

Drug–drug interaction study of imatinib and voriconazole in vitro and in vivo

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Background: In clinical practice, common problem polypharmacy could result in the increased risks of drug–drug interactions (DDIs). Co-administered imatinib (IMA) and voriconazole (VOR) as one treatment protocol in cancer patients with fungal infections are common.

Purpose: The aim of the present study was to assess the potential DDIs associated with the concurrent use of IMA and VOR in rat liver microsomes (RLMs) and in rats.

Methods and results: The concentration levels of IMA, VOR, and their metabolites N-desmethyl IMA (CGP74588) and N-oxide voriconazole (N-oxide VOR) were determined by ultra performance liquid chromatography-tandem mass spectrometry. In vitro study of RLMs, VOR inhibited the IMA metabolism with the half-maximal inhibitory concentration (IC_{50}) of 105.20 μ M, while IC_{50} for IMA against VOR was 61.30 μ M. After co-administered IMA and VOR in rats, the C_{max} of IMA was increased significantly, while the $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, and C_{max} of CGP74588 were decreased significantly. In addition, similar results were also found that the main pharmacokinetic parameters ($AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, $MRT_{0\rightarrow\infty}$, T_{max} , and C_{max}) of VOR were increased significantly, while the $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, and C_{max} of N-oxide VOR were decreased significantly. Incorporation of all the results indicated that both drugs had a inhibitory effect on each other's metabolism in vitro and in vivo.

Conclusion: Thus, it is of great value to monitor the concomitant use of IMA and VOR in the clinic to reduce the risks of unexpected clinical outcomes.

Keywords: drug–drug interaction, imatinib, voriconazole, rat liver microsome, metabolism

Introduction

Drug–drug interactions (DDIs) often occur, especially for patients with multiple underlying diseases who use various kinds of drugs.¹ In clinical practice, polypharmacy is a common problem and results in the increased risks of DDIs.^{2,3} A primary reason of DDIs is the change of the cytochrome P450 (CYP450) isozyme activity by inducing or inhibiting.^{4,5} Therefore, it is very important to identify the potential DDIs in order to reduce the risks of unexpected outcomes.

In the clinic, invasive fungal disease is a serious problem with high mortality and morbidity rate, which could cause significant damage to human health, especially for hematological malignancies patients.^{6,7} As the first-line drug for the treatment of invasive aspergillosis, voriconazole (VOR) has a poor correlation between plasma levels and the drug dosing, because of its narrow therapeutic window (1.0–5.5 μ g/mL) and variable pharmacokinetic profile.^{8,9} In addition, CYP2C19, CYP2C9, and CYP3A4 are the major enzymes responsible for VOR metabolized to N-oxide voriconazole (N-oxide VOR).¹⁰ Therefore, therapeutic drug monitoring (TDM) is proposed to ensure optimal VOR exposure for its wide variability and narrow therapeutic range.¹¹

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Imatinib (IMA) is the first synthetic tyrosine kinase inhibitor and is currently approved as standard care in patients with BCR-ABL-positive chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GIST).^{12,13} It is mainly metabolized by CYP3A4 enzyme to the primary circulating product N-desmethyl IMA (CGP74588), which was proved to be similar pharmacologic with the parent drug.^{14,15} Although IMA is considered to have an excellent pharmacokinetic profile, intra- and inter-individual variability of drug exposure is largely documented.¹⁶

In CML and GIST patients, the most serious fungal infection is invasive aspergillosis, which can lead to death.¹⁷ Co-administered IMA and VOR as one treatment protocol in those patients have been recognized, and the effect of VOR on the metabolism of IMA also has been studied in vivo¹⁸ and in vitro.¹⁹ However, to the best of our knowledge, there are currently no studies examining DDIs associated with the concurrent use of IMA and VOR, especially the effect of IMA on VOR metabolism. IMA was found to be a potent inhibitor of CYP3A4,²⁰ which can interact with CYP3A4 substrates, like VOR. Thus, it is unclear what dosage of VOR to administer with IMA in the clinic is chosen.

In this study, we attempted to use an ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method for the determination of IMA, VOR, and their metabolites in plasma and investigate the DDIs of IMA and VOR in rats. Moreover, the potential DDIs in rat liver microsomes (RLMs) were also identified.

Materials and methods

Chemicals

IMA (purity >98%), CGP74588 (purity >98%), VOR (purity >98%), and N-oxide VOR (purity >98%) were bought from National Institutes for Food and Drug Control (Beijing, China). Diazepam was purchased from Sigma (St. Louis, MO, USA), and used as the internal standard (IS). The reduced nicotinamide adenine dinucleotide phosphate (NADPH) was obtained from Roche Pharmaceutical Ltd (Basel, Switzerland). High-performance liquid chromatography grade acetonitrile and methanol were obtained from Merck Company (Darmstadt, Germany). Deionized water was produced using a Milli-Q academic reagent grade water purification system (Millipore, Bedford, USA).

Instrumentation and operation conditions

The LC and MS/MS condition were based on our report in the literature.²¹ An Acquity ultra-high performance liquid

chromatography (UPLC) system (Waters Corp., Milford, MA, USA) with an Acquity BEH C18 column (2.1 mm×50 mm, 1.7 μm) at 45°C was used for the chromatographic separation. Acetonitrile (A) and water with 0.1% formic acid (B) were used as the gradient elution solvents, and were conducted with the 0.40 mL/min flow rate as follow for the gradient program: 0–1.0 mins (20–90% A), 1.0–2.0 mins (90–90% A), 2.0–2.1 mins (90–20% A), and 2.1–4.0 mins (20–20% A).

In positive ionization mode, a XEVO TQ-S triple quadrupole mass spectrometer with electrospray ionization was employed for the quantitation. In the multiple reaction monitoring mode, the measurement was achieved with transitions of m/z 494.3→394.2 for IMA, m/z 480.3→394.2 for CGP74588, m/z 350.1→281.1 for VOR, m/z 366.1→224.1 for N-oxide VOR, and m/z 285.0→154.0 for IS, respectively. Masslynx 4.1 software (Waters Corp., Milford, MA, USA) was used to control the instrument and acquire the data.

Preparation of RLMs

The liver obtained from eight different rats were weighed and homogenized in a cold 0.01 mM PBS, which contains 0.25 mM sucrose. After centrifuged at 11,000 rpm for 15 mins, the supernatants separated from the homogenates were then transferred to a new tube and centrifuged at 11,000 rpm for 15 mins again. Moreover, the supernatants were then ultra-centrifuged at 100,000×g at 4°C for 1 hr. The microsomal pellets were reconstituted with 0.01 mM cold PBS and stored at –80°C.²² The protein concentrations of the liver microsomes were assayed by Bradford Protein Assay Kit (Thermo Scientific, Waltham, MA, USA).

VOR–IMA interaction studies in RLMs

When VOR was used as the inhibitor to determine the half-maximal inhibitory concentration (IC₅₀), the incubation mixture (total volume, 200 μL) contained 0.5 mg/mL RLMs, 1 M potassium phosphate buffer (pH 7.4), IMA (5.0 μM, approximately the K_m of RLMs, which was determined as reported¹⁹), VOR (0, 0.01, 0.1, 1, 10, 50, 100, and 1,000 μM) and 1 mM NADPH. In a shaking water bath at 37°C, NADPH was added to initiate the reaction after pre-incubation for 5 mins. The final volume of the mixture was 200 μL, and was performed for 40 mins, stopped by cooling to –80°C immediately. Then, 400 μL IS working solution (5 ng/mL IS in acetonitrile) was added. After vortex mixing for 1 min, the tubes were centrifuged at 15,000×g for 15 mins. The supernatant mixture (2 μL) was injected for analysis.

When IMA was used as the inhibitor, the incubation mixture and sample preparation were as the same as the above mentioned, except for VOR (2.0 μM , approximately the K_m of RLMs) and IMA (0, 0.01, 0.1, 1, 10, 20, 50, and 100 μM). All incubations were performed in triplicate and data are presented as means \pm SD.

In vivo pharmacokinetic interaction studies

Male Sprague–Dawley rats (200 \pm 20 g) obtained from the Laboratory Animal Center of Henan University of Science and Technology (Luoyang, China) were used to study the pharmacokinetic interaction of IMA and VOR. All experimental procedures and protocols were reviewed and approved by the Animal Care and Use Committee of Henan University of Science and Technology and were in accordance with the Guide for the Care and Use of Laboratory Animals.

Twenty-four SD rats were divided randomly into three groups: the IMA group (Group A, $n=8$), the VOR group (Group B, $n=8$), and the co-administered IMA and VOR group (Group C, $n=8$). All animals were fasted overnight and allowed free to water within the period of the experiment. IMA and VOR were dissolved in 0.5% sodium carboxymethyl cellulose (CMC-Na) solution alone or together. The Group A and B were treated with 20 mg/kg IMA and 20 mg/kg VOR, respectively, while the Group C with an equivalent amount of 20 mg/kg IMA and 20 mg/kg VOR together. Blood samples (300 μL) were collected via tail vein to 1.5 mL centrifuge tube at the time points of 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 36 hrs after oral administration. The obtained samples were immediately centrifuged at 4,000 $\times g$ for 8 mins, and the supernatant (100 μL plasma samples) were collected and stored at -80°C until analysis. As for sample preparation, 200 μL

IS working solution (5 ng/mL IS in acetonitrile) was added to each plasma sample for the extraction. After vortex-mixed for 1 min, the mixture was centrifuged at 15,000 $\times g$ for 15 mins, and the supernatant (2 μL) was injected into the UPLC-MS/MS system for analysis.

Statistical analysis

The non-compartmental analysis was used to calculate the pharmacokinetic parameters by DAS version 2.0 (Shanghai University of Traditional Chinese Medicine, China). The mean plasma concentration-time curve was plotted by Origin 8.0 (Originlab Company, Northampton, MA, USA), and the IC_{50} was calculated by GraphPad (Version 6.0; Graphpad Software Inc., San Diego, CA, USA). Statistical comparisons of the main pharmacokinetic parameters within each group were carried out with the Statistical Package for the Social Sciences (version 17.0; SPSS Inc., Chicago, IL, USA) by one-way analysis of variance for repeated measures coupled with the Dunnett's test. In all cases, $P<0.05$ was considered to be of statistical significance.

Results

Effects of VOR on the metabolism of IMA in RLMs

As shown in Figure 1, when the concentration of VOR (100 μM) was used, VOR inhibited the IMA metabolism rate in RLMs to 54.4%. Furthermore, the IC_{50} for inhibition activity in RLMs was 105.20 μM (Figure 1).

Effects of IMA on the metabolism of VOR in RLMs

Figure 2 exhibits the inhibitory effect of IMA on VOR metabolism. It indicated that 100 μM IMA inhibited the VOR

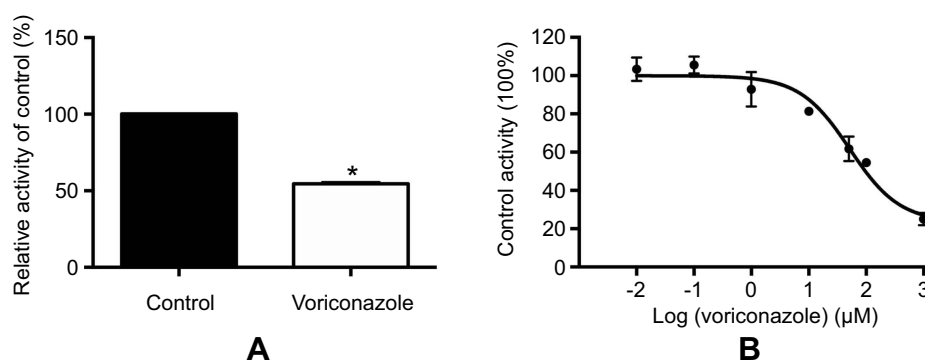


Figure 1 The effect of 100 μM VOR on IMA metabolite (CGP74588) formation (A) and various concentrations (0, 0.01, 0.1, 1, 10, 50, 100, and 1,000 μM) of VOR for IC_{50} (B) in RLMs. Values are Mean \pm SD, $n=3$.

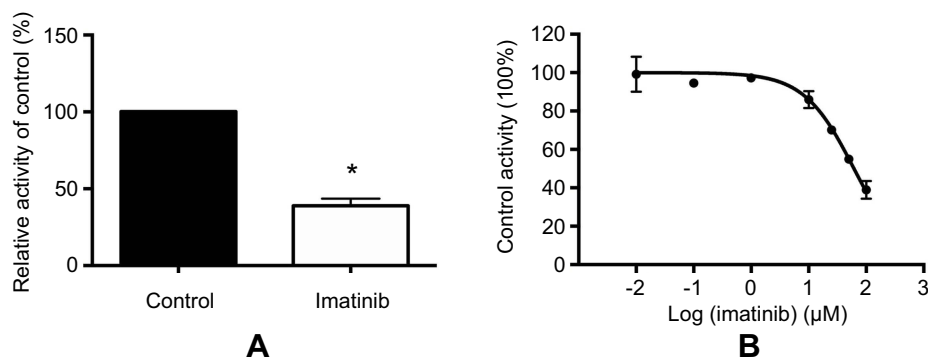


Figure 2 The effect of 100 µM IMA on VOR metabolite (N-oxide VOR) formation (A) and various concentrations (0, 0.01, 0.1, 1, 10, 20, 50, and 100 µM) of IMA for IC₅₀ (B) in RLMs. Values are Mean ± SD, n=3. *P<0.05.

metabolism rate in RLMs to 38.9%. In addition, the IC₅₀ for inhibition activity in RLMs was 61.30 µM (Figure 2).

Pharmacokinetic interaction studies in rats

Table 1 shows the statistical analysis results for the mean pharmacokinetic parameters of IMA (Group A), VOR (Group B) administered alone, and in combination (Group C), which were analyzed by DAS 2.0. Mean plasma concentration–time curves of IMA, VOR, and their metabolites in three groups are presented in Figure 3.

The mean plasma concentration–time curve and mean pharmacokinetic parameters showed that the C_{max} of IMA in Group C was increased significantly by 18.8%, when compared to Group A (P<0.05). In addition, the AUC_{0→t}, AUC_{0→∞}, and C_{max} of CGP74588 were decreased significantly by 23.5%, 25.1%, and 29.4%, respectively, compared to those of the Group A, while CL of CGP74588 was increased significantly by 33.9%. These results indicated that VOR had the inhibitory effect on the IMA metabolism in rats, which were consistent with the results of DDIs in RLMs.

As for VOR, the main pharmacokinetic parameters (AUC_{0→t}, AUC_{0→∞}, MRT_{0→∞}, T_{max}, and C_{max}) of VOR in Group C were increased significantly by 96.1%, 94.3%, 18.2%, 74.4%, and 43.5%, respectively, compared to those of the Group A, while CL of VOR was decreased significantly by 50.7%. Moreover, the AUC_{0→t}, AUC_{0→∞}, and C_{max} of N-oxide VOR in Group C were decreased significantly by 41.2%, 39.6%, and 21.0%, respectively. Our results indicated that IMA had the inhibitory effect on the VOR metabolism in rats, which were also consistent with the results of DDIs in RLMs.

Discussion

IMA has been considered as the first-line treatment for CML, as well as for GIST and other hematological disorders. It is primarily metabolized by CYP3A4, and its bioavailability is thus expected to be drastically affected by the co-administration of drug known to alter the CYP activity in vitro^{19,23} and in vivo.²⁴ In cancer patients with low immune function, especially under chemotherapy, opportunistic fungal infections are common problems and

Table 1 Pharmacokinetic parameters of IMA, VOR, and their metabolites in three different groups (n=8)

Parameters	IMA		CGP74588		VOR		N-oxide VOR	
	Group A	Group C	Group A	Group C	Group B	Group C	Group B	Group C
AUC _{0→t} (µg/mL·h)	38.37±6.33	43.52±8.65	4.42±0.51	3.38±0.60**	30.47±8.52	59.76±5.36***	31.42±6.80	18.49±6.05**
AUC _{0→∞} (µg/mL·h)	38.89±6.31	44.01±8.74	4.71±0.71	3.53±0.61**	30.81±8.21	59.87±5.37***	32.74±6.91	19.77±6.37**
MRT _{0→t} (h)	9.43±0.43	9.34±0.61	10.93±1.09	10.83±0.87	6.65±0.89	7.83±0.25*	11.20±1.28	10.62±1.68
MRT _{0→∞} (h)	9.91±0.45	9.75±0.82	11.16±1.25	11.58±0.88	6.69±0.96	7.91±0.24*	11.37±1.25	10.94±1.74
t _{1/2} (h)	5.39±0.85	5.14±0.74	8.30±1.27	7.34±1.54	3.31±0.53	3.66±0.45	8.67±0.49	7.24±0.37
T _{max} (h)	3.86±0.69	5.00±0.82	3.71±0.56	5.00±1.10	1.64±0.24	2.86±0.28*	7.43±0.98	6.00±0.63
CL (L/h)	0.52±0.04	0.47±0.07	4.33±0.60	5.80±0.90**	0.69±0.17	0.34±0.03**	1.12±0.24	1.33±0.27
C _{max} (µg/mL)	2.77±0.22	3.29±0.55*	0.34±0.07	0.24±0.05*	3.08±0.26	4.42±0.20***	2.38±0.45	1.88±0.41*

Notes: Compared to the control group, *P<0.05, **P<0.01, ***P<0.001.

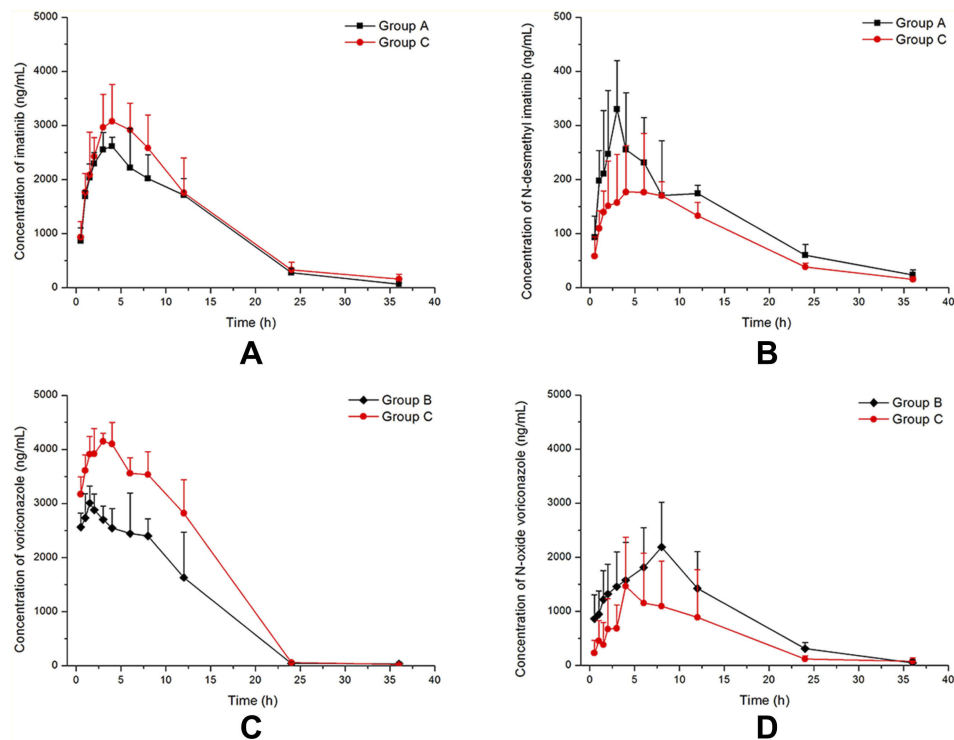


Figure 3 Mean plasma concentration versus time of IMA (A), CGP74588 (B), VOR (C), N-oxide VOR (D) in three group rats (Mean \pm SD, n=8).

result in a high mortality rate. Because of individual variation and narrow therapeutic index in plasma concentration levels, VOR requires TDM as the first-line drug for the treatment of fungal infection. VOR is a CYP3A4 inhibitor, and can lead to high plasma levels of IMA, which result in a severe adverse drug event.²⁵ Although IMA and VOR are co-administered to cancer patients, DDIs associated with the concurrent use have not been fully explored.

In this study, we investigated the effect of VOR on the metabolism of IMA via the formation of CGP74588 in RLMs. The results of our study showed that VOR had a slight inhibition on the IMA metabolism based on IC_{50} value (105.20 μ M) in our vitro assay, which was consistent with the reported findings.¹⁹ In pharmacokinetic interaction studies, the results indicated that VOR had no impact on the clearance or bioavailability of IMA except an 18.8% increase of the C_{max} in rats. In addition, the main pharmacokinetic parameters ($AUC_{0 \rightarrow t}$, $AUC_{0 \rightarrow \infty}$, and C_{max}) of CGP74588 were decreased significantly. Our results of the pharmacokinetic interaction studies in rats were in agreement with the reported article by Lin et al¹⁸. These results in a combination of in vitro and in vivo demonstrated that VOR would increase the IMA exposure. Although a previous study showed that

strong CYP3A4 inhibitor ritonavir had no significant effect on the pharmacokinetic parameters of IMA,²⁶ there was sufficient evidence to confirm that VOR would increase the IMA exposure by inhibiting CYP3A4 activity.

To the best of our knowledge, this is the first report about the inhibitory effect of IMA on the metabolism of VOR via the formation of N-oxide VOR in RLMs. Our vitro study indicated that IMA had a moderate inhibition on the VOR metabolism based on IC_{50} value (61.30 μ M). Moreover, the results of pharmacokinetic interaction studies in rats exhibited that the concentration of VOR increased and the formation of N-oxide VOR decreased, which showed IMA inhibited the metabolism of VOR in rats. Therefore, the results in vitro and in vivo were consistent. VOR is extensively metabolized in the liver, primarily through CYP2C19 and, to a lesser extent, through CYP3A4 and CYP2C9.¹⁰ The relative importance of the pathways in conjunction with the relative higher abundance of the CYP3A4 compared with low contents of CYP2C19 in human livers may still translate to higher overall contribution of CYP3A4, even having lower CYP3A activities compared with CYP2C19.²⁷ It was suggested that CYP3A4 is important in the metabolism of VOR, which occurred DDI with ritonavir in individuals

with poor CYP2C19 catalytic function.²⁸ It was also validated that coadministration of drugs that modulate CYP3A4 activity could effect VOR plasma levels.^{10,29} IMA was found to be a potent inhibitor of CYP3A4 from the finding of the IMA-simvastatin interaction in patients with CML.²⁰ It was reported that IMA could increase the exposure of a single dose of simvastatin when given concomitantly, and the reason most likely to be the inhibition of CYP3A4-mediated metabolism of simvastatin in the liver. Potent mechanism-based inhibition of CYP3A4 by IMA in vitro was confirmed and suggested that IMA could markedly increase plasma concentrations of CYP3A4 substrates by reducing the clearance rate of the latter.³⁰ This may explain why IMA inhibits the metabolism of VOR. Therefore, caution is required when administering IMA with CYP3A4 substrates with a narrow therapeutic window, especially VOR.

Conclusions

In conclusion, the present study exhibited IMA and VOR inhibited the metabolism of each other and confirmed the importance of CYP3A4 in DDI of IMA and VOR. For the first time, we found that IMA can inhibit the metabolism of VOR in vitro and alter the pharmacokinetic profiles of both VOR and N-oxide VOR in vivo. Given a big chance of IMA co-formulated with VOR, our study gives a novel direction to the guidance of clinical medication and treatment. Clearly, further studies to elucidate the DDI of IMA and VOR are warranted.

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Disclosure

The authors declare that there are no conflicts of interest in this work.

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