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Can COVID-19 Be a Potential Risk Factor for Voriconazole-Induced Hyperkalemia?

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ABSTRACT

Voriconazole is an antifungal agent that is commonly used to treat fungal infections. Like any drug, it can cause side effects, especially in the case of overdose. Few cases of hyperkalemia have been reported, which presented when the serum voriconazole level was elevated or when there was voriconazole-drug interaction. We present here a case of voriconazole-induced hyperkalemia, prescribed for an oral candidiasis due to *Candida glabrata* in a patient hospitalized for severe COVID-19 pulmonary infection. Inflammation due to COVID-19 may play a role in the variability of voriconazole concentrations and then in hyperkalemia.

Keywords: COVID-19, candida glabrata, voriconazole, hyperkalemia

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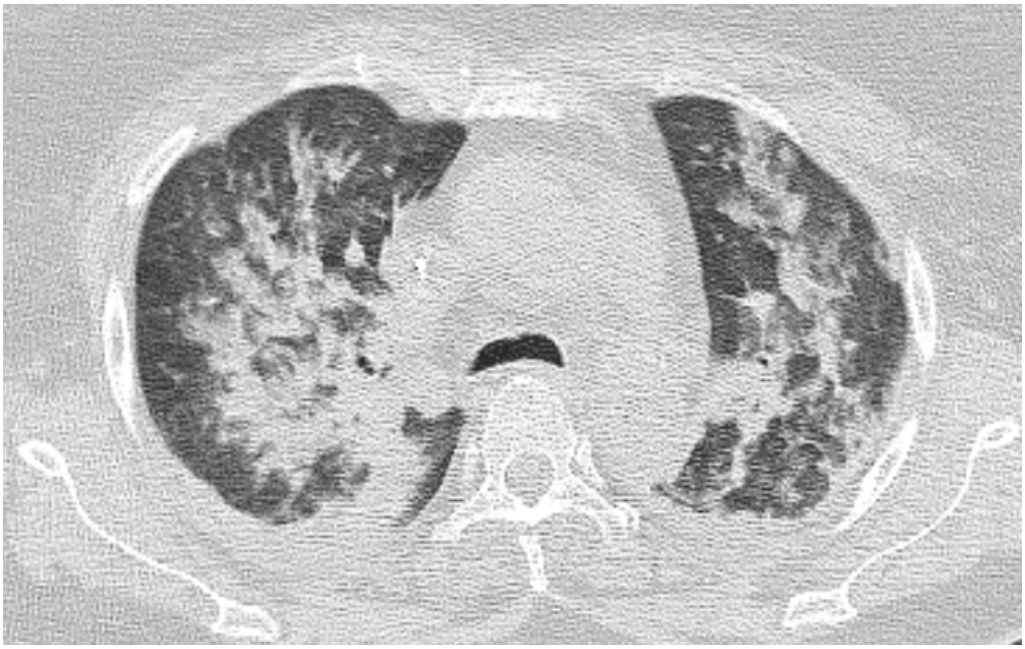

***Figure 1**. Chest computed tomography showing bilateral parenchymal condensations suggestive of COVID-19 pneumonia*

INTRODUCTION

Voriconazole is a second-generation triazole antifungal agent [1]. It is generally well tolerated [2]. Voriconazole-induced hyperkalemia has been reported in few cases. We present here a case of acute severe hyperkalemia caused by voriconazole in a patient having a severe inflammation due to COVID-19. A causal relationship between voriconazole and hyperkalemia was concluded because hyperkalemia was resolved by discontinuing this drug. Also, we review by searching in Pub Med from inception to February 2021, all cases of voriconazole-associated hyperkalemia.

CASE REPORT

A 66-year-old female was admitted in the emergency room in December 2020 for acute dyspnea and altered consciousness. She had multiple comorbidities: hypothyroidism, dyslipidemia, diabetes mellitus, high blood pressure, obliterative arteriopathy of the lower limbs and previous ischemic stroke. She received since a long-time insulin, levothyroxine, atorvastatin, valsartan and sulodexide. At admission, she was febrile and neurological exam was normal. Her oxygen saturation was 74%. Results of laboratory investigations included: white cells count (15000/mm^3), lymphocytes count (1820/ mm^3), hemoglobin (10.1g/dl), platelets (100000/mm3), C-reactive protein (CRP) (502 mg/l), procalcitonine (77.33 ng/ml) and D-dimer (2500). Blood ionogram, creatinine, glucose, calcium and transaminases were normal. The patient required artificial ventilation and she was treated by empirical intravenous antibiotherapy (ceftazidime and teicoplanin). In face of this severe acute respiratory syndrome and considering the current epidemic context, a coronavirus disease 19 (COVID-19) was suspected. A thoracic and cerebral CT scan was realised revealing sequelae cerebral ischemic lesions, bilateral parenchymal condensations suggestive of COVID-19 pneumonia with damage estimated at 50%, acute pulmonary edema and a low bilateral pleural effusion (**Figure 1**).

Cardiac ultrasound revealed moderate hypertensive heart disease with left ventricular ejection fraction estimated at 60%. Diagnosis of COVID-19 was confirmed through nasopharyngeal PCR (polymerase chain reaction). Thus, we prescribed: vitamin C, vitamin D, clarithromycin (500 mg daily), furosemide (40 mg daily), cetirizine dichlorhydrate (10 mg daily), famotidine (40 mg daily), enoxaparin (6000 UI twice a day) and dexamethasone (8 mg twice a day). Three days later, blood culture returned positive for *Streptococcus pneumoniae* and empiric antibiotherapy was changed to ceftriaxone according to the results of the antibiotic susceptibility testing. The patient's respiratory function was improved, but blood pressure was disordered requiring the addition of nebivolol. During hospitalization, the patient developed oral candidiasis

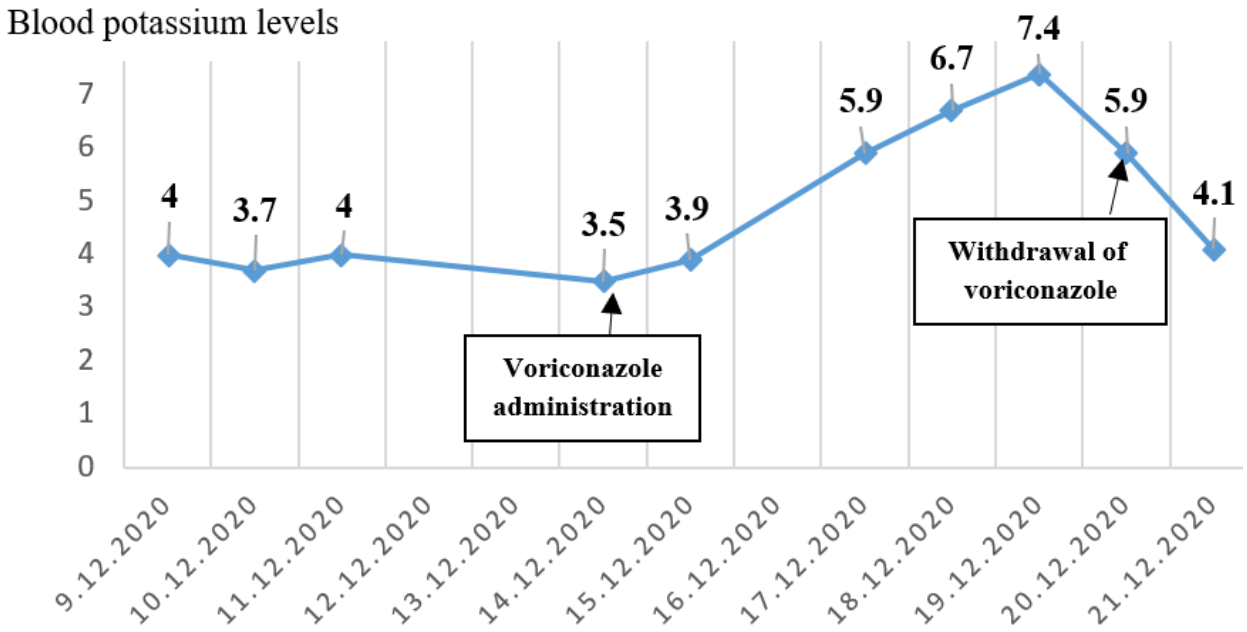

***Figure 2**. Blood potassium levels before and after oral voriconazole's administration and then after withdrawal of this drug*

with dysphagia. We practiced lingual specimen, then we prescribed fluconazole (400 mg daily). Three days later, the lingual sample returned positive for *Candida glabrata* resistant to fluconazole. Thus, we switched fluconazole by oral voriconazole (200 mg twice daily). At this time, serum sodium was 133 mmol/l, serum potassium was 3.5 mmol/l and creatininemia was 111 µmol/l. Few days after voriconazole's administration, the kalemia was increased up to 7.4 mmol/l (**Figure 2**).

Kidney and liver-function were normal. Electrocardiogram had shown sinus arrhythmia without repolarization disorders. The patient received kayexalate at each peak of hyperkalemia. Concurrently, oral candidiasis was improved, and we decided to stop using voriconazole. Just one day after, hyperkalemia was resolved (**Figure 2**). We therefore conducted a pharmacovigilance investigation. This one incriminated voriconazole in the genesis of hyperkalemia. The patient was hospitalized for 12 days with a favorable clinical and biological evolution (apyrexia, good general condition, correct oxygen saturation in ambient air, CRP at 14 mg/l and normokalemia).

Voriconazole is a new generation triazole antifungal agent with potent activity against a wide range of clinically significant pathogens, including *Candida glabrata* [3]. The voriconazole's mechanism of action, similar to that of all azole agents, is inhibition of the action of the cytochrome P-450-dependent C-14α demethylase enzyme, which blocks ergosterol synthesis and impairs fungal cell membrane function [4]. Voriconazole has non-linear pharmacokinetics and undergoes extensive hepatic metabolism by the cytochrome P450 system that depends on age, genetic factors, and interactions with other drugs [5]. Voriconazole has many well-described adverse effects such as visual disturbances, skin rashes, hallucinations, peripheral neuropathy, hepatotoxicity, nausea, vomiting and QT interval prolongation [6,7]. Electrolyte disturbances such as hyponatremia and hypokalemia are rarely reported [8,9]. By reviewing the literature, we found only three cases of voriconazole-associated hyperkalemia [5,10,11].

In the first case, hyperkalemia was possibly attributable to high voriconazole concentration [7]. In the second case, hyperkalemia was caused by voriconazole (potent inhibitor of CPYP3A4) - tacrolimus (CPYP3A4 risk substrate) interaction. This interaction increased the concentration of tacrolimus, resulting in hyperkalemia by reducing urinary potassium excretion [4]. The third case was a patient treated by oral voriconazole for pulmonary aspergillosis. He presented three episodes of hyperkalemia. The first one was caused by renin-angiotensin-aldosterone system inhibitors (telmisartan, spironolactone). The second one was caused by

***Table 1**. Summary of all reported cases of voriconazole-associated hyperkalemia*

Author	Age/Sex	Underlying disease and therapy	Voriconazole indication	Voriconazole posology	Kalemia (mmol/l)	Time to hyperkalemia (days)	Voriconazole trough level (µg/ml)	Interacted drugs
Boyd et al. [10]	77/M	Several exacerbations of chronic obstructive pulmonary disease requiring frequent courses of oral steroids *Pseudomonas* lung infections	Acute invasive *Aspergillus fumigatus* lung infection	3 mg/kg/12h (intraveinous)	7.2	13	17.5 (high)	No drug interaction
Nazmul et al. [5]	29/M	Kidney transplant patient treated with immunosuppressant (tacrolimus)	Histoplasmosis	-	8.5	40	Unknown	Tacrolimus
Jae Young Choi et al. [11]	69/M	Pulmonary tuberculosis Alcoholic liver cirrhosis Diabetes mellitus High blood pressure	Pulmonary aspergillosis	SE: 200 mg/12h (per os) TE: 100 mg/12h (per os)	SE : 7.5 TE : 8	SE: 9 TE: 16	Unknown	SE: Dronedarone TE: No drug interaction
Current case	66/F	Hypothyroidism Dyslipidemia Diabetes mellitus High blood pressure Obliterative arteriopathy of the lower limbs Ischemic stroke COVID-19 Pneumococcal lung infection	Esophageal candidiasis with *C.glabrata* in a patient hospitalized for COVID-19 pulmonary infection	200 mg/ 12h (per os)	7.4	4	Unknown	No drug interaction

M: male; F: female; SE: second episode of hyperkalemia; TE: third episode of hyperkalemia

voriconazole - dronedarone interaction. Dronedarone might have increased the voriconazole level, resulting in hyperkalemia. The third one was attributed to the use of voriconazole without drug interactions [8]. In our case, three hypotheses could explain the hyperkalemia: the atorvastatin-voriconazole interaction, the valsartan-voriconazole interaction or the own effect of voriconazole (probable elevated serum concentration mediated by significant inflammation of COVID-19). Atorvastatin is metabolized in the liver predominantly by the CYP3A4 isoenzyme and azole antifungals can increase serum statin concentrations by competing for catabolism [9]. High dose atorvastatin will induce rhabdomyolysis leading to onset of severe hyperkalemia due to renal failure [10,11]. In our case, the patient had not reported myalgia or cramps and her serum creatinine level was normal during hyperkalemia episodes. So, we have not retained the first hypothesis. Valsartan, the patient's usual treatment for a long time, is an angiotensin II receptor antagonist and so can lead to hyperkalemia by reducing urinary potassium excretion. This drug is excreted predominantly in the faeces via the bile largely as unchanged compound and it undergoes little in the way of metabolic conversion [12]. There have been a study reporting identification of cytochrome P450 forms involved in the 4-hydroxylation of valsartan. These results showed that the 4-hydroxylation of valsartan is predominantly mediated by a single CYP enzyme, namely CYP2C9 in human liver microsomes. However, although CYP2C9 is involved in valsartan metabolism, CYP-mediated drug-drug interaction between valsartan and other co-administered drugs would be negligible [12]. The second hypothesis was therefore eliminated. We retained in our case that voriconazole had induced by itself this hyperkalemia. The pharmacovigilance survey supported this third hypothesis. In the literature, the mechanism of voriconazole-induced hyperkalemia by itself remains not well known. Azole antifungals may interfere with the biosynthesis of adrenal steroids and therefore can predispose patients to aldosterone deficiency. However, it is unclear whether voriconazole itself can induce hypoaldosteronism or hyperkalemia [8]. In fact, voriconazole could not significantly inhibit human steroidogenesis when given at the recommended dosage [4]. Boyd and *al* reported a case of voriconazole-induced hyperkalemia without drug interactions, possibly attributable to high voriconazole concentration [10]. Inflammation may play a role in the variability of voriconazole concentrations. Many studies showed that

higher serum levels of C-reactive protein were significantly associated with higher voriconazole trough concentrations [3,15,16]. These findings can be explained by the negative regulation of various drug-metabolizing enzymes by proinflammatory cytokines, particularly interleukin-6 and tumor necrosis factor-α [3]. In our case, the patient had severe inflammation related to COVID-19 pulmonary infection. But, we were unable to measure the serum concentration of voriconazole at the time of hyperkalemia.

CONCLUSION

Clinicians should be aware that voriconazole can induce by itself severe hyperkalemia, especially in patients with severe inflammation like infection with COVID-19. In such situation, voriconazole level monitoring is necessary for a safe drug use.

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