Effect of metamizole on plasma levels of voriconazole

Efecto del metamizol en los niveles plasmáticos de voriconazol

Voriconazole is a broad-spectrum antifungal drug indicated for the prevention and treatment of invasive fungal infections. It undergoes complex metabolism mediated by cytochrome P450 enzymes. Thus, voriconazole has been shown to be a substrate of isoenzymes CYP2C9, CYP2C19 and CYP3A4, with minimal involvement of CYP2C9 in human hepatic microsomes.[1]

Metamizole is a pyrazolone derivative with analgesic, antipyretic and antispasmodic activity, It is a moderate inducer of the isoenzymes CYP2C19 and CYP3A4, and a weak inducer of CYP2C9.[2]

We present two clinical cases in which metamizole was found to be responsible for reducing the plasma concentration (Cp) of voriconazole, thereby compromising the clinical outcome.

An 8-year-old male, diagnosed with acute lymphoblastic leukemia subjected to chemotherapy. He presented to the Emergency Department and was diagnosed with febrile neutropenia and respiratory failure. The patient was transferred to the Intensive Care Unit (ICU) where he received broad-spectrum antimicrobial therapy and intravenous (iv) voriconazole with therapeutic intent (target Cp voriconazole 1.0-5.0 mg/L).[3] Following clinical and respiratory improvement, he was transferred to the ward 19 days later. Once pulmonary aspergillosis was ruled out, he was maintained on voriconazole as prophylaxis for invasive fungal infection (target Cp voriconazole > 0.5 mg/L),[4] and was eventually discharged.

During admission, therapeutic drug monitoring (TDM) of voriconazole was requested from the Pharmacy Department.

The patient started voriconazole at the doses indicated in the Summary of Product Characteristics (SmPC), presenting supratherapeutic levels on days +2 and +5; the antifungal was therefore discontinued. On day +7, the Cp was 0.57 mg/L, and treatment was restarted. However, on day +10, the levels were undetectable (trough Cp <0.05 mg/L); despite an increase in dose, the concentration was still 0.08 mg/L on day +12. It was noted that the patient had been receiving metamizole 480 mg/8 h iv since day +8; the decision therefore was made to discontinue the analgesic (day +12). The Cp values on days +15 and +17 were in the therapeutic range. In addition, during outpatient follow-up, the levels again proved undetectable, and it was confirmed that the patient had been taking oral metamizole on the days prior to the control (day +37). We therefore insisted on suspending the drug, and the target levels of voriconazole were restored on day +45 (Fig. 1).

A 72-year-old male, subjected to lower lobectomy for small cell lung carcinoma. He was admitted to the ICU with febrile neutropenia and septic shock of respiratory origin. Bilateral pulmonary infiltrates were observed in the imaging study, and broad-spectrum antibiotherapy was thus started together with intravenous voriconazole, due to clinical suspicion of pulmonary aspergillosis. It was then decided to perform TDM of voriconazole.

On day +5, the Cp of voriconazole was supratherapeutic (6.3 mg/L). The drug was therefore suspended and, on day +8, it was restarted at lower doses after verifying Cp in the therapeutic range (2.2 mg/L). On day +9, metamizole 2 g/8 h iv was started after the onset of severe low back pain. In this context, the patient had undetectable Cp (<0.5 mg/L) on days +12 and +14, despite increasing the antifungal dose. It was then recommended to discontinue treatment with metamizole (day +15), replacing it morphine and maintaining the same voriconazole regimen. On day +19, the Cp was 1.7 mg/L, and remained within the range in the subsequent measurements (Fig. 2).

Metamizole was marketed in Germany in 1922, but due to its association with the occurrence of agranulocytosis, it was withdrawn from the market in many Western countries; nevertheless, it is still used in Europe, America, Asia and Africa. In Spain, it was marketed in 1969 for the treatment of acute postoperative or post-traumatic pain, of colic or tumor origin, and for high fever refractory to other therapeutic options. In certain situations, its use is preferred as a safer alternative to other anti-inflammatory drugs because of its potentially lower risk of gastrointestinal and renal adverse effects.[5] The use of metamizole in Spain has doubled in the last 10 years, making it the second most commonly used analgesic after paracetamol.

Therapeutic monitoring of voriconazole is aimed at maximizing efficacy and avoiding adverse effects, such as neurologic and hepatic toxicity. Such toxicity is a consequence of the inter- and intra-individual differences observed in Cp, mostly related to liver function, age, weight, inflammation, CYP2C19 cytochrome polymorphism and drug-drug interactions.[6]

Several studies have shown interactions between metamizole and other drugs that are metabolized by the same cytochrome isoenzymes as voriconazole. The area under the curve (AUC) of efavirenz and diazepam was reduced by 79% and 68%, respectively, due to the effect of metamizole.[7] Similarly, the Cp of cyclosporine may also be decreased by interaction with this drug.[8] However, no studies have been found that directly compare the effect of metamizole upon voriconazole metabolism, possibly because of its limited use in the Anglo-Saxon world. The cases reported here show that metamizole can reduce the Cp of voriconazole to below the therapeutic range, thereby compromising the efficacy of the latter. The fact that the reintroduction of metamizole in Case 1 again resulted in an undetectable Cp would strengthen this causal relationship.

In the cases described, loading doses of voriconazole were not used for reintroduction because of initial concerns about the relationship between the achieved Cp of voriconazole and interaction with metamizole. However, it should be noted that metamizole was the only CYP3A4 inducer that both patients were receiving. According to the results of the study by Breithaupt et al., who analyzed the time course of CYP3A4 activity by measuring midazolam concentrations after repeated doses of metamizole were administered to healthy patients, CYP3A activity was already induced within three days, reaching its maximum after 6 days. Five days

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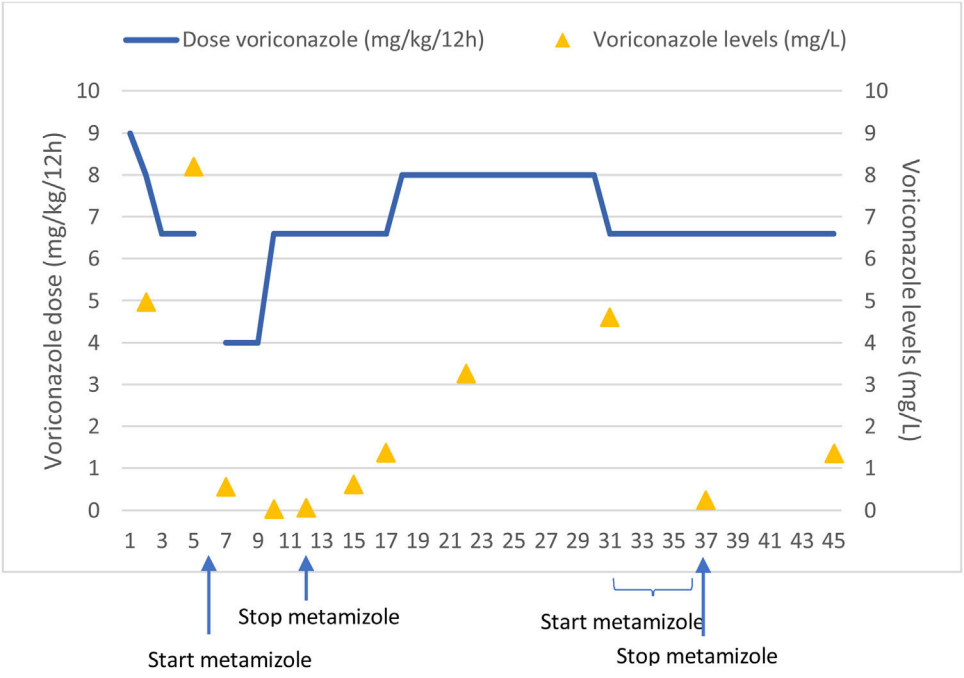

Figure 1 Doses and levels of voriconazole Case 1.

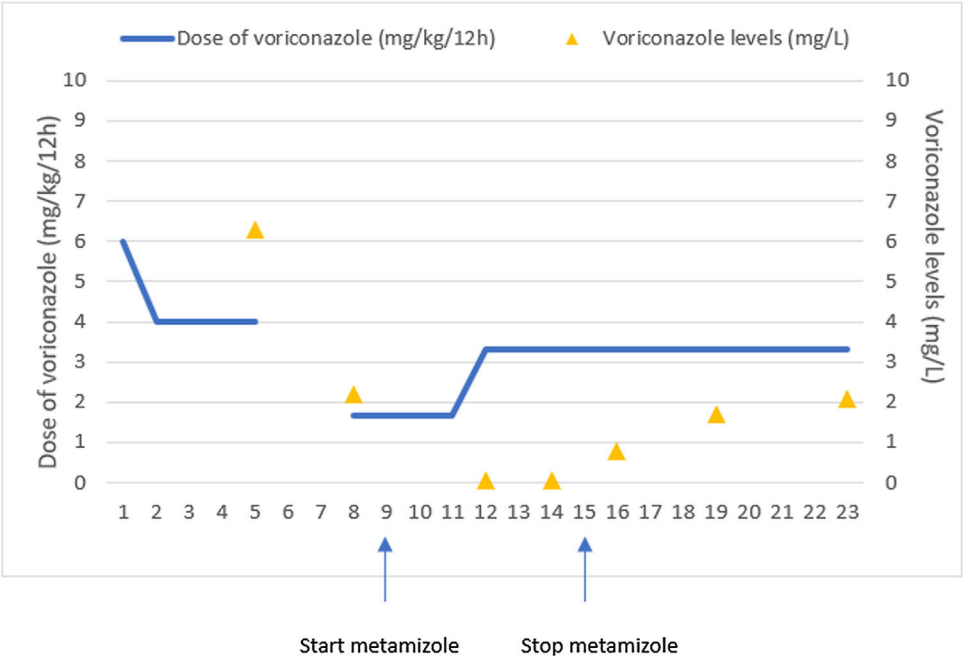

Figure 2 Dosage and levels of voriconazole Case 2.

after the discontinuation of metamizole, the enzyme induction effect was still present.[9] In view of the effect upon the Cp of voriconazole observed with the concomitant administration of metamizole, it would be logical to avoid joint use of the two drugs. However, should the interaction occur, and in light of the results, it would seem reasonable to reintroduce voriconazole with loading doses.

Ethical considerations

The present study was designed and carried out in abidance with the Ethical Code of the World Medical Association (Declaration of Helsinki).

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Declaration of competing interest

The authors declare that they have no conflicts of interest.

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