) as the mobile phase was used with the flow rate of 0.3 mL/min for 3.0 min in each analysis process. A gradient elution was employed as follows: 0–0.3 min (10–70% A), 0.3–1.5 min (70–70% A), 1.5–1.6 min (70–10% A), 1.6–3.0 min (10–10% A). Multiple reaction monitoring (MRM) was used for the quantitation operated in the positive mode. The transitions were m/z 299.0 → 149.9, m/z 328.9 → 285.9 and m/z 298.1 → 44.0 for vortioxetine, Lu AA34443 and duloxetine (IS), respectively. In the range of 0.5–50 ng/mL, the assay displayed obvious linearity for vortioxetine, which can be observed in the range of 5–1000 ng/mL for Lu AA34443 as well. It was demonstrated in the results of this method that the accuracy, precision, recovery, matrix effect, and stability of vortioxetine and Lu AA34443 all met the standards for plasma samples for the quantitation (Gu et al., 2020). Instrument control and data acquisition were finished using the Masslynx 4.1 software (Milford, MA, USA).

2.3. Preparation of rat liver microsomes (RLMs)

The preparation of RLMs were done according to the published literature (Wang et al., 2015). Eight different rats were euthanized, and the livers were obtained and weighed for the preparation of RLMs. After homogenized in a cold 0.01 mM phosphate buffer saline (PBS, pH 7.4, including Na_2HPO_4 、 KH_2PO_4 、 NaCl and KCl) with 0.25 mM sucrose dissolved, centrifugation would immediately run at 11,000 rpm for 15 min, in order to obtain the supernatants. Then, we transferred them to a new tube, which needed to be centrifuged at 11,000 rpm for another 15 min. Besides, ultra-centrifugation at 100,000*g* for 1 h at 4 °C was used to obtain the final supernatants. Moreover, 0.01 mM cold PBS was used to reconstitute the microsomal pellets, which then were stored at −80 °C. Finally, Bradford Protein Assay Kit (Thermo Scientific, Waltham, MA, USA) was employed to assay the protein concentrations of RLMs before use.

2.4. Inhibitory effect of propafenone on vortioxetine metabolism in HLMs and RLMs

The incubation mixture was composed of 0.3 mg/mL HLMs or 0.5 mg/mL RLMs, 1 M PBS, vortioxetine (20 μM for HLMs and 10 μM for RLMs, which were similar to the corresponding K_m values), propafenone and 1 mM NADPH. The concentrations of propafenone were set to be 0.001, 0.01, 0.1, 1, 10, 50 and 100 μM for HLMs, and 0.01, 0.1, 1, 10, 25, 50 and 100 μM for RLMs, to determine the IC_{50} of propafenone that inhibit vortioxetine metabolism. To explore the inhibitory mechanisms of propafenone on vortioxetine, we set the concentrations of propafenone and vortioxetine according to the IC_{50} and K_m values, respectively. The concentrations of propafenone were 0, 5, 10, 20, and 40 μM in the RLMs incubation system; while the concentrations in the HLMs incubation system were 0, 0.125, 0.25, 0.5 and 1 μM. The concentrations of vortioxetine in the RLMs incubation system were 2.5, 5, 10 and 20 μM; while the concentrations in the HLMs incubation system were 5, 10, 20 and 40 μM.

In a shaking water bath, a preincubation was initiated for 5 min at 37 °C, and the reaction of incubation was formally started after adding the NADPH into the incubation system with a total volume of 200 μL. Cooling the mixture to −80 °C and adding cold 400 μL acetonitrile (containing IS 50 ng/mL) to terminate it, after incubated for 40 min. Then, the mixture was vortexed for 3.0 min and centrifugated at 13,000 rpm at 4 °C for 10 min. Finally, only 2.0 μL clear supernatant was used for testing in the UPLC-MS/MS system before the obtained 100 μL supernatant being transferred to the autosampler vials.

2.5. In vivo pharmacokinetic studies

Healthy male Sprague-Dawley (SD) rats (weighed 200 ± 20 g) were supplied by Laboratory Animal Center of Wenzhou Medical University (Zhejiang, China), and were performed to investigate the effect of propafenone on the pharmacokinetic of vortioxetine in rats. This study was allowed by the Animal Care and Use Committee of Wenzhou Medical University (wydw2018-0002) in accordance with National Institutes of Health (NIH) Guidelines for the welfare and use of animals (Clark et al., 1997).

We randomly divided the twelve SD rats into control group (Group A, n = 6) and 90 mg/kg propafenone group (Group B, n = 6). Before the experiment, the rats can drink water at will but fast for 12 h. Vortioxetine and propafenone were all dissolved and suspended in 0.5% sodium carboxy methyl cellulose (CMC-Na) solution for oral administration. The Group B were orally given a single dose of 90 mg/kg propafenone, and Group A were treated with corresponding amount of 0.5% CMC-Na. Half an hour later, to each rat, a single dose of 4.0 mg/kg vortioxetine was administrated. At different time points of 0, 0.333, 0.667, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 36 h after oral administration of vortioxetine, blood samples (0.15 mL) were obtained into 1.5 mL centrifuge tube from the tail vein. Subsequently, the blood sample was centrifuged at 4000*g* for 10 min at normal temperature to obtain the plasma sample, which would be frozen at −80 °C until analysis. A volume of 150 μL acetonitrile (containing IS 50 ng/mL) was spiked for each 50 μL plasma for protein precipitation. After being subjected to vortex for 3 min and centrifugation at 13,000 rpm for 10 min, the obtained supernatant (2.0 μL) was then injected into the UPLC-MS/MS system for further analysis.

2.6. Statistical analysis

All data in this study were listed as the mean ± SD. The main pharmacokinetic parameters of the analytes were calculated by DAS version 3.0 (Bontz Inc., Beijing, China) in a non-compartmental mode, and the average plasma concentration vs time profile was conducted through Origin 8.0 (Originlab Company, Northampton, MA, USA). GraphPad (Version 5.0; Graphpad Software Inc., San Diego, CA, USA) was used to calculate the IC_{50} for propafenone. In addition, the Statistical Package for the Social Sciences (version 17.0; SPSS Inc., Chicago, IL, USA) in unpaired *t*-test analysis was employed to compare the main pharmacokinetic parameters of vortioxetine and Lu AA34443 in different groups. In all cases, P value < 0.05 was deemed to be statistically significant.

3. Results

3.1. Inhibitory effect of propafenone on vortioxetine metabolism in HLMs and RLMs

From our results indicated in Fig. 2, the inhibitory effect of propafenone on vortioxetine metabolism in vitro was of great significance. When 100 μM as the maximum concentration for propafenone was performed, the metabolism rate of vortioxetine decreased to 10.70% in HLMs and 29.76% in RLMs, respectively. Besides, the calculated IC_{50} of propafenone for inhibition activity on vortioxetine metabolism in HLMs and RLMs were 0.48 μM and 16.5 μM, respectively (Fig. 3). Our results exhibited that the inhibitory effect of propafenone on vortioxetine metabolism in vitro was of great significance. Moreover, it indicated that propafenone can competitively inhibit vortioxetine in both HLMs and RLMs (Fig. 4).

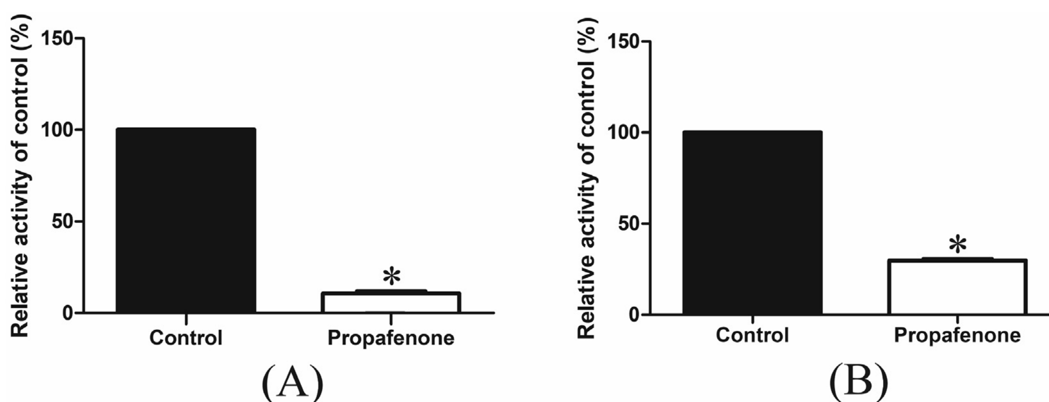

Fig. 2 Effects of propafenone (100 μM) on vortioxetine metabolite formation in (A) HLMs and (B) RLMs. Activity was measured by the generating rate of metabolite in the presence of 100 μM propafenone compared with no inhibitor (Control group). Values are mean ± SD, n = 3. *$P < 0.05$ in comparison to control.

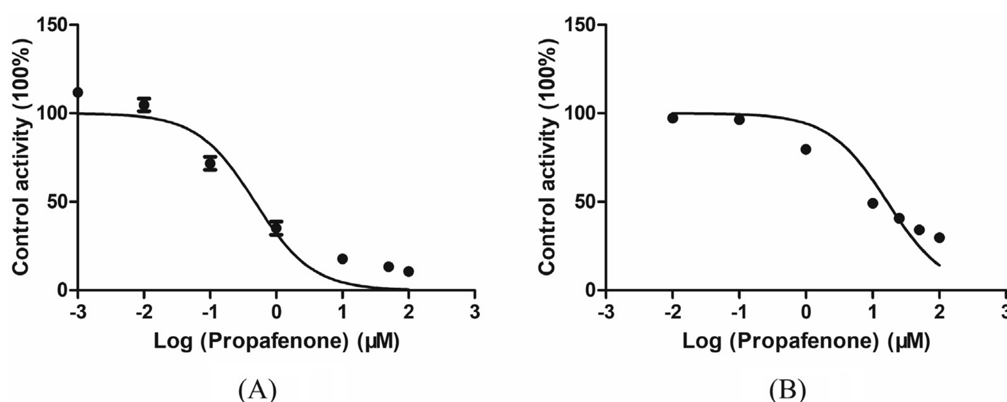

Fig. 3 Various concentrations of propafenone for half-maximal inhibitory concentration (IC_{50}) in the activity of (A) HLMs and (B) RLMs. Values are mean ± SD, n = 3.

3.2. Effects of propafenone on the pharmacokinetic of vortioxetine in rats

We calculated the main pharmacokinetic parameters of vortioxetine and Lu AA34443 in both two groups, and the results of statistical analysis were showed in Tables 1 and 2. The average plasma concentration vs time profiles of vortioxetine and Lu AA34443 in two groups were also shown in Fig. 5. From our results, it demonstrated that the values of $AUC_{0\to t}$, $AUC_{0\to\infty}$, C_{max} and T_{max} of vortioxetine in Group B raise to 1.59-fold, 1.59-fold, 2.13-fold and 1.99-fold, respectively, when compared with Group A ($P < 0.05$). Moreover, $t_{1/2}$ of vortioxetine in Group B prolonged 1.68-fold, while CL decreased to 75.3% relative to Group A. However, there were no notable changes in the pharmacokinetic parameters ($AUC_{0\to t}$, $AUC_{0\to\infty}$, C_{max}, T_{max} and $t_{1/2}$) of Lu AA34443 in Group A and Group B ($P > 0.05$). From above results, it indicated that propafenone also can inhibit vortioxetine metabolism in rats.

4. Discussion

As CYP2D6 takes an important part in the oxidative metabolism of vortioxetine, so drug-drug interactions may occur when vortioxetine is combined with some drugs which can change the activity of this enzyme. Moreover, it was reported that there was 100% increase in vortioxetine exposure when added bupropion to vortioxetine from the drug-drug interaction study (Chen et al., 2013). Therefore, the possiblity that strong CYP2D6 inhibitors (such as fluoxetine, quinidine, bupropion, and paroxetine) can significantly affect the pharmacokinetics of vortioxetine need to be caution, and the oral dose of vortioxetine may be considered to lower in MDD patients.

As a common antiarrhythmic drug, propafenone is extensively used in the treatment of supraventricular and ventricular arrhythmias (Stoschitzky et al., 2016). It also undergoes wide first-pass metabolism by CYP2D6, CYP3A4 and CYP1A2 to produce several metabolites (Afshar and Thormann, 2006). Moreover, propafenone is a well known CYP2D6 inhibitor that has the potential to increase the plasma concentrations of coadministered CYP2D6 substrates (Labbe et al., 2000; Shams et al., 2006). However, the effect of propafenone on the metabolism of vortioxetine is not evaluated until now.

In our present study, we aimed to investigate the inhibitory effect of propafenone on vortioxetine metabolism in terms of pharmacokinetics in vivo. The dose of vortioxetine for oral administration to rats was in terms of the literature reported previously (Huang et al., 2016). In addition, the inhibitory

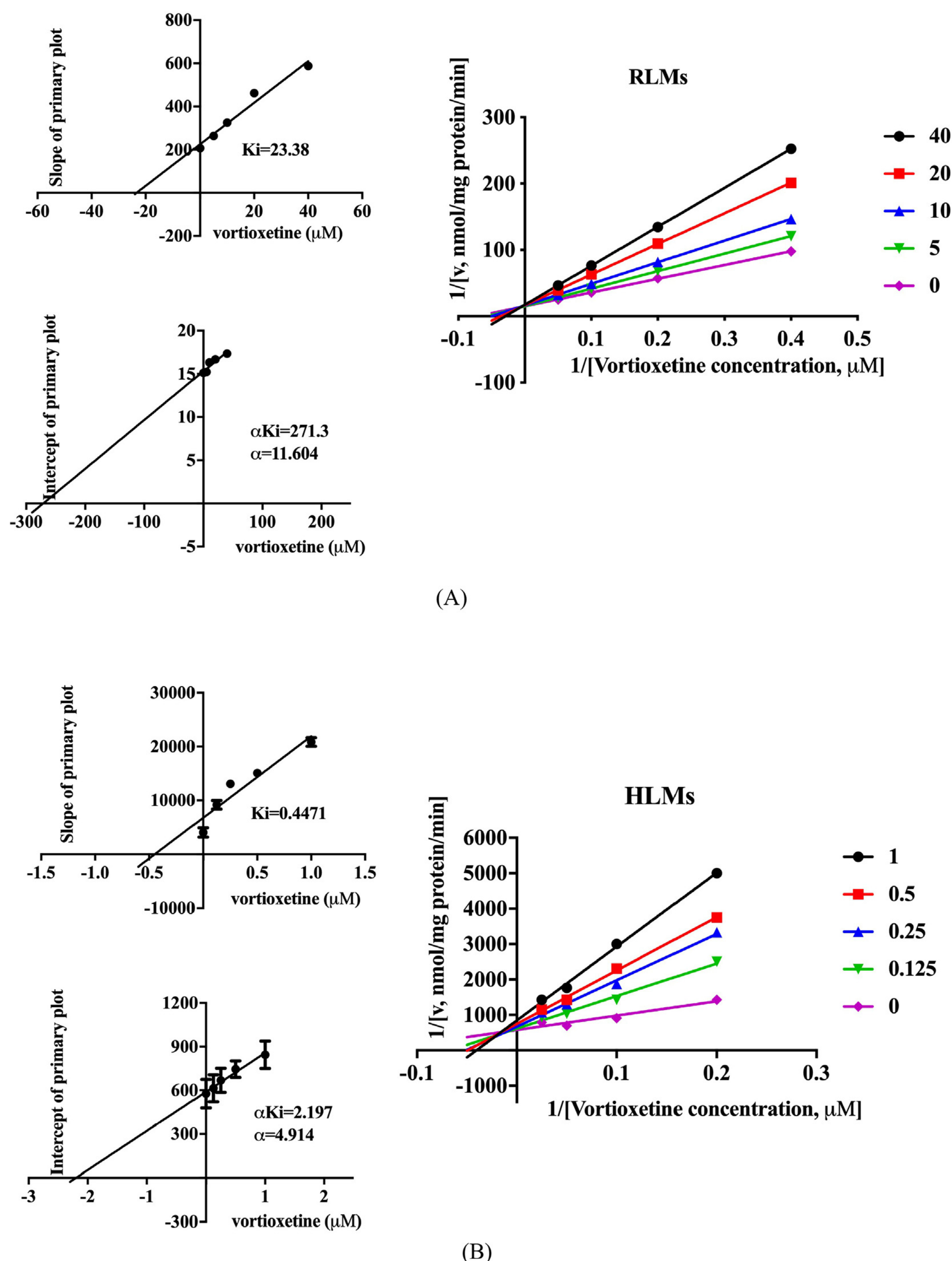

Fig. 4 Lineweaver-Burk plot and the secondary plot for K_i in the inhibition of vortioxetine metabolism by propafenone with various concentrations in (A) RLMs, and (B) HLMs. Values are the mean ± SD, n = 3.

effect of propafenone on vortioxetine metabolism in RLMs and HLMs were also assessed. As exhibited in Fig. 4, and Tables 1 and 2 for the pharmacokinetic study in rats, compared to the control group, propafenone (90 mg/kg) significantly increased the values of $AUC_{0\to t}$, $AUC_{0\to\infty}$, C_{max}, T_{max} and $t_{1/2}$ of vortioxetine. In addition, CL decreased to 75.3%. These results indicated that a single dose of propafenone can inhibit vortioxetine metabolism in vivo clearly, which were the same as the in vitro outcomes. Besides, this inhibitory effect could also be evaluated in HLMs and RLMs from the vitro studies. As indicated in Fig. 2, 100 μM propafenone significantly inhibited the metabolism of vortioxetine to 10.70% in HLMs and 29.76% in RLMs. The same results were found in Fig. 3, which exhibited the IC_{50} of 0.48 μM for HLMs and 16.5 μM for RLMs, respectively. These results from the vitro studies demonstrated that in HLMs and RLMs, propafenone also can inhibit the metabolism of vortioxetine. We explored the inhibitory mechanisms in RLMs and HLMs to figure out

Table 1 The main pharmacokinetic parameters of vortioxetine in two different groups of rats after orally administrated a single dose of 4.0 mg/kg vortioxetine (n = 6).

Parameters	Vortioxetine	
	Group A	Group B
$AUC_{0\to t}$ (ng/mL•h)	179.92 ± 56.62	286.21 ± 68.59*
$AUC_{0\to\infty}$ (ng/mL•h)	180.10 ± 56.60	286.73 ± 67.92*
C_{max} (ng/mL)	15.38 ± 3.04	32.76 ± 5.59*
$t_{1/2}$ (h)	3.09 ± 0.72	5.19 ± 1.37*
T_{max} (h)	3.17 ± 0.78	6.30 ± 2.82*
CL (L/h/kg)	24.58 ± 9.56	18.52 ± 4.89*

Compared to the control group, *P < 0.05.

Table 2 The main pharmacokinetic parameters of Lu AA34443 in two different groups of rats after orally administrated a single dose of 4.0 mg/kg vortioxetine (n = 6).

Parameters	Lu AA34443	
	Group A	Group B
$AUC_{0\to t}$ (ng/mL•h)	5830.24 ± 611.65	5171.68 ± 774.70
$AUC_{0\to\infty}$ (ng/mL•h)	6465.35 ± 707.17	6030.54 ± 850.42
C_{max} (ng/mL)	463.75 ± 102.99	517.22 ± 147.09
$t_{1/2}$ (h)	10.21 ± 2.27	10.01 ± 2.35
T_{max} (h)	3.83 ± 1.04	5.10 ± 1.46
CL (L/h/kg)	0.63 ± 0.08	0.60 ± 0.12

the potential inhibitory effects of propafenone on vortioxetine. The results (Fig. 4) demonstrated that propafenone was a competitive inhibitor of vortioxetine in RLMs and HLMs.

Interesting, these in vitro results from HLMs and RLMs supported to the pharmacokinetic interaction study in vivo from rats. Despite the inhibition of the vortioxetine metabolism in the presence of propafenone, the concentrations of the metabolite Lu AA34443 were unchanged. This may be because propafenone inhibit the metabolism and excretion of vortioxetine, which leads to prolong retention time of vortioxetine in vivo and enhance exposure. This leaves vortioxetine more opportunities to form the metabolite. Additionally, propafenone probably can inhibit the further metabolism of the metabolite, prevent it from converting into glucuronide, then maintain the concentration of the metabolite. In addition, it was found that the concentration of the metabolite Lu AA34443 in comparison to the parent drug vortioxetine is higher in rats, and these similar findings also had been observed in other species (Kall et al., 2015).

Similary, previous studies demonstrated inhibitory effects of propafenone on CYP2D6 substrates (metoprolol and mexiletine) resulting in the pharmacokinetic changes (Duricova et al., 2013; Labbe et al., 2000). In addition, it was observed in healthy subjects that there may be a pharmacokinetic interaction between vortioxetine and bupropion due to substantial increases in vortioxetine concentrations (Chen et al., 2013). Combined with our results in vivo and in vitro study, propafenone is expected to influence the concentration of vortioxetine through the inhibitory effect on CYP2D6. At high plasma vortioxetine concentrations, patients may experience different adverse events, with the most frequent being nausea, headache, nasopharyngitis and dizziness. Serious adverse events including left hemispheric ischaemic stroke, depression, major depression and tachycardia (paroxysmal and supraventricular) are considered to be related with vortioxetine (Alam et al., 2014). Therefore, if vortioxetine is co-administered with propafenone, it may be necessary to adjust the dosage.

5. Conclusion

In conclusions, these findings from our study demonstrated that the addition of propafenone could inhibit the metabolism of vortioxetine in vivo and in vitro, and increase the exposure of vortioxetine. It is the first research that explore the effect of propafenone on vortioxetine metabolism, which may help in guiding clinic medication when clinicians prescribe this combination. Therapeutic drug monitoring could serve as a valuable tool in mastering the vortioxetine concentration.

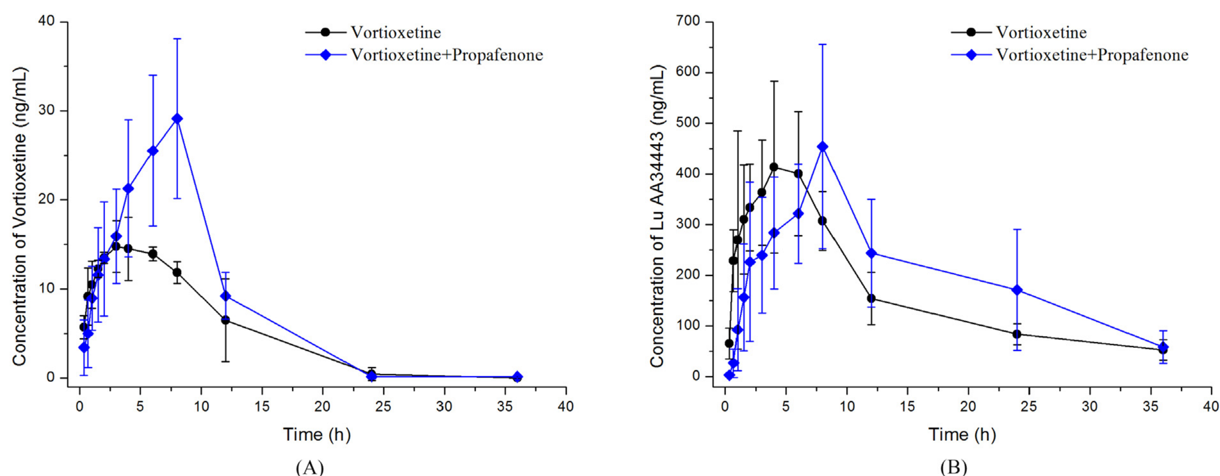

Fig. 5 Mean plasma concentration–time curves of vortioxetine (A) and its metabolite Lu AA34443 (B) in two groups after orally administrated a single dose of 4.0 mg/kg vortioxetine with or without 90 mg/kg propafenone (Mean ± SD, n = 6).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This study was supported by grants from Wenzhou City Science and Technology Bureau (Grant No. Y2020834), Wu Jieping Medical Foundation (Grant No. LCYX-Q011) and Young Talents Program of The First Affiliated Hospital of Wenzhou Medical University (Grant No. qnyc111).

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