Case report: Unusual Interaction Between Voriconazole and Ritonavir/Lopinavir in a COVID-19 Patient Due to CYP2C19 Gene Polymorphism

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Abstract

Drug–drug interactions may be a serious issue for COVID-19-infected patients needed kinds of conminant medications. voriconazole and lopinavir/ritonavir were involved in interaction with cytochrome P450 enzymes, Therefore, coadministration of voriconazole and lopinavir/ritonavir is estimated to interfere the effect of voriconazole. However, the gene polymorphisms make these interactions more complicating.

Introduction

As COVID-19-infected patients are immunocompromised and highly susceptible to serious opportunistic fungal infections,[1] there is a need to understand and manage drug–drug interactions between antiretroviral and antifungal agents, particularly broad-spectrum voriconazole.[2,3]

The antiretroviral drug lopinavir/ritonavir is widely used for the treatment of HIV and is a potential candidate for the treatment of COVID-19. Ritonavir induces the hepatic activity of cytochrome P450 enzymes, namely CYP2C9, CYP2C19, and CYP1A2, but it inhibits the hepatic and intestinal activity of CYP3A[4-6]. Voriconazole is extensively metabolized by CYP2C19 and, to a lesser extent, by CYP2C9 and CYP3A. Therefore, concominant of voriconazole and lopinavir/ritonavir is not recommended as the AUC and Cmax of voriconazole have been shown to decrease 39% and 24% respectively, due to possible induction of CYP450 by ritonavir[7]. However, in this study, the voriconazole concentration was unexpectedly increased in the context of lopinavir/ritonavir coadministration in a COVID-19 patient.

Case presentation

A 73-year-old man weighing 60 kg developed a fever of 38.3 °C, with no other apparent symptoms, on 20th January 2020. He came to the fever clinic at the Third People's Hospital of Shenzhen.

He disclosed that he lived in Erzhou of Hubei and took the train from Wuhan to Shenzhen on 19th January. He denied any exposure to the Huanan seafood market or wild animals.

A nasal swab for testing COVID-19 was performed immediately, and the result was positive. Given his travel history and nasal swab findings, the patient was admitted to an airborne isolation unit as a suspected case of COVID-19 on 23rd January 2020. On 24 January, the Centers for Disease Control (CDC) confirmed that the patient's oropharyngeal swab test for SARS-CoV-2 by qualitative real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay was positive.

On admission, he was administered symptomatic treatment and antimicrobial therapy, including oseltamivir, lopinavir/ritonavir, and azithromycin. On 3rd February, physicians added voriconazole with a loading dose

of 360 mg q12 h on day 1; the patient also received a maintenance dose of 200 mg q12 h because of the continuous fever and suspected fungal infection. Therapeutic drug monitoring (TDM) of voriconazole was performed almost daily beginning on 7th February. Unexpectedly, the concentration of voriconazole was almost twice as high as the normal therapeutic range (figure 1)[17]. The dose of voriconazole was decreased to 160 mg q 12 h on 8th February; TDM showed that the trough concentration was still unexpectedly high. As a result, the dose was adjusted to 130 mg q12h, but the though concentration was still higher than 8 mg/L. The concentration decreased to 0.7 mg/l after two days of voriconazole withdrawal, which led to our suspicion that lopinavir/ritonavir decreased the concentration of voriconazole by inducing CYP2C19 expression. Other concomitant medications are listed in figure 2. Several studies have discovered that coadministration of CYP3A4 inhibitors might induce a voriconazole plasma level increase among CYP2C19 activity-reduced patients [8-9]. We supposed that CYP2C19 activity was impaired in this patient due to gene polymorphisms, so the patient's CYP450 genotype was detected; the CYP450 genotype result was CYP2C19 *1/*2; CYP3A4 *1/*1; CYP2C9*1/*1.

However, on 23rd March, voriconazole was administered again with a load dose of 350 mg q 12 h and a maintenance dose 200 mg, q12 h; the trough concentration on 24th March was lower than 2 mg/l. Even after increasing the dose to 300 mg q 12 h for 5 days, the concentration still lower than 1.6 mg/L, which could not be explained by impaired CYP2C19 activity. At the same time, ECMO was used, and no circuits were changed. During the observation period, there were no significant CYP450 enzyme inhibitors or inducers among the concomitant medications and recently used medications.

Discussion

Voriconazole is a triazole antifungal agent that is a first-line drug applied in the treatment of a wide number of fungal infections, including pulmonary invasive aspergillosis, fluconazole-resistant Candida spp.[10-13] Voriconazole is metabolized by cytochrome P450 (CYP), mostly by the CYP2C19 isoenzyme and, to a lesser extent, by CYP3A4 and CYP2C9. CYP2C19*1 is the wild-type allele with enzymatic activity, whereas the most common loss-of-function alleles are CYP2C19*2 and CYP2C19*3.[14]. Individuals having one functional allele plus one loss-of-function allele are also referred to as intermediate metabolizers. There were higher dose-adjusted trough concentrations of Voriconazole in intermediate metabolizers compared with normal metabolizers; therefore, the Dutch Pharmacogenetics Working Group recommended standard of care dosing and monitoring of the plasma concentration. In theory, our patient was determined to be an intermediate metabolizer with CYP2C19*1/*2 accompanied by a higher concentration of voriconazole due to the absence of a functional CYP2C19 enzyme; however, the experience in this patient's second exposure to voriconazole did not coincide with the abovementioned interpretation and could not completely explain such obvious and long-term loss with adsorption of the ECMO circuit.

Because CYP2C19 activity was impaired, other metabolic pathways, such as the CYP3A-mediated pathway, may have become the major clearance mechanism and been influenced by CYP3A modulators. Brad and his colleagues explored a poor metabolizer with CYP2C19*2/*3 coadministered vincristine, a CYP3A4 inhibitor, which induced a significant increase in voriconazole concentration[15]. Sara et al., Li et al., and Andreas et al. discovered a 2-way interaction between voriconazole and other drugs connected to the CYP2C19 genotype and concomitant medication[8,9,16]. Therefore, we hypothesized that CYP2C19 activity may be impaired in patients who metabolize voriconazole mainly via CYP3A or/and CYP2C9; therefore, concomitant strong CYP3A4/CYP2C9 inhibitors might decrease voriconazole metabolism and increase its concentration. In this case, ritonavir is a CYP3A4 inhibitor, which may decrease voriconazole metabolism. Furthermore, azithromycin, a strong CYP3A4 inhibitor, was prescribed from the 27th to the 31st of January, and the inhibitory effect of azithromycin should not be ignored because the published mean CYP3A4 turnover half-life values ranged from 10 to 140 h. Using the highest estimate, recovery of full CYP3A4 activity may therefore take up to 23-29 days (4-5 turnover half-lives) after complete inhibition[18]. Therefore, though azithromycin was stopped 3 days before voriconazole use, its effect on CYP3A4 inhibition should be taken into account.

For CYP2C19 IMs and PMs, taking voriconazole with concurrent potent CYP3A inhibitors would result in a substantially higher risk of developing severe adverse events (AEs), including neurotoxicity and hepatotoxi-

city. In this case, the consciousness of the patient did not improve even when the infection was controlled and the dose of sedatives was reduced until voriconazole was withdrawn; therefore, neurotoxicity of voriconazole could not be excluded (data not shown).

Conclusions

The current case presents an unexpected interaction between voriconazole and atazanavir/ritonavir due to impaired CYP2C19 activity and concomitant CYP3A4 inhibitors, which reminded us to consider the effect of gene polymorphisms on the drug interaction and the time of CYP450 recovery after inhibition, which was easily overlooked because the suspected drug was already stopped. Otherwise, regular dose adjustment would have resulted in severe adverse events or unsatisfactory therapeutic effects.

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