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Using unusual drug-drug interactions to maximize voriconazole treatment efficacy

Recours inhabituel aux interactions médicamenteuses pour augmenter l'efficacité d'un traitement par voriconazole

Keywords: Voriconazole; *Scedosporium prolificans*; Pharmacokinetics

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Voriconazole is a broad-spectrum triazole used in the treatment of invasive fungal infections including those caused by *Scedosporium* spp. Voriconazole has a variable inter-individual pharmacokinetics, a narrow therapeutic index, and can be involved in several drug interactions, requiring therapeutic drug monitoring [1].

Successful treatment of disseminated *Scedosporium prolificans* infection can be obtained with a combination of voriconazole and terbinafine [2].

We report a disseminated *S. prolificans* infection in a patient treated with voriconazole, but unable to achieve therapeutic levels. Treatment optimization was implemented with the collaboration of a therapeutic drug monitoring (TDM) consultant.

A 61-year-old Caucasian patient (66.5 kg; 182 cm) presenting with multiple myeloma (IgG kappa) underwent autograft with hematopoietic stem cell from peripheral blood in 2017 and then presented with prolonged aplasia. At the end of aplasia, *S. prolificans* invasive fungal infection was documented with positive blood cultures associated with a right-eye infection and meningitis with brain abscess. Resistance to antifungal drugs was observed after in vitro susceptibility testing using the E-test method (BioMérieux, France), with very high minimum inhibitory concentrations (MIC) for azoles (MIC > 32 mg/L for posaconazole and isavuconazole, MIC = 8 mg/L for voriconazole) and contact resistance for amphotericin B as usually observed with this species. An antifungal triple therapy regimen with oral voriconazole (200 mg twice daily [BID] following a loading dose of 6 mg/kg every 12 hours for 24 hours), combined with terbinafine and miltefosine (50 mg every 8 hours), was initiated according to the previous clinical experience described by Trubiano et al. [3]. To ensure drug efficacy and to limit its toxicity, therapeutic drug monitoring of voriconazole trough concentration (Cmin) is recommended, with a Cmin between 2 and 5.5 μg/mL [1]. The various steps of therapeutic drug monitoring are presented in Fig. 1. Voriconazole Cmin remained suboptimal despite adequate treatment compliance and absence of any drug-drug interactions with a cytochrome P450 (CYP) inducer. It was then suggested to gradually increase the dosage by 100 mg step dose guided by therapeutic drug monitoring, until achieving an oral dose of 500 mg BID on day 31 after initiation of treatment.

Ocular lesions progressed with a purulent cast of the right eye leading to a decrease in visual acuity and then complete blindness of this eye. Increased dosages did not increase Cmin. Intravitreous voriconazole injections were added twice a week from day 19.

Moreover, the addition of a CYP2C19 inhibitor, the predominant CYP implicated in the metabolism of voriconazole, was proposed by the therapeutic drug monitoring consultant on day 26. Lansoprazole was introduced at the dose of 30 mg/day without any real positive impact on voriconazole exposure. The patient was switched to the intravenous route on day 38.

On day 40, the therapeutic drug monitoring consultant suggested initiating a CYP3A4 inhibitor to increase voriconazole concentrations: grapefruit juice was chosen (one glass of 200 milliliters per day, increased one week later to two glasses daily) because of the absence of drug interaction on comedications, and its absence of adverse effects. Concentrations slightly increased to reach trough levels between 1.60 and 1.90 μg/mL for approximately three weeks resulting in clinical improvement (decreased eye inflammation, disappearance of meningitis, and decreased brain abscess), before decreasing again. However, on day 60, the patient became febrile with lumbar and abdominal pain. Obstructive pyelonephritis was diagnosed. The patient underwent surgery to remove a urinary tract stone positive for *S. prolificans*. Just after the surgery, the patient presented with *Citrobacter koseri sepsis* complicated by septic shock leading to death, which was not considered to be related to the fungal infection.

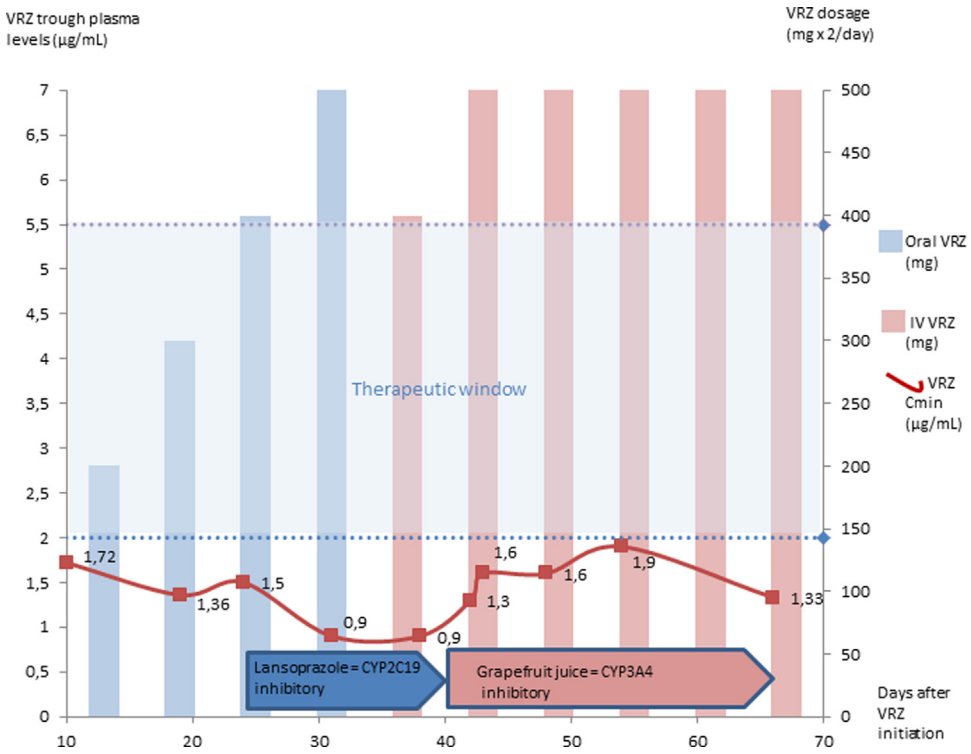

Fig. 1. Voriconazole (VRZ) trough plasma levels (Cmin) in µg/mL (red line) and VRZ dosage in mg twice daily (blue bar for oral VRZ and red bar for injectable VRZ) versus days after VRZ initiation. VRZ therapeutic window ranges from 2 to 5.5 µg/mL. Lansoprazole (CYP2C19 inhibitor) was initiated on day 26, and grapefruit juice (CYP3A4 inhibitor) was initiated on day 40 after VRZ initiation.
Concentrations résiduelles plasmatiques de voriconazole (VRZ) en µg/ml (ligne rouge) et posologie du voriconazole en mg x2/jour (barre bleue pour la forme orale de VRZ et barre rouge pour la forme injectable de VRZ) versus la durée en jours (j) après l'initiation du traitement. La zone thérapeutique du voriconazole s'étend de 2 à 5,5 µg/mL. Le lansoprazole inhibiteur du CYP2C19 a été initié à j26, et le jus de pamplemousse inhibiteur du CYP3A4 a été initié à j40 après le début du VRZ.

This case report underlines the use of interacting substances to increase voriconazole concentrations by inhibiting CYP450 metabolism pathway. Drug interactions should be avoided in most treatments because of the risk of failure or toxicity but may be used as a modulating factor of drug pharmacokinetics in association with therapeutic drug monitoring in specific cases.

The increase in voriconazole dosage and the change in the administration route to infusions did not lead to reach voriconazole concentration threshold. The first decision was to add a proton-pump inhibitor (PPI), a well-known CYP2C19 inhibitor (i.e., the main metabolic pathway of voriconazole) to the treatment aiming at decreasing metabolism and increasing drug exposure. Lansoprazole was chosen because it is the most potent PPI for blocking CYP2C19 function. Hence, its inhibition constant (Ki) is lower than omeprazole, esomeprazole, rabeprazole, and pantoprazole [4]. However, since CYP2C19 genotyping in our patient revealed that this metabolic pathway was not accelerated, the effect of the drug interaction seemed to be limited. This potentially suggests a higher activation of CYP3A4 metabolic pathway, which usually supports about one-third of the metabolism of voriconazole. We then decided to give grapefruit juice to the patient because of the important inhibitory effect on voriconazole showed on a mouse model and because of its safety [5]. This approach led to reaching higher drug concentrations, although below the optimal threshold. Switching voriconazole to the intravenous route may have limited the inhibitory effect of grapefruit juice on CYP3A4, and may partly explain the limited increase in drug concentrations, as grapefruit juice mainly exerts its inhibitory effect on pre-systemic metabolism of drugs. The maintenance of low voriconazole concentrations has already been described for high-dose or long-term treatments of more than two months, which is the case in our patient [6]. The hypothesis of an auto-induction of voriconazole metabolism can be advanced in this clinical case, as it has already been suggested by Moriyama in adults or by Hsu in children [6,7].

This case report illustrates a complex and difficult-to-treat case of *S. prolificans* infection. The multidisciplinary approach allowed the use of unusual drug interacting substance particularly grapefruit juice, a potent CYP450 metabolism inhibitor, to overcome persistent low voriconazole concentrations and contributed to improving the patient's clinical condition. However, considering the wide-range effects of grapefruit juice on the pharmacokinetics of various drugs, its use as an adjunctive booster with other drugs should not be recommended and, whenever its use is required, it should be closely monitored by a team with pharmacological skills.

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Contribution

CBK and FL designed the case report. MR was in charge of the patient's clinical care. SB was in charge of the patient's mycological monitoring. CBK was involved with clinical data acquisition. MCV, EGV, and BH performed genotyping. CBK, FL, and MCV contributed to therapeutic drug monitoring of voriconazole. CBK, MCV, and FL wrote the article. FL gave final approval to the article in its submitted form. All authors reviewed the article for important intellectual content and approved the article in its submitted form.

Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

Disclosure of interest

The authors declare that they have no competing interest.

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