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The impact of proton pump inhibitors on the pharmacokinetics of voriconazole in vitro and in vivo

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ABSTRACT

Voriconazole (VRC) and proton pump inhibitors (PPIs) have similar metabolic pathways. The objectives of the study are to evaluate the impact of PPIs on the pharmacokinetics of VRC. Human liver microsomes model was applied to assess the inhibitory effects of PPIs on the metabolism of VRC in vitro. A retrospective study was also carried out to explore the relationship between the plasma VRC trough concentrations and PPIs uses. Patients were divided into six groups: control (n = 166), lansoprazole (LAN, n = 38), esomeprazole (ESO, n = 19), omeprazole (OME, n = 45), pantoprazole (PAN, n = 43), and ilaprazole (ILA, n = 38) groups. All five PPIs showed concentration-dependent inhibitory effects on the VRC metabolism in human liver microsomes, among which LAN, OME and ESO were three of the most potent inhibitors. Consistently, co-administered with LAN, OME and ESO significantly increased the plasma VRC trough levels ($p < 0.05$), whereas there was no significant association between VRC concentrations and PAN or ILA use. Interestingly, patients in the PPIs groups were more likely to reach the therapeutic VRC range of 1–5.5 μg/mL in steady state when compared with control patients (75–81% VS 69%). In conclusion, although all PPIs showed inhibitory effects on the VRC metabolism in vitro, only LAN, OME and ESO significantly increased VRC plasma concentrations. This study should be helpful for choice of the type of PPIs for patients administered with VRC.

1. Introduction

Drug-drug interactions (DDIs) often occur when one drug affects another drug's absorption, distribution, metabolism, or excretion by altering metabolic enzymes and/or transporters activities [1,2]. In some instances, DDIs also may occur when co-administered drugs had similar or opposite effects on the body [3]. Unrecognized, unanticipated or mismanaged DDIs account for a part of clinical ineffectiveness or adverse reactions of the drugs [4,5]. However, polypharmacy is a common problem in clinical practice, resulting in the increased risks of DDIs. Therefore, it is of great value to identify the potential DDIs to reduce the risks of unexpected clinical outcomes.

Voriconazole (VRC) is a broad-spectrum antifungal agent and widely used for the treatment of invasive fungal diseases [6,7]. VRC is extensively metabolized in the liver and about 1% excreted in the urine unchangeably. Several hepatic cytochrome P450 (CYP) enzymes, namely, mainly CYP2C19 and to lesser extent CYP2C9 as well as CYP3A4, account for the metabolism of VRC [8]. In addition, plasma VRC concentrations show greatly intra and inter-individual variability depending on age, actual body weight, CYP2C19 polymorphisms, liver functions and drug interactions [8]. The therapeutic index for VRC is very narrow (1–5.5 μg/mL) [9]. Subtherapeutic plasma concentrations are associated with the increased mortality on patients with life-threatening invasive fungal infections, while supratherapeutic

Abbreviations: VRC, voriconazole; PPIs, proton pump inhibitors; LAN, lansoprazole; ESO, esomeprazol; OME, omeprazole; PAN, pantoprazole; ILA, ilaprazole; DDIs, drug-drug interactions; CYP, cytochrome P450; TDM, therapeutic drug monitoring; HLM, human liver microsomes; NADPH, nicotinamide adenine dinucleotide phosphate; UPLC–QTOF/MS, ultra-performance liquid chromatography quadrupole time of flight mass spectrometry; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; SD, standard deviation

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concentrations are related to unexpected side effects [10]. Therefore, therapeutic drug monitoring (TDM) is recommended for patients received VRC to optimize dosing adjustment [11].

Proton pump inhibitors (PPIs) such as omeprazole (OME), lansoprazole (LAN), pantoprazole (PAN), esomeprazole (ESO) and ilaprazole (ILA) are widely used for the treatment of peptic ulcer disease and gastrointestinal hemorrhage [12,13]. Because these gastrointestinal problems are common in patients at different clinical departments, the likelihood of concomitant medication of PPIs and VRC was high in patients with invasive fungal infections. In addition, PPIs also undergo CYP-mediated metabolism, mainly through CYP2C19, CYP2C9 and CYP3A4, indicating the potential pharmacokinetic interactions between VRC and PPIs [14]. Unsurprisingly, it has been reported that concomitant use of PPIs affect VRC trough concentration in multivariate analyses [15,16]. The inhibition capacity of numerous PPIs on CYP enzymes depends on the type PPI [17].

However, pharmacokinetic interaction profiles of VRC in combination with PPIs are still unknown. Here, the objectives of this study are to evaluate the impact of five PPIs (i.e., LAN, OME, PAN, ILA and ESO) on the VRC pharmacokinetic characters. Human liver microsomes (HLM) model was used to assess inhibitory capacities of PPIs on the metabolism of VRC. In addition, the impact of each PPI on trough plasma VRC concentrations was also evaluated by a retrospective study.

2. Materials and methods

2.1. Materials

Pooled HLM was bought from BD Biosciences (Woburn, Massachusetts). VRC, LAN, ESO. OME, PAN, and ILA with a purity > 98% were purchased from Shanghai Shifeng biological technology Co., LTD (Shanghai, China). Nicotinamide adenine dinucleotide phosphate (NADPH) was obtained from Aladdin chemicals (Shanghai, China). All other reagents (typically analytical grade or better) were used as received.

2.2. In vitro metabolism of voriconazole in human liver microsomes

The VRC was incubated with HLM in the absence or presence of PPI to determine the rates of reaction. Incubations were conducted at 37 °C in 200 μl phosphate buffers (pH 7.4) containing 5 mM $MgCl_2$ and 1 mg/mL HLM. NADPH was added to mixtures to start reaction. All incubations in this study were performed in triplicate for 30 min. At the end of incubation, the reaction was terminated by adding 200 μl ice-cold acetonitrile, followed by vortex and centrifugation (14 min; 14,000 *g*). The supernatant was collected for ultra-performance liquid chromatography quadrupole time of flight mass spectrometry (UPLC–QTOF/MS) analysis.

2.3. Quantification of voriconazole by UPLC–QTOF/MS analysis

The concentrations of VRC in microsomal samples were determined by UPLC-QTOF/MS system equipped with ACQUITY UPLC and Xevo G2 QTOF mass spectrometry (Waters Corp., Milford, USA). Chromatographic separation was conducted via a BEH column (2.1 × 50 mm, 1.7 μm; Waters). Besides, column temperature was maintained at 45 °C. The mobile phase was consisted of formic acid (0.1%) in water (solvent A) and acetonitrile (solvent B). The flow rate was set as 0.45 mL/min over a run time of 4.0 min. The gradient elution program was 5% B at 0–1 min, 5%–80% B at 1–3 min, 80% B at 3–3.5 min, and 80% to 5% B at 3.5–4 min. The tandem mass spectrometer was operated in positive mode.

2.4. Patients selection and data collection

A retrospective study was approved by the Ethics Research Committee of the Second Xiangya Hospital of Central South University. The clinical trial registration number was ChiCTR1800015710. Plasma VRC concentrations were analyzed and recorded for 1827 patients from different clinical departments by TDM department between 2014 and 2017. Information of plasma concentrations collected at the trough level under steady-state conditions was only used in this study. Patients received concomitant drugs that were CYP inducers such as phenobarbital, rifampin, phenytoin, and carbamazepine, or CYP inhibitors such as cimetidine, erythromycin and vincaleukoblastinum, were excluded [18]. Patients were also excluded from study if they were less than 18 years old. Demographics such as age, sex, and actual body weight were collected. Liver function indices such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB) and total bilirubin (TBIL) were also collected.

To evaluate the impact of PPIs on VRC metabolism, patients administered with VRC were divided into six groups: control, OME, LAN, ILA, ESO and PAN groups. Patients in the control group were without concomitant medication of any PPIs. The OME, LAN, ILA, ESO and PAN groups included patients that had concomitant use of omeprazole, lansoprazole, ilaprazole, esomeprazole and pantoprazole, respectively.

2.5. Determination of plasma voriconazole concentration

The plasma concentrations of VRC were determined by automatic 2-dimensional liquid chromatography (2D-HPLC, Demeter Instrument Co., Ltd., Hunan, China). Sample pre-separation performed on a FRO C18 column (100 mm × 3.0 mm, 5 μm, ANAX) was accomplished by first liquid chromatography. At this step, elution was implemented using 20 mmol/L ammonium acetate–acetonitrile (48:52, V/V) at a flow rate of 1.0 mL/min. The second liquid chromatography consisted of a quaternary pump, a column heater, an autosampler and a multichannel rapid scanning UV-VIS detector was applied to sample separation and detection. Chromatographic separation was performed on an ASTON HD C18 column (150 mm × 4.6 mm, 5 μm, ANAX) at 45 °C. The elution was implemented using 40 mmol/L ammonium acetate–acetonitrile (85:15, V/V) at a flow rate of 1.2 mL/min. The detection wavelength was 273 nm. The analytical method was fully validated in regard to linearity (0.35–11.26 μg/mL), intra-day precision (1.94%–2.22%), inter-day precision (2.15%–6.78%), the absolute recovery (88.2%–93.6%) and the relative recovery (94.2%–105.3%), the limit of quantification (0.1 μg/mL).

2.6. Statistical analysis

In vitro data were presented as mean ± standard deviation (SD) and analyzed by unpaired student's *t*-test Patients information such as age, actual body weight, liver function indices (i.e. ALT, AST, TBIL and ALB) was analyzed by one-way analysis of variance. Sex expressed as absolute number was analyzed by Goodman's test. The Kruskal-Wallis test was used to compare the plasma trough concentration between six groups. The comparisons of trough concentration between the control group and each PPI group were performed using the Mann-Whitney test. Statistically significant was set as $P < 0.05$. All statistical analyses were conducted by GraphPad Prism 5 (San Diego, CA, USA).

3. Results

3.1. In vitro inhibitory effects of PPIs on VRC metabolism

The inhibitory effects of five PPIs on the VRC metabolism were investigated at three distinct PPI concentrations (0.2, 2, 20 μg/mL) (Fig. 1). The results clearly showed that in vitro inhibitory effects were found in all PPIs. Of note, OME, LAN, ESO showed the more potent inhibitory effects than ILA and PAN on VRC metabolism. Also, inhibition of HLM-mediated metabolism by all five PPIs was concentration-dependent.