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To cite this version:

HAL Id: hal-00910224
https://hal-univ-rennes1.archives-ouvertes.fr/hal-00910224
Submitted on 27 Nov 2013

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A Case-report of Unpredictable and Massive Voriconazole Intoxication in a Patient with Extensive CYP2C19 and CYP2C9 Polymorphisms

Florian LEMAITRE1,2,3,4,*, Mathilde BARBAZ5, Lucie-Marie SCAILTEUX1, Fabrice UHEL3,5, Jean-Marc TADIE3,5, Marie-Clémente VERDIER1,2,3 and Eric BELLISSANT1,2,3

1Department of Clinical and Biological Pharmacology and Pharmacovigilance, Pharmacoepidemiology and Drug Information Center, Rennes University Hospital, Rennes, France
2Laboratory of Experimental and Clinical Pharmacology, Faculty of Medicine, Rennes 1 University, Rennes, France
3Clinical Investigation Center, CIC-P 0203, INSERM, Rennes, France
4EA4123 Barrières Physiologiques et Réponses Thérapeutiques, Faculty of Pharmacy, Paris XI University, Châtenay-Malabry, France
5Department of Infectious Diseases and Medical Intensive Care, Rennes University Hospital, Rennes, France

Summary: This case-report describes a massive voriconazole (VRZ) intoxication in a patient with a poor metabolizer profile, highlighted by low plasma main metabolite concentrations (N-oxide voriconazole), despite an extensive genetic profile for CYP2C19 and CYP2C9. The patient was treated with a therapeutic dose of VRZ but developed a neurotoxicity leading to hallucinations and coma while the plasma concentration of VRZ reached an exceptional level (20.0 µg/mL on day 10 of the treatment). Since neurological disorders diminished in parallel with the decrease of VRZ plasma concentrations, the coma was likely due to VRZ. The VRZ half-life, calculated to 58 h in this patient, was by far higher than the values reported in the literature. While VRZ concentrations slowly decreased, the N-oxide voriconazole concentrations slowly increased from day 15. Hypotheses for this lack of metabolization of VRZ are an inhibition of the metabolism by esomeprazole, a saturation of the metabolism or an enzymatic auto-inhibition of VRZ metabolism but none of these hypotheses have yet been explored. This case-report of unpredictable accumulation of VRZ in a patient without any genetic risk factor is an advocacy for systematic therapeutic drug monitoring of VRZ.

Keywords: voriconazole; N-oxide voriconazole; toxicology; pharmacokinetics; pharmacogenetics; therapeutic drug monitoring; neurotoxicity
This 36-year-old Caucasian male patient, with acute myeloblastic leukemia, was hospitalized in the hematological unit of our hospital. He had no particular medical history. His bodyweight was 60 kg. Upon hospital arrival, the patient presented a creatininemia of 65 µmol/L [normal range (n) = 64–104 µmol/L] and an urea of 3.3 mmol/L (n = 2.5–7.5 mmol/L), a total bilirubinemia of 7 µmol/L (n = 5–18 µmol/L), an aspartate aminotransferase (ASAT) of 32 UI/L (n = 0–35 UI/L) and an alanine aminotransferase (ALAT) of 47 UI/L (n = 0–45 UI/L). The patient was hemodynamically stable. He had received chemotherapy treatment (hydroxy-carbamide 3,000 mg, cytarabine 200 mg/m²/24 h, daunorubicine 60 mg/m²/24 h, dexamethasone 40 mg and intrathecal methotrexate 15 mg) with rasburicase. Six days after treatment initiation, confusion and behavioral disorders led to a cerebral MRI being performed, which revealed a left frontal ischemic lesion (later attributed to leukostasis). Simultaneously, the patient presented a fever and a biological inflammatory syndrome. Treatment with antibiotics was then initiated [ceftriaxone 2 g plus spiramycin 3 million units thrice a day (TID) initially, then, because a translocation of the intestinal flora was suspected, the antibiotic treatment was modified to piperacillin-tazobactam 4 g TID and metronidazole 500 mg TID and finally vancomycin 2 g was introduced followed by meropenem 2 g TID for a positive culture of coagulase negative staphylococcus]. An increase in Aspergillus antigen, associated with nodular lung lesions on a chest CT-scan, led to the start of an intravenous treatment with VRZ 280 mg (4.4 mg/kg/12 h) BID without any loading dose. The patient was also treated with esomeprazole 40 mg daily until day 10. No other substrate, inhibitor or inducer of CYP2C19, CYP2C9 or CYP3A4 was administered to the patient. The patient was intubated and received no oral food which could have influenced the pharmacokinetics of VRZ. During the hospitalization, the patient presented a mild degradation of liver function with an increase of bilirubinemia up to 3N associated with liver cytolysis (ASAT elevated VRZ trough concentrations and neurological adverse events (mainly visual disturbance and hallucinations) has already been reported.4 No adverse event is usually attributed to the metabolites of VRZ. Imhof et al. reported 6 cases of encephalopathy among 26 patients (23.1%) treated with VRZ.4 Patients with neurological adverse events had significantly higher VRZ trough concentrations. Pascual et al. described an incidence of 31.2% in a cohort of 16 patients treated with VRZ and whose plasma concentrations were above 5.5 µg/mL (range 5.6–11.2 µg/mL).14 Boyd et al. reported two cases of patients who displayed neurological disorders after high exposure to VRZ (VRZ trough concentrations ranged from 9.0 to 17.5 µg/mL).15 One of these patients presented confusion and hallucination (VRZ troughs were 9 µg/mL on day 10 and 9.4 µg/mL on day 13). The second patient with an extremely high VRZ trough concentration (17.5 µg/mL) became hypotensive and unresponsive after 13 days of treatment (Glasgow score 11/15). Weiler et al. also reported the case of an extremely high VRZ trough concentration associated with unconsciousness in a patient with liver cirrhosis, but the maximum VRZ trough concentration was reached on day 30 and was lower than in our patient (13.9 µg/mL).16 Finally, a case of poisoning attempt with VRZ was reported by Rozé et al. The patient absorbed 9.8 g and VRZ trough concentrations reached levels above 30 µg/mL.17 Since neurological disorders diminished in parallel to the decrease of VRZ plasma concentrations, the coma was likely due to VRZ.

Although the correlation between VRZ trough concentrations and hepatic disturbances appears controversial, a link between elevated VRZ trough concentrations and neurological adverse events (mainly visual disturbance and hallucinations) has already been reported.4,12–15) No adverse event is usually attributed to the metabolites of VRZ. Imhof et al. reported 6 cases of encephalopathy among 26 patients (23.1%) treated with VRZ.4 Patients with neurological adverse events had significantly higher VRZ trough concentrations. Pascual et al. described an incidence of 31.2% in a cohort of 16 patients treated with VRZ and whose plasma concentrations were above 5.5 µg/mL (range 5.6–11.2 µg/mL).14) Boyd et al. reported two cases of patients who displayed neurological disorders after high exposure to VRZ (VRZ trough concentrations ranged from 9.0 to 17.5 µg/mL).15) One of these patients presented confusion and hallucination (VRZ troughs were 9 µg/mL on day 10 and 9.4 µg/mL on day 13). The second patient with an extremely high VRZ trough concentration (17.5 µg/mL) became hypotensive and unresponsive after 13 days of treatment (Glasgow score 11/15). Weiler et al. also reported the case of an extremely high VRZ trough concentration associated with unconsciousness in a patient with liver cirrhosis, but the maximum VRZ trough concentration was reached on day 30 and was lower than in our patient (13.9 µg/mL).16) Finally, a case of poisoning attempt with VRZ was reported by Rozé et al. The patient absorbed 9.8 g and VRZ trough concentrations reached levels above 30 µg/mL.17)

Since neurological disorders diminished in parallel to the decrease of VRZ plasma concentrations, the coma was likely due to VRZ.

The VRZ half-life, calculated as 58 h in our patient, was by far higher than the values reported in the literature (6 h).13 This finding is in favor of an important decrease in VRZ clearance. A medication administration error was investigated and not evidenced. The patient was treated with esomeprazole, a well-known CYP2C19 inhibitor, but this kind of drug-drug interaction has been found to be associated with a mild (15%) increase in VRZ exposure, judged as not clinically relevant by Wood et al.18) This could have
led to a decrease in VRZ clearance but is unlikely to have resulted in such an accumulation. The patient presented as well a mild decrease in hepatic function which could have decreased VRZ clearance. Jeu et al. reported indeed, only a half-decrease of VRZ clearance in a patient with moderate liver dysfunction.19

Taken together, all these findings could hardly explain the rapid and massive accumulation of VRZ in this patient treated with a therapeutic dose of VRZ. Thus, we made the hypothesis of a PM profile and investigated the different polymorphisms which could explain VRZ intoxication by sequencing the gene. PMs for CYP2C19 and CYP2C9 are rare among the Caucasian population (3% and 0.2–1.0% respectively).14,15 CYP2C19 and CYP2C9 genotypes have been determined by direct sequencing of the promoter-region, exons and 3’UTR-region. The patient was shown to be homozygous for a normal sequence of CYP2C19 and heterozygous *2/*3 for the CYP2C9 gene. This genetic profile is likely to lead to an extensive metabolizing profile. On day 5 of treatment and in spite of the discontinuation of the therapy for 24 h during this period, the patient presented a VRZ plasma concentration by far higher (12.6 µg/mL) than the plasma concentration during this period, the patient presented a VRZ plasma concentration of 12.6 µg/mL. On this day, by determining a low N-oxide VRZ trough concentration and a high N-oxide VRZ over VRZ ratio, we found a lack of VRZ metabolism into his major metabolite. Thereafter, the VRZ concentrations decreased while the VRZ ratio, we found a lack of VRZ metabolism into his major metabolite. Thereafter, the VRZ concentrations decreased while the N-oxide VRZ concentrations increased slowly. The resumption of VRZ metabolite levels. Thereafter, the VRZ concentrations decreased while the N-oxide VRZ concentrations increased slowly. The resumption of the metabolism on day 15 could be attributed either to the discontinuation of the esomeprazole treatment on day 10, to a saturation of the metabolism or to an enzymatic auto-inhibition of VRZ metabolism, but none of these hypothesis have yet been explored.

In conclusion, the present case depicted a massive accumulation in a patient with hallucinations and coma during a VRZ treatment at a therapeutic dose. While no evidence for VRZ accumulation could be highlighted, the high VRZ trough concentrations reported in a patient with moderate liver dysfunction.19

Acknowledgment: The authors would like to thank Dr. Céline Eiden, Dr. Olivier Mathieu, Dr. Nicolas Potter and Prof. Franck Broly for their help with this work.

References


