A probable drug-to-drug interaction between voriconazole and haloperidol in a slow metabolizer of CYP2C19

Caso clinico di una probabile interazione farmacologica tra voriconazolo e alopeperidolo in un metabolizzatore lento del CYP2C19

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INTRODUCTION

Voriconazole (VOR) pharmacokinetics is characterized by a high interpatient variability and a relatively narrow therapeutic index between 1000 ng/mL and 5500 ng/mL, thus supporting the use of therapeutic drug monitoring [1-3]. VOR is metabolized in the liver through cytochrome P450 isoenzyme 2C19 (CYP2C19) and to a lesser extent by CYP2C9 and CYP3A4 [4]. Several drug-to-drug interactions (DDIs) have been reported and they may vary according to CYP2C19 genotype. CYP2C19*2 loss of function allele indicates a poor metabolizing cytochrome leading to voriconazole higher exposure and potentially to drug-to drug interactions through CYP3A4 or CYP2C9 isoenzymes; this might increase the risk of drug-related adverse events [6, 7].

CASE REPORT

We here report the case of a HIV-positive 43-year-old male patient born in Sub-Saharan Africa with several opportunistic infections (neurotoxoplasmosis, disseminated Kaposi’s sarcoma) that developed an Aspergillus fumigatus renal abscess five months after receiving six cycles of vinblastine and etoposide. He was admitted while receiving tenofovir/emtricitabine, raltegravir, atovaquone and azithromycin (as secondary prophylaxis for neurotoxoplasmosis), pantoprazole, tramadol and pregabalin (for peripheral neuropathy). Intravenous weight-based VOR was started (450 mg on the first day followed by 300 mg twice-daily, patient’s weight was 75 kg). At day 8 (D8) oral haloperidol (1 mg three times/day) and oral delorazepam (1 mg/day) were prescribed for recurrent auditory hallucinations; at D13 VOR was orally administered and reduced to 250 mg twice-daily. Figure 1 represents the time course of liver function tests (LFTs, namely AST and ALT), VOR dose and trough concentrations measured with validated methods: after haloperidol introduction VOR trough levels increased steeply (from 3931 ng/mL at D6 to 11063 ng/mL at D18) as well as liver function tests despite its dose-reduction (250 mg twice-daily) [8]. Reducing VOR dose to 250 mg (D13) and 200 mg twice-daily (D20) a further slight increase in exposure (12055 ng/mL at D21) was observed as well as AST and ALT elevation (205/172 UI/mL and 84/75 UI/mL, respectively). Given the persistence of hepatotoxicity and high plasma concentrations, VOR was reduced to 100 mg twice-daily at D21 and haloperidol withdrawn (and replaced with paliperidone and promazone). Six days later (D25) VOR Ctrough was 2188 ng/mL but it was stopped due to the persistence of mild
liver impairment [102 UI/mL (AST) and 52 UI/mL (ALT)]; intravenous liposomal amphotericin B (3 mg/kg) was started and patient’s symptoms and LFTs slowly normalized. CYP2C19 genotype was investigated: he was carrying the AA loss of function allele in CYP2C19 encoding gene (CYP2C19*2, rs4244285).

**DISCUSSION**

This case describes a clinically significant DDI in a patient receiving VOR and several other drugs; HIV-positive subjects have high risk of DDIs since they often receive multiple medications for several comorbidities [9]. Surprisingly when VOR was orally administered its exposure increased approximately three times and he developed grade 3 hepatotoxicity. When revising this patient multiple medications, haloperidol was found to be a weak inhibitor of CYP2D6 and CYP3A4, pantoprazole a weak inhibitor of CYP2C19/1A2, tramadol inhibitor of CYP2D6, atovaquone a weak inhibitor of CYP3A4 and tenofovir disoproxil fumarate inhibits OAT1 whereas raltegravir has not major DDIs [10, 11]. After the loading dose VOR reaches its steady state at D3; at D6 our patient presented VOR \(C_{\text{trough}}\) 3931 ng/mL thus possibly suggesting that the increase of concentration observed at D18 (\(C_{\text{trough}}\) 11063 ng/mL) was associated with haloperidol introduction at D8 [12]. The time course of VOR exposure, LFTs elevation and patient’s CYP2C19 genotype (poor metabolizer status) support this hypothesis; the Drug Interaction Probability Scale define this as “probable” with a total score of 5 considering the known interactive properties of VOR, the reasonable time course, the high VOR plasma concentrations, the symptoms and confirmed liver toxicity and that no reasonable alternative causes are present [13, 14]. However haloperidol weak CYP3A4 inhibition, unknown patient’s CYP3A4 genotype and the absence of VOR re-challenge may question this association. Therapeutic drug monitoring and CYP2C19 genotyping may be suggested when administering voriconazole to complex patients.

**Declaration of interests**

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**Keywords**: voriconazole, haloperidol, pharmacokinetics, CYP2C19, CYP3A4, pharmacogenetics.
We present a case of Aspergillus fumigatus renal abscess treated with voriconazole of a HIV-positive 43-year-old male patient. Following haloperidol treatment we observed an unexpected increase in voriconazole through concentrations and liver function tests. CYP2C19*2 loss of function allele was stated, an interaction probably explained by the introduction of haloperidol, a weak CYP3A4 inhibitor. Therapeutic drug monitoring and CYP2C19 genotyping may be suggested when administering voriconazole to complex patients.

Viene discusso un caso di ascesso renale da Aspergillus fumigatus; dopo l’introduzione di aloperidolo si è osservato un inaspettato aumento delle concentrazioni di valle di voriconazolo e degli enzimi di citolisi epatica. Il paziente è risultato portatore della variante genetica CYP2C19*2 e la somministrazione di aloperidolo, quale debole inibitore del CYP3A4, sembrerebbe spiegare quanto osservato. Il therapeautic drug monitoring e la tipizzazione del genotipo CYP2C19 sono pertanto consigliati quando voriconazolo viene somministrato a pazienti complessi.

**REFERENCES**