

# Elevation of blood ciclosporin levels by voriconazole leading to leukoencephalopathy

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## ABSTRACT

We report that one 18-year-old female patient with no epilepsy history developed severe epileptiform seizures while she was receiving “ciclosporin A (CsA)-mycophenolate-methylprednisolone” antirejection therapy after combining one week’s voriconazole administration following allogeneic hematopoietic stem cell transplantation (allo-HSCT) for myelodysplastic syndromes (MDS). Her blood concentration of CsA was 378 ng/ml (elevated ↑64%, contrasted with the level before the addition of voriconazole) on the second day of admission, and the MRI of head showed leukoencephalopathy in bilateral occipital and left frontal lobe on the 4<sup>th</sup> day of admission. The most likely mechanism is that because of voriconazole’s enzyme inhibition and CsA as the substrate of hepatic enzymes, voriconazole elevated the blood concentration of CsA and enhanced its toxicity. This case highlights the importance of clinical pharmacists joining the medical team and optimizing the patients’ treatment protocols by performing a systematic literature research, accumulating the knowledge of the potential drug interaction and examining prescriptions.

**Key words:** CsA, drug–drug interaction, epileptiform seizures, leukoencephalopathy, voriconazole

## INTRODUCTION

Ciclosporin A (CsA) is used to treat and prevent rejection and graft-versus-host disease (GVHD) after solid organ transplantation (SOT) as well as hematopoietic stem cell transplantation (HSCT).<sup>[1,2]</sup> Voriconazole is frequently used in HSCT or SOT recipients for prevention or treatment of invasive fungal infections (IFIs). Because voriconazole can inhibit the P450 enzyme system potently, it has many potential

drug interactions. The interaction between voriconazole and CsA may result in the enhancement of the toxicity of CsA. Here, we report one case in which one 18-year-old female patient of allogeneic HSCT without epilepsy history developed headache, dizziness, blurred vision, and worsened to epileptiform seizures on the 70<sup>th</sup> day postoperative when she was receiving “CsA-mycophenolate-methylprednisolone” antirejection in case of combination with one week’s voriconazole administration. Her blood concentration of CsA was 378 ng/ml (elevated ↑64%, contrasted with the average level before the addition of voriconazole) on the second day of admission. Therefore, interaction between voriconazole and CsA was suspected.

## CASE REPORT

One 18-year-old 46-kg female patient was admitted on the 70<sup>th</sup> day postoperative with complaints of dizziness, headaches,

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and blurred vision for 2 days. Her consciousness was distinct without nausea, vomiting, cough, expectoration, urinary, or fecal incontinence on admission. Her vital signs suggested normal body temperature and normal blood pressure with heart rate (HR) of 98 bpm. Examination of ocular fundus was normal. She did not have pre-existing neurological disorders and had not received significant amounts of psychotropic drugs before. Her medication history revealed that she was receiving “CsA (100 mg, q12h, po)-mycophenolate (1g, q12h, po)-methylprednisolone (8 mg, q12h, po)” antirejection therapy, because she had received allogeneic HSCT for myelodysplastic syndromes (MDS) 70 days before. The patient suffered from coughing accompanying expectoration 14 days ago, and the chest computed tomography (CT) showed pulmonary infections in the superior lobe of right lung. Cefaclor sustained release table had been administrated for one week, however symptoms did not improve. Fungus infection was suspected. Tablet voriconazole (400 mg, q12h, po) on the first day, followed by 200 mg every 12 h orally was added for the prophylaxis of IFI one week later. During this period, other medications, including herbal remedies and vitamins, had not been used; her liver function and renal function tests during the past 2 months were normal. After admission carbamazepine, rotundine, and citicoline sodium were administrated immediately for symptomatic treatment and supportive management; however, her condition continued to deteriorate in the next 2 hours, she dropped into locked jaw and convulsion of limbs, presented with epileptiform seizures, which was gradually improved by 10 mg diazepam (once) and 7 days of phenobarbital (0.1 g, bid, im) afterwards.

A standard fluorescence polarization immunoassay (FPIA) was used to detect the trough blood concentration of CsA before the next administration. Historical trough whole blood concentration of CsA (reference range 150-300 ng/ml) was collected within the past month (average 230 ng/ml) before the combination with voriconazole. On the second day of admission, the blood concentration of CsA was 378 ng/ml. On the same day other examinations such as blood counts, cerebrospinal fluid, and serum chemistries are shown in Table 1. Blood smear showed plenty of leukocytes which were well distributed, and the immunochemical assay for cytomegalovirus (CMV) showed negative result on the third day of admission, the chest CT showed inflammation in anterior segment of superior lobe and median lobe in the right lung on the same day. Magnetic resonance imaging (MRI) of head showed leukoencephalopathy in bilateral occipital and left frontal lobe on the 4<sup>th</sup> day of admission.

According to the clinical symptoms, laboratory examinations, and imaging examinations, the interaction between CsA and voriconazole was suspected. The concentration of CsA had risen slowly to 378 ng/ml during the past 7 days of co-administration with voriconazole. So voriconazole was suspended, and alprostadir, clopidogrel, and atorvastatin were

**Table 1: Laboratory data on the second day of admission**

Measurement	Value	Reference range
White cell count (x10 <sup>9</sup> /l)	9.64	3.69–9.16
Neutrophilic granulocyte (%)	0.909	0.500–0.700
Lymphocyte (%)	0.063	0.200–0.400
Blood urea nitrogen (mmol/l)	9.21	2.4–8.2
Uric acid (mmol/l)	568	90–420
Cholesterol (mmol/l)	7.87	3.08–6.35
Low-density lipoprotein (mmol/l)	5.17	2.07–3.10
Triglycerides (mmol/l)	4.27	0.34–1.92
Lipoprotein A (mg/l)	610.3	0–300
C-reactive protein (mg/l)	17.6	0–6
Erythrocyte sedimentation rate (mm/H)	28	0–20
Lactate dehydrogenase (U/l)	425	71–231
$\alpha$ -hydroxybutyrate dehydrogenase (U/l)	280	71–200
Myoglobin (ug/l)	135.8	0–70
Acid-fast bacilli of cerebrospinal fluid	not found	not found
Tubercule bacillus antibody	negative	negative
EB virus VCA-IgA antibody	negative	negative
1-3- $\beta$ -D polyglucosan (pg/ml)	42.16	0-20

administered from the second day of hospital stay to improve microcirculation and decrease hyperlipemia. From the third day of hospital stay, cefoperazone sodium and sulbactam sodium for injection were added to control the inflammation in the right lung. Her condition improved gradually. Because of the phenobarbital’s induction of enzymes, the blood concentration of CsA dropped to 57 ng/ml on the 8<sup>th</sup> day of hospital stay; therefore, phenobarbital was suspended after 7 days’ medication under the circumstances of improved neurologic signs. On the 9<sup>th</sup> day of admission, the CT in chest showed amelioration in superior lobe of right lung comparing to anterior results besides miliary tuberosity in bilateral lungs, probable fungus infection, and the 1-3- $\beta$ -D polyglucosan elevated to 89.57 pg/ml on the 10<sup>th</sup> day of admission. Voriconazole treatment was administered again to control fungus infection in bilateral lungs. To prevent drug toxicity, the dose of CsA was adjusted to 3/4 compared to the initial dose. Satisfactory steady-state blood concentration of CsA was achieved (250 ng/ml around). She was discharged 12 days later. The trough concentration of CsA and the important co-administered drugs (including enzyme inhibitors or enzyme inductors) during different time periods are shown in Table 2.

## DISCUSSION

Voriconazole and its metabolites are inhibitors of CYP450 liver enzymes, including CYP2C9, CYP2C19, and CYP3A4 isoenzymes. CsA, a calcineurin inhibitor, is a substrate for CYP450 enzymes. Voriconazole can inhibit the metabolism of CsA and prolong its action. The interaction between

**Table 2: The change of CsA trough concentration with the combination of voriconazole or phenobarbital**

Postoperative day	CsA dose	Important co-administered drugs		CsA trough concentration (ng/ml)
		Enzyme inhibitors	Enzyme inducers	
35 <sup>th</sup>	100 mg, q12h, po	None	None	190
42 <sup>th</sup>				178
48 <sup>th</sup>				266
55 <sup>th</sup>				283
63 <sup>th</sup>				235
70 <sup>th</sup>	75 mg, q12h, po	Voriconazole (0.2 g, q12h, po)	phenobarbital (0.1g, bid, im)	378
77 <sup>th</sup>				57
80 <sup>th</sup>				237
83 <sup>th</sup>				263

voriconazole and CsA can cause unexpected adverse effects even under standard therapeutic doses. According to Naranjo Adverse Drug Reaction Probability Scale (NADRS), the score of this severe adverse drug reaction (ADR) is 6, which indicates a probable ADR due to the drug–drug interaction (DDI) between voriconazole and CsA. This score is based on the following points: First, the studies on the DDI between voriconazole and CsA have been reported and widely recognized; second, the ADR occurred after voriconazole was administered with the presentation of dizziness, headaches, blurred vision, locked jaw, convulsion of limbs, and elevated blood concentration of CsA (↑64%); third, the ADR improved by discontinuing voriconazole, administering 7 days' phenobarbital as specific treatment, other symptomatic treatment, and supportive management for epileptiform seizures; fourth, the patient did not have pre-existing neurological disorders or epilepsy history; and the last, in this patient, the possibility of mycophenolate and methylprednisolone causing neuropathy are scarce and lack of monitoring of its blood concentration; though voriconazole can also cause tremor, dizziness, and disordered vision, but convulsion and encephalopathy associated with voriconazole are a rare phenomena. Therefore, the possibility of the ADR associated with other co-administered drugs was low. To sum up, we inferred that epileptiform seizures were induced by leukoencephalopathy in bilateral occipital and left frontal lobe, leukoencephalopathy was caused by the elevation of blood concentration of CsA, and the elevation of the blood concentration of CsA was induced by enzyme inhibition of voriconazole.

According to literature, neurotoxicity of CsA may be different, which may display arterial hypertension, headache, visual disturbances, hemiparesis,<sup>[3,4]</sup> parkinsonism,<sup>[5]</sup> leukoencephalopathy, and so on.<sup>[6,7]</sup> Its possible reason is that CsA can permeate the blood brain barrier and impact on mitochondrial function in endothelial cells.<sup>[8]</sup> These pathological changes are reversible, which can relieve gradually or disappear through lowering dosage, suspending, or changing to other immunosuppressive agents.

Since up to 21% of adverse drug event-related hospital admissions are due to drug interactions,<sup>[9]</sup> therapeutic drug monitoring (TDM) of CsA is necessary not only before and after combination with voriconazole treatment for safe and convenient modification of immunosuppressive agents, but also when voriconazole is not added in the regimen, and even if it is in standard therapeutic dose.<sup>[10]</sup> As several studies have shown the variable magnitude of DDI between voriconazole and CsA as well as the P-gp inhibition of voriconazole-mediated,<sup>[11-13]</sup> therefore, dose adjustment of CsA should be determined on an individual basis by closely monitoring the blood levels of CsA, and the concentration of CsA maintaining at a the low serum and high intracellular cyclosporine levels may contribute to an immunosuppressive state on initiating voriconazole administration.

## CONCLUSION

This case highlights the importance that clinical pharmacists should collaborate with the medical team by analyzing TDM results in case of integrating prescriptions and accumulating the knowledge of potential drug interaction through performing a systematic literature research. In this patient, the concentration of CsA increased from 230 to 378 ng/ml, with a percentage of 64% after initiating voriconazole, which presented headache, dizziness, blurred vision, and worsened to epileptiform seizures. Therefore, it is clinical pharmacists' responsibility to manage drug–drug interactions and optimize the patients' treatment protocols by tabling proposals to clinicians when it is necessary. This severe ADR caused by DDI between voriconazole and CsA has been reported to the national centre for ADR monitoring of China (registered as number 20100011) and evaluated as “probably”.

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