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Therapeutic Drug Monitoring for Voriconazole in an Intensive Care Unit: A Case Report

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Abstract

Patients in the intensive care unit need a strict follow-up of their levels of voriconazole because this drug has a narrow therapeutic index and a great intra, and it also presents a great rate of variability related to intra and interindividual pharmacokinetic. Monitoring the plasma levels of voriconazole has demonstrated its efficacy, but data on its safety and adequate dose in patients with liver failure are lacking and it is not recommended intravenously in renal impairment. We present a case report of invasive pulmonary fungal infection in a patient with diagnosis of liver failure who was managed with intravenous voriconazole, the dose was lowered according to the monitoring data; given that he presented hepatotoxicity by voriconazole despite having levels within range. Finally, the patient presents a renal failure and the clinical pharmacist recommends switching to an oral route, using the suspension of voriconazole.

Keywords: Voriconazole • Therapeutic drug

Introduction

The invasive fungal infections are an important cause of morbidity and mortality in patients involved with concomitant underlying immunosuppressive diseases. Voriconazole is the drug chosen for the treatment of invasive aspergillosis. Recent guidelines indicated that the pharmacokinetic profile of voriconazole is the consequence of diverse factors like sex, age, race genotypic variation, liver dysfunction and drug-drug interactions with CYP450 inhibitors and inducers [1,2]. Voriconazole has high bioavailability and non-linear pharmacokinetics, its hepatic metabolism, with enzymes CYP2C19 and CYP3A4 is a potent inhibitor of cytochrome P450 [3]. However, some patients present problems of effectiveness and safety. Therefore, it is necessary to monitor the plasma levels of voriconazole to adjust the dose; according to recent studies, it is also recommended to identify the polymorphisms of CYP2C19 and CYP3A to examine the pharmacological susceptibility of the causal *Aspergillus* spp [4]. Several studies indicate that plasma concentrations of voriconazole are strongly influenced by the CYP2C19 polymorphism, and that it is necessary to adjust the dose by monitoring and taking into consideration the patient's genes in order to maximize the response and minimize hepatotoxicity [5-8]. The methods employed for the determination of voriconazole in human plasma, included agar-well diffusion bioassays and High-Performance Liquid Chromatography (HPLC) with fluorescence, Mass Spectrometry (MS), or Ultraviolet (UV) detection and homogeneous enzyme immunoassay [9].

The recommended target plasma levels are: Voriconazole ≥ 0.5 mg/L dose for prophylaxis; 1.5-5.0 mg/L for treatment; <5.5 mg/L dose of safety; and recommendation according to the level of evidence is weak and moderate. About the suggested triazole dose adjustment the strategies for patients treated for invasive fungal infections is <0.5 Increase by 50%, Level of evidence weak, low; ≥ 0. 5- <1.5 Increase by 25%, Level of evidence Weak Low; ≥ 1.5- <5.5 None Weak level of evidence, low; ≥ 5.5 and toxicities related to the drug Decrease by 25% weak, low [2-10]. Liver failure is generally characterized by an acute deterioration of liver function and it is associated with significant morbidity and mortality; therefore, it is important to control the level of voriconazole in plasma and adjust the dose according to the condition of the patient. When, in addition to this, the patient has renal failure, it is necessary to change to the oral route; however, the use of intravenous voriconazole in intensive care in patients with kidney damage does not report an increase in mortality [11]. This condition is frequent in patients in intensive care, so interdisciplinary care is required to achieve efficacy and safety during treatment with voriconazole. In this case report, a patient in intensive care with invasive pulmonary fungal infection was studied. He was treated with voriconazole in low doses, because he presented hepatotoxicity by voriconazole despite levels in range. Finally, he presented renal failure as well; so, the route of administration was changed, and an effective plasma concentration was achieved without serious adverse events.

Case Report

The patient was a 60-year-old man with diagnosis of left ventricular hypertrophy, acute heart failure, chronic obstructive pulmonary disease, flu A+, and Invasive Aspergillosis (IA). The patient started with voriconazole with a dose of 400 mg and that was increased to 450 mg; according to the monitoring data, the dose was later adjusted to 300 mg and then the patient presented liver impairment, so the dose was adjusted to 225 mg. Finally, he presented renal insufficiency and the route of administration was changed; in the end, plasma concentrations required for the effectiveness of voriconazole were reached. In our laboratory of clinical pharmacokinetics, the HPLC high performance liquid chromatography analysis technique was used to monitor plasma concentrations of voriconazole. The method was validated according to the FDA's guidelines for bioanalytical method validation [10]. A blood sample was collected 48 hours after the first administration of voriconazole (steady state) and trough levels were measured within 30 min before patient dosing [11]. Monitoring of voriconazole began with a plasma concentration of 1.5 mcg/mL and it was recommended to increase the dose; then, it passed to 4.33 mcg/mL and, although the optimal range was 1.5-5.5 mcg/mL, it was recommended to decrease the dose; consequently, the plasma levels of voriconazoles changed to 6.09 mcg/mL, so it was recommended to decrease the dose. In the following monitoring, hepatic insufficiency and 6.9 mcg/mL were reported, so it was recommended to reduce the dose again and finally, as the patient showed

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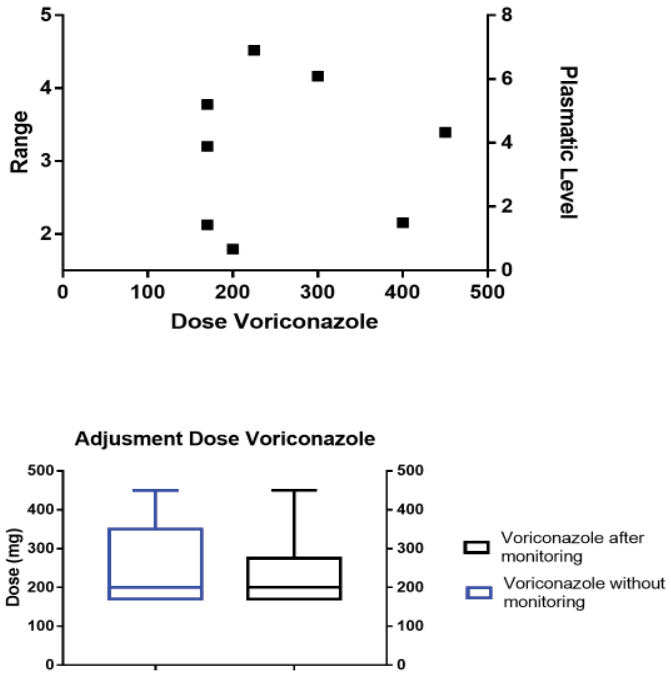
renal failure, it was recommended to reduce the dose and switch to the oral route, with voriconazole in suspension.

Discussion

Although the patient presented renal failure and voriconazole hepatotoxicity despite maintaining optimal levels; after the follow-up and thanks to the recommendations of the pharmacist, the patient in intensive care received the appropriate dose of voriconazole. This case report is relevant because it shows how to monitor the plasmatic concentration of voriconazole in a patient who is in intensive care and presents liver and kidney failure. In Graph 1 the change of the dose of voriconazole according to plasmatic concentration is shown as well as how the voriconazole dose is adjusted according to the monitoring, until it is maintained at optimal voriconazole plasma levels. Voriconazole is a drug that has a saturable metabolism, that is, a nonlinear kinetics, in which the dose is not proportional to plasma concentrations; therefore, it is required to have the recommendations of the pharmacist and thus achieve appropriate dose adjustments. It is important that in the decision making of dose adjustment, kidney and liver function is checked. In this case report, the dose monitoring data are observed. So that pharmacists can recommend the appropriate dose for the patient, it is necessary to classify the severity of the liver disease; in this case the Child Pugh classification was used.

The patient goes from moderate to severe hepatic damage, being classified in C according to the Child Pugh scale. This information is important for the pharmacist because voriconazole has a hepatic metabolism and the Child Pug classification is necessary to recommend dose adjustments, after the monitoring results. Additionally, during patient monitor, to include pharmacogenomic tests is important to optimize therapies in clinical practice, [12,13] especially in CYP2C19, to optimize therapy with voriconazole. The pharmacokinetic challenges of voriconazole in oral suspension continue to require therapeutic monitoring of the drug, to individualize therapy and achieve therapeutic goals [14]. With the emerging knowledge about the impact of pharmacogenomics on the metabolism of agents such as voriconazole, it is important to include in addition to the monitoring of plasma concentrations, specific pharmacogenomic tests [15]. Efficacy of voriconazole in patients in the intensive care unit is essential to ensure positive results and reduce mortality [16]. Voriconazole presents non-linear pharmacokinetics in adults, while the interactions between medications and the presence of Cytochrome P450 2C19 polymorphisms (CYP2C19) are of great concern because the efficacy is not achieved. Therapeutic monitoring of voriconazole, Child Pugh classification and the testing of genotypes like CYP2C19, is necessary in the clinical practice, especially in patients in the intensive care unit who have renal and / or hepatic failure [17-20].



Graph 1. Plasmatic level voriconazole according dose.

Conclusion

In this case report, although the patient died of mixed shock; thanks to the interdisciplinary treatment, dose was adjusted according to the liver damage, voriconazole monitoring and the route of administration was changed when he presented renal damage; reaching thus, optimal levels of voriconazole. According to the target plasma levels recommended for voriconazole, the degree of evidence is limited to adjust the dose exactly according to the plasma concentration levels of voriconazole; however, the monitoring of therapeutic levels of voriconazole in patients in intensive care units with hepatic and / or renal failure allows both to reach better clinical decisions and to achieve optimal levels of voriconazole plasma concentrations, with the lowest adverse effects.

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