Case Report

ISSN 1738-5997 (Print) • ISSN 2092-9935 (Online)
Electrolyte Blood Press 18:10-15, 2020
https://doi.org/10.5049/EBP.2020.18.1.10

Voriconazole-induced Severe Hyperkalemia Precipitated by Multiple Drug Interactions

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Received: April 13, 2020
Revised: May 15, 2020
Accepted: May 16, 2020
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Voriconazole is a triazole antifungal agent used to treat serious fungal infections and undergoes hepatic metabolism by the cytochrome P450 system. Severe hyperkalemia was reported in a kidney transplant recipient when voriconazole and tacrolimus were coadministered. The azole antifungals may interfere with the biosynthesis of adrenal steroids and therefore can predispose patients to aldosterone deficiency. However, it is unclear whether voriconazole by itself can induce hypoaldosteronism or hyperkalemia. Here, we report a case of voriconazole-induced hyperkalemia who had concurrent medications to treat comorbidities. Voriconazole was orally administered for pulmonary aspergillosis, and three episodes of severe hyperkalemia recurred and were improved by emergency treatment. At the first episode, renin-angiotensin-aldosterone system inhibitors were associated. We found that dronedarone might have increased the voriconazole level at the second episode. At this time, severe hypercalcemia was concurrent and improved by acute hemodialysis and eliminating dronedarone. Finally, severe hyperkalemia recurred without concurrent medications known to interact with voriconazole. We switched voriconazole into itraconazole, and his hyperkalemia was resolved. Drug level monitoring is necessary when voriconazole is used. Genetic susceptibility such as CYP2C19 polymorphism may be investigated in patients with adverse reactions to voriconazole.

Key Words: Dronedarone, Drug interactions, Hypercalcemia, Hyperkalemia, Voriconazole

Introduction

Voriconazole is a triazole antifungal agent used to treat serious fungal infections. It is the first line treatment of invasive aspergillosis, but its therapeutic window is narrow because of unpredictable, nonlinear pharmacokinetics with extensive interpatient and intrapatient variation in serum levels[1,2].

Many adverse effects were described while voriconazole use has been increased. Visual disturbances, skin rashes, hallucinations, and hepatotoxicity are well known[2], and the increased risk of skin cancer is most concerning[3]. Electrolyte disturbances such as hyponatremia were rarely reported as adverse reactions to voriconazole[4], and it is unclear whether hyperkalemia can be induced by voriconazole alone.

Here, we report the case of voriconazole-associated severe recurrent hyperkalemia which required emergency treatment including acute hemodialysis. Voriconazole was used to treat pulmonary aspergillosis, and the patient was taking multiple medications for accompanying diseases. Thus, it was probable that drug interactions might occur between medications undergoing hepatic metabolism by

the cytochrome P450 system. The causal relationship between voriconazole and hyperkalemia was concluded because hyperkalemia was recurrently provoked by voriconazole administration and resolved by discontinuing the offending agent. We discuss potential mechanism by which hyperkalemia can be induced and drug interactions between voriconazole and cardiovascular medications.

Case Report

A 69-year-old male was admitted due to quadriparesis *via* emergency room (ER). He had multiple comorbidities: old pulmonary tuberculosis, alcoholic liver cirrhosis, diabetes mellitus and hypertension. His medications included spironolactone, glimepiride, metformin, amlodipine, and telmisartan. Two weeks earlier, however, he was diagnosed to have pulmonary aspergillosis and paroxysmal atrial fibrillation at the outpatient department (OPD). A pulmonologist and a cardiologist prescribed oral voriconazole (200 mg twice a day) and dronedarone (400 mg twice a day), respectively. At this time, serum sodium was 135 mmol/L, potassium 5.5 mmol/L, and creatinine 0.91 mg/dL. Figure 1 shows chest radiographic findings.

At admission, blood pressure was 124/52 mmHg, and no focal neurologic deficit was noted on physical examination. Serum sodium was 133 mmol/L, potassium 8.0 mmol/L, calcium 9.3 mg/dL, phosphorus 4.7 mg/dL, and creatinine 1.57 mg/dL. Electrocardiography (ECG) showed atrial fibrillation and left bundle branch block (Fig. 2A). The severe hyperkalemia appeared to be caused by spironolactone and telmisartan coadministration, and these offending agents were discontinued. In addition, hyperkalemia was antagonized by intravenous calcium gluconate and corrected by administration of intravenous insulin lispro and calcium polystyrene sulfonate. His proteinuria was persistent, reaching 1,131 mg/d in 24-h urine collection. Urinalysis showed specific gravity 1.007, pH 5.0, albumin 1+, red blood cells 5-9/high power field (HPF), and white blood cells 3-4/HPF. Because monoclonal gammopathy was suggested from serum and urine protein elec-

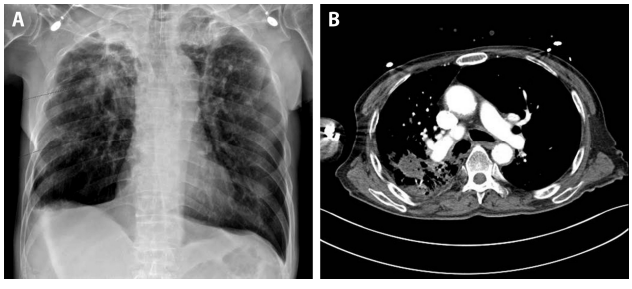

Fig. 1. Chest radiologic findings. Chest PA suggests old tuberculous destroyed lung lesions at upper lobes (A). Chest computed tomography shows ill-defined infiltrations at right middle and lower lung field (B). Serologic test for aspergillus antigen was positive from both serum and bronchoalveolar lavage.

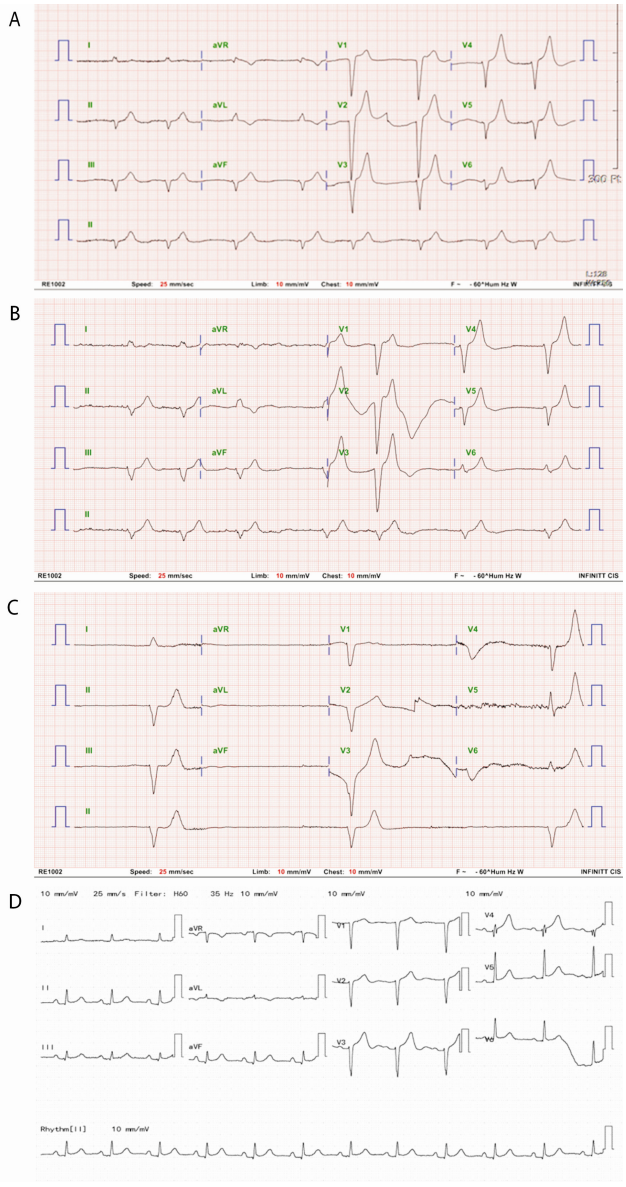

Fig. 2. Serial electrocardiographic findings. Atrial fibrillation and left bundle branch block were initially noted (A), bradycardia was aggravated (heart rate 43, B), and then complete atrioventricular block was induced (C). Finally, normal sinus rhythm was recovered (D).

trophoresis, kidney biopsy was performed. Light microscopic examination revealed two global sclerosis among 17 glomeruli sampled, and showed marked mesangial expansion with mesangial hypercellularity and global thickening of the glomerular capillary walls. Immunofluorescence revealed lambda light chain-restricted glomerular mesangial and linear capillary loop staining (Fig. 3). Electron microscopic evaluation showed vague, fine granular, amorphous deposits in the mesangium and along the peripheral capillary walls. These pathologic findings were compatible with light chain deposition disease. The immunofixation test revealed that heavy and light chain were IgG and λ, respectively. However, no osteolytic lesions were found, and bone marrow was normocellular. Thus, he was discharged without specific treatment while maintaining voriconazole.

In nine days, he was readmitted because of gait disturbance and dysarthria. His brain imaging revealed no acute lesion. Bradyarrhythmia was noted (Fig. 2B), and acute hemodialysis was undertaken to treat both hypercalcemia (11.7 mg/dL) and hyperkalemia (7.5 mmol/L). Urine sodium was 127 mmol/L, potassium 19 mmol/L, chloride 125 mmol/L, creatinine 36 mg/dL, and osmolality 372 mOsm/kg H_2O. Transtubular potassium gradient (TTKG) was calculated as 2.02, and arterial blood gas analysis showed pH 7.354, pCO_2 38.5 mmHg, pO_2 110 mmHg, and HCO_3^- 20.9 mmol/L. Results of the following endocrine tests were unremarkable: plasma renin activity, serum aldosterone concentration, intact-PTH, and stimulated cortisol. Vitamin D levels were low, and PTH-related peptide was undetectable. We considered the possibility of voriconazole-induced hyperkalemia, and voriconazole was discontinued. Because the follow-up ECG showed that atrial fibrillation was resolved, dronedarone was not given any longer. When he was discharged, his serum sodium was 135 mmol/L, potassium 4.1 mmol/L, calcium 9.5 mg/dL, phosphorus 3.7 mg/dL, protein 7.5 g/dL, albumin 3.1 g/dL, and creatinine 0.69 mg/dL.

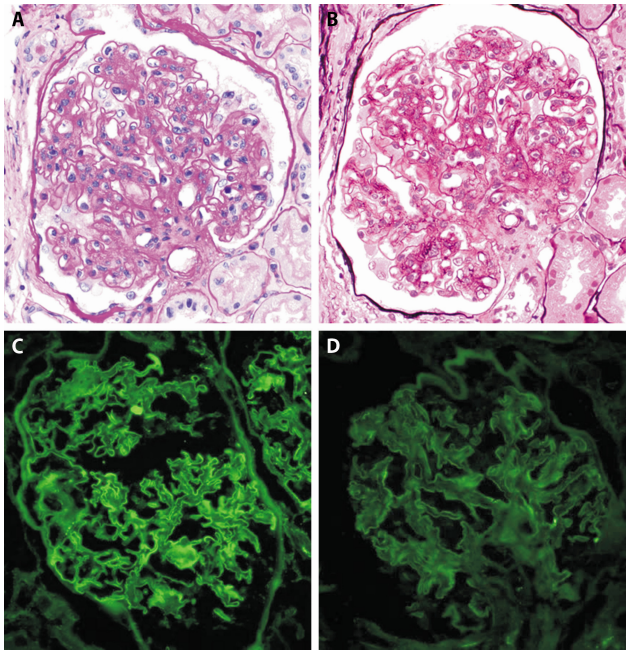

Fig. 3. Kidney biopsy findings on glomerular pathology. Periodic acid-Schiff stain shows global thickening of the glomerular basement membrane and mesangial expansion with mesangial cell proliferation (**A**). Jone's methanamine silver stain highlights early nodular mesangial sclerosis (**B**). Congo-red staining was negative (not shown). Immunofluorescence was reactive for lambda light chain in the mesangium and along the glomerular basement membrane (**C**). In contrast, kappa light chain was negative (**D**).

In about one month later, he was readmitted because of massive hemoptysis and had to receive bronchial artery embolization. The pulmonologist decided to have him take itraconazole to treat pulmonary aspergillosis. One week later, however, it was switched into a reduced dose (100 mg twice a day) of voriconazole. In the meantime, antihypertensives were switched into manidipine and propranolol.

Serum potassium was raised to 5.7 mmol/L after voriconazole was resumed for 16 days. On the next day, he visited ER again because of chest tightness. His serum sodium was 130 mmol/L, potassium 8.0 mmol/L, calcium 8.9 mg/dL, phosphorus 5.8 mg/dL, and creatinine 1.63 mg/dL. ECG suggested complete atrioventricular block (Fig. 2C), and he recovered normal sinus rhythm after acute hemodialysis (Fig. 2D). Once again, we changed voriconazole into itraconazole (200 mg once a day). Manidipine was withdrawn because of the potential drug interaction between azole antifungals and calcium channel blockers[2]. Plasma renin activity and serum aldosterone were 0.26 (normal, 0.32-1.84) ng/mL/h and 3.0 (normal, 4.2-20.9) ng/dL, respectively. No further electrolyte disturbances were noted during the admission for three weeks, and his final follow-up laboratory findings were:

serum sodium 136 mmol/L, potassium 4.4 mmol/L, calcium 9.6 mg/dL, phosphorus 4.4 mg/dL, and creatinine 0.85 mg/dL.

Discussion

Table 1 summarizes laboratory findings at each episode of acute severe hyperkalemia and medications that we suspect to cause hyperkalemia. At the first episode, hyperkalemia was thought to be induced by the combined use of an angiotensin II receptor blocker (telmisartan) and a mineralocorticoid receptor antagonist (spironolactone). During the admission, serum potassium was maintained within the normal range while calcium polystyrene sulfonate was orally administered[5].

We addressed the possibility of voriconazole-induced hyperkalemia at the second episode of acute severe hyperkalemia. Although serum creatinine was elevated to 1.53 mg/dL, the decline in kidney function was not enough to explain hyperkalemia. We excluded the possibility of hyporeninemic hypoaldosteronism during the previous admission. Voriconazole-associated electrolyte disturbances were described in only a few reports[4,6,7], and no previous studies found that hyperkalemia was induced by voriconazole alone.

Review articles say that ketoconazole may induce hyperkalemia by impairing aldosterone secretion[8,9]. Ketoconazole is an imidazole antifungal agent, and voriconazole is a triazole antifungal. Both have a common chemical structure (azole), and the azole antifungals may interfere with the biosynthesis of adrenal steroids and therefore can predispose patients to aldosterone deficiency[9]. However, our results of plasma renin activity and serum aldosterone concentration were not consistent with primary hypoaldosteronism. Hyporeninemic hypoaldosteronism might be an alternative mechanism of hyperkalemia, but renal pathology in our case was not compatible with diabetic nephropathy.

Triazole antifungals include fluconazole, itraconazole, posaconazole, and voriconazole. They are not the same in disturbing potassium balance. Unlike fluconazole and voriconazole, itraconazole and posaconazole were reported to show pseudohyperaldosteronism presenting with low-renin hypertension and hypokalemic metabolic alkalosis[10]. The plausible mechanism is inhibition of 11β-hydroxysteroid dehydrogenase 2, with resultant apparent mineralocorticoid excess[11]. It is interesting that serum potassium could be increased or decreased according to different agents among triazole antifungals.

Another enigma to the second episode is the concurrence of hypercalcemia. However, voriconazole-associated hypercalcemia was reported to occur in patients with acute leukemia[12,13]. Voriconazole alone was not considered to cause hypercalcemia, but it should exert a synergistic effect on hypercalcemia via drug interactions[12] or an addition to the underlying hypercalcemia-prone disease such as fungal granulomas[13]. Our case had monoclonal gammopathy with light chain deposition disease, but it was not linked to hypercalcemic conditions because no osteolytic lesions were involved.

On the other hand, dronedarone, a class III antiarrhythmic drug, was concurrently used in our patient. Because both dronedarone and voriconazole undergo extensive hepatic metabolism by the cytochrome P450 system, interactions can occur between these two drugs[1]. Although we could not find any report of dronedarone-associated hypercalcemia, hypercalcemia was described in a patient using amiodarone, the prototype of class III antiarrhythmic[14].

Previous reports of voriconazole-associated hyperkale-

Table 1. Literature review: voriconazole-associated hyperkalemia

	Boyd, et al.[4]	Nazmul, et al.[6]	Current case
Voriconazole dosage	3 mg/kg i.v. every 12 h	No data available	200 mg p.o. twice a day
Peak serum K^+ (mmol/L)	7.2	8.5	8.0
Interacted drugs	Amiloride	Tacrolimus	Telmisartan, spironolactone, dronedarone
Other electrolyte disturbance	Hyponatremia	None reported	Hyponatremia, hypercalcemia

i.v., intravenous; p.o., per os.

mia were also from patients with concurrent medication inhibiting cytochrome P450 such as calcineurin inhibitors [6,7]. Only at the second episode of severe hyperkalemia, we were aware of the potential drug-drug interaction between dronedarone and voriconazole. However, the third episode of severe hyperkalemia was encountered without using dronedarone. Thus, we conclude that voriconazole may induce hyperkalemia by itself. Voriconazole was switched into intraconazole after the second episode, but it was resumed by the pulmonologist because of its effectiveness.

At the third episode of severe hyperkalemia, we scrutinized the list of drug-drug interactions with voriconazole. Calcium channel blockers including diltiazem, verapamil, israpidine, and nicardipine may potentially increase the level of voriconazole[2]. Although manidipine was not listed among calcium channel blockers, we decided not to use it any more. It was a pity that therapeutic drug monitoring was unavailable for voriconazole.

The other possibility of raising the voriconazole level is genetic polymorphism of the isoenzyme CYP 2C19[4]. A CYP 2C19 was found in 15 to 20% of Asians[15], but we did not obtain this result from our patient. Hepatic dysfunction is another factor to affect the voriconazole level, but it was not thought to be applied to our case because his liver function was stable and well-compensated.

It was interesting that each episode of voriconazole-induced hyperkalemia was accompanied by hyponatremia and mild azotemia (Table 1). The latter features were rapidly reversible, and it is unclear whether they are caused by voriconazole. Voriconazole is not nephrotoxic, and oral formulation without dosage adjustment can be safely used in patients with renal failure[1]. In summary, adverse effects including hyperkalemia, hyponatremia, and nephrotoxicity should be concerned when the trough voriconazole concentration was elevated to a toxic level[4,7]. It is postulated that pharmacogenetic susceptibility may have a role in voriconazole-induced hyperkalemia.

Conflict of interest

The authors declare no relevant financial interests.

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