

LETTER TO THE EDITOR

Voriconazole hepatotoxicity as a result of steroid withdrawal in a patient with allergic bronchopulmonary aspergillosis

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Voriconazole is a triazole antifungal agent usually used for the treatment of allergic bronchopulmonary aspergillosis (ABPA) in combination with glucocorticoids [1, 2]. This drug is extensively metabolized to inactive metabolites by hepatic cytochrome P450. [3, 4]. Several studies have demonstrated that trough concentrations $>1 \mu\text{g ml}^{-1}$ and $<6 \mu\text{g ml}^{-1}$ are associated with treatment success and minimized toxicity [5–8]. In this context, therapeutic drug monitoring of voriconazole is of particular interest. It has been demonstrated that some commonly used drugs can affect the plasma concentration of voriconazole. However, there is limited data regarding voriconazole interaction with glucocorticoids. Due to the wide administration of both voriconazole and glucocorticoids in patients with ABPA, it is necessary to understand the onset and severity of this interaction. Here, we describe a case report of voriconazole hepatotoxicity as a result of steroid withdrawal in a patient with allergic bronchopulmonary aspergillosis (ABPA).

An 82-year-old woman diagnosed with ABPA started long-term treatment with 0.5 mg kg^{-1} prednisone for 28 days and voriconazole (200 mg every 12 h for 16 weeks). On day +14,

the patient progressed satisfactorily and the plasma concentration of voriconazole was in therapeutic range ($2.58 \mu\text{g ml}^{-1}$). On day +28, a clinical decision was made to remove the prednisone but voriconazole was maintained. One month after prednisone discontinuation, the patient presented photophobia, proximal myalgia and asthenia. In the physical exam, the patient presented icteric coloration. A blood test showed elevated bilirubin (6.8 mg dl^{-1} , direct bilirubin 5.9 mg dl^{-1}) and high liver enzymes: AST 869 UI/L , ALT 1085 UI/L , GGT 1283 UI/L , AP 291 UI/L and moderate hyponatremia, 129 mmol l^{-1} . Plasma concentration of voriconazole was determined resulting in $14.47 \mu\text{g ml}^{-1}$. All medications received by the patient were checked to find probable interactions, which could explain the high concentration. The only change in the medication between the first determination of voriconazole and the second one had been the suspension of prednisone. DIPS Algorithm (Drug Interaction Probability Scale) [9] was used to evaluate the causation of a potential drug interaction between prednisone and voriconazole (Table 1). The score was 7 points, suggesting this

Table 1

DIPS Algorithm (Drug Interaction Probability Scale); the interaction is considered highly probable if the score is 8 or higher, probable if 5 to 8, possible if 2 to 4, and doubtful if 2 or less

Question	Yes	No	Do not know
Are there previous credible reports of this interaction in humans?	+1	−1	0
Is the observed interaction consistent with the known interactive properties of precipitant drug?	+1	−1	0
Is the observed interaction consistent with the known interactive properties of object drug?	+1	−1	0
Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	+1	−1	0
Did the interaction remit upon dechallenge of the precipitant drug with no change in the object drug?	+1	−2	0
Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?	+2	−1	0
Are there reasonable alternative causes for the event?	−1	+1	0
Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	+1	0	0
Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from previous question)? (serum concentration of ALT, AST)	+1	0	0
Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?	+1	−1	0
Total score	7		

Numbers in bold are the punctuation in the patient

drug interaction as the probable cause of the patient's hepatotoxicity. In addition, due to a transaminases rise of 19 times above the upper limit of normal with a hepatocellular pattern of liver injury (R factor = 8.5) [10], voriconazole met the criteria necessary to be qualified as DILI (Drug-Induced Liver Injury). Thus, treatment with voriconazole was removed and progressive decreases in plasma concentrations were observed. Photophobia and muscular weakness disappeared few days after voriconazole discontinuation. However, the recovery of liver parameters was very slow, taking 2 months until complete normalization.

Voriconazole has the potential to interact with multiple medications. The main pathway for these interactions is the hepatic enzyme induction or inhibition involving **CYP2C19**, **CYP3A4** and/or **CYP2C9** [4]. An in vitro study has identified glucocorticoid receptor binding sites in the promoter region of the CYP2C19 gene and demonstrated up-regulation of CYP2C19, supporting an inductive effect of glucocorticoids on CYP2C19 [11, 12]. There are limited data regarding the interaction between voriconazole and corticosteroids in clinical practice [13–17]. Dolton et al. found that concomitant dexamethasone use was associated with a 3.75-fold decrease in voriconazole concentrations [13]. Similarly, Cojutti et al. found that coadministration of methylprednisolone and dexamethasone was associated with a 1.65 and 1.93-fold decrease in voriconazole concentration, respectively [14]. Finally, Wallace et al. observed a two-fold increase in the plasma concentration of voriconazole when the dexamethasone dose was reduced gradually in one patient with a fungal brain abscess treated with both drugs [16].

Our patient presented plasma concentrations of voriconazole in a therapeutic range during treatment with prednisone. Upon discontinuation of prednisone, an

increase in voriconazole serum concentrations was observed along with toxicity, suggesting that prednisone had been inducing metabolism of voriconazole. On the other hand, it should be noted that genetic polymorphisms in *CYP2C19*, as a primary elimination pathway of voriconazole, is another factor influencing trough plasma concentration. Poor metabolizers have an increased risk of achieving higher plasma concentration compared with other genotypes [18]. We observed that our patient was an extensive metabolizer (*CYP2C19**1*1); therefore, the high concentrations of voriconazole were not attributed to *CYP2C19* polymorphism. This is the first clinical case describing probable voriconazole hepatotoxicity as a result of steroid withdrawal. Nevertheless, we need further studies investigating the effect of corticosteroid dosing on voriconazole metabolism as well as the effect of different glucocorticoids. In addition, the effect on voriconazole concentration caused by prednisone in the present case was higher to the observed in previous studies (a 5.60-fold increase in voriconazole concentration when prednisone was discontinued); therefore, other causes may have contributed to decrease the elimination of the drug from the blood such as the inflammatory state of the patient [19–21].

Considering that the concomitant treatment of glucocorticoids and voriconazole is relatively frequent, we must take into account this possible pharmacokinetic interaction and its possible clinical repercussion in the future. A proper knowledge of this interaction will allow healthcare professionals to improve the treatment of patients. Future pharmacokinetic, pharmacodynamic and pharmacogenetic studies are needed to better understand these complex interactions. In the meantime, routine therapeutic drug monitoring of voriconazole is a useful tool that can help us to optimize the

management of these patients. We must pay special attention to changes in the treatments, such as the withdrawal of glucocorticoids, and consider a voriconazole dose adjustment if necessary in order to avoid toxicity.

Considering the clinical relevance of the adverse reaction it was reported to the Spanish Pharmacovigilance System, and the sample for the genetic determination was collected after obtaining the informed consent of the patient. The study of pharmacokinetic-pharmacogenetic of voriconazole was approved by the local ethics committee.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [22], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 [23].

Competing Interests

There are no competing interests to declare.

References

- Blanco-Dorado S, Cea-Arestin C, González Carballo A, Latorre-Pellicer A, Maroñas Amigo O, Barbeito Castiñeiras G, *et al.* An observational study of the efficacy and safety of voriconazole in a real-life clinical setting. *Chemotherapy* Accepted on 05 Sep 2018 (In Press).
- Patterson TF, Thompson GR, 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, *et al.* Practice guidelines for the diagnosis and Management of Aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016; 63: e1–60.
- Bellmann R, Smuszkiewicz P. Pharmacokinetics of antifungal drugs: practical implications for optimized treatment of patients. *Infection* 2017; 45: 757–79.
- Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/pharmacodynamic profile of voriconazole. *Clin Pharmacokinet* 2006; 45: 649–63.
- Pascual A, Csajka C, Buclin T, Bolay S, Bille J, Calandra T, *et al.* Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: population pharmacokinetics-based analysis of adult patients with invasive fungal infections. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2012 Aug; 55: 381–90.
- Troke PF, Hockey HP, Hope WW. Observational study of the clinical efficacy of voriconazole and its relationship to plasma concentrations in patients. *Antimicrob Agents Chemother* 2011 Oct; 55: 4782–8.
- Jin H, Wang T, Falcione BA, Olsen KM, Chen K, Tang H, *et al.* Trough concentration of voriconazole and its relationship with efficacy and safety: a systematic review and meta-analysis. *J Antimicrob Chemother* 2016; 71: 1772–85.
- Dolton MJ, McLachlan AJ. Voriconazole pharmacokinetics and exposure-response relationships: assessing the links between exposure, efficacy and toxicity. *Int J Antimicrob Agents* 2014; 44: 183–93.
- Horn JR, Hansten PD, Chan L-N. Proposal for a new tool to evaluate drug interaction cases. *Ann Pharmacother* 2007; 41: 674–80.
- Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, *et al.* Case definition and phenotype standardization in drug-induced liver injury. *Clin Pharmacol Ther* 2011; 89: 806–15.
- Chen Y, Ferguson SS, Negishi M, Goldstein JA. Identification of constitutive androstane receptor and glucocorticoid receptor binding sites in the CYP2C19 promoter. *Mol Pharmacol* 2003; 64: 316–24.
- Matoulková P, Pávek P, Malý J, Vlček J. Cytochrome P450 enzyme regulation by glucocorticoids and consequences in terms of drug interaction. *Expert Opin Drug Metab Toxicol* 2014; 10: 425–35.
- Dolton MJ, Ray JE, Chen SC, Ng K, Pont LG, McLachlan AJ. Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. *Antimicrob Agents Chemother* 2012; 56: 4793–9.
- Cojutti P, Candoni A, Forghieri F, Isola M, Zannier ME, Bigliardi S, *et al.* Variability of Voriconazole trough levels in Haematological patients: influence of Comedications with cytochrome P450(CYP) inhibitors and/or with CYP inhibitors plus CYP inducers. *Basic Clin Pharmacol Toxicol* 2016; 118: 474–9.
- Imataki O, Yamaguchi K, Uemura M, Fukuoka N. Voriconazole concentration is inversely correlated with corticosteroid usage in immunocompromised patients. *Transpl Infect Dis Off J Transplant Soc* 2018; 20: e12886.
- Wallace KL, Filipek RL, La Hoz RM, Williamson JC. Subtherapeutic voriconazole concentrations associated with concomitant dexamethasone: case report and review of the literature. *J Clin Pharm Ther* 2016; 41: 441–3.
- Taghvaye Masoumi H, Hadjibabaie M, Gholami K, Zarif-Yeganeh M, Ghavamzadeh A. Significant drug interaction between voriconazole and dexamethasone: a case report. *J Oncol Pharm Pract* 2018; <https://doi.org/10.1177/1078155218783248>.
- Owusu Obeng A, Egelund EF, Alsultan A, Peloquin CA, Johnson JA. CYP2C19 polymorphisms and therapeutic drug monitoring of voriconazole: are we ready for clinical implementation of pharmacogenomics? *Pharmacotherapy* 2014; 34: 703–18.
- Veringa A, Ter Avest M, Span LFR, van den Heuvel ER, Touw DJ, Zijlstra JG, *et al.* Voriconazole metabolism is influenced by severe inflammation: a prospective study. *J Antimicrob Chemother* 2017; 72: 261–7.
- Encalada Ventura MA, van Wanrooy MJP, Span LFR, Rodgers MGG, van den Heuvel ER, Uges DRA, *et al.* Longitudinal analysis of the effect of inflammation on voriconazole trough concentrations. *Antimicrob Agents Chemother* 2016; 60: 2727–31.
- Khalilieh S, Hussain A, Montgomery D, Levine V, Shaw PM, Bodrug I, *et al.* Effect of tildrakizumab (MK-3222), a high affinity, selective anti-IL23p19 monoclonal antibody, on cytochrome P450 metabolism in subjects with moderate to severe psoriasis. *Br J Clin Pharmacol* 2018; 84: 2292–302.
- Harding SD, Sharman JL, Faccenda E, Southan C, Pawson AJ, Ireland S, *et al.* The IUPHAR/BPS guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. *Nucl Acid Res* 2018; 46: D1091–106.
- Alexander SPH, Fabbro D, Kelly E, Marrión NV, Peters JA, Faccenda E, *et al.* The Concise Guide to PHARMACOLOGY 2017/18: Enzymes. *Br J Pharmacol* 2017; 174: S272–359.