Case Report

Voriconazole-induced Severe Hyperkalemia Precipitated by Multiple Drug Interactions

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Voriconazole, a triazole antifungal agent used to treat serious fungal infections, has a pharmacokinetic characteristic of undergoing hepatic metabolism by the cytochrome P450 system. Few cases of hyperkalemia have been reported, which presented only when the serum voriconazole level was exceptionally elevated by drug-drug interactions. Additionally, 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. Here, we report a case of voriconazole-induced hyperkalemia in a patient administered concurrent medications to treat comorbidities. Voriconazole was orally administered for pulmonary aspergillosis, and three episodes of severe hyperkalemia recurred, which improved with emergency treatment. In the first episode, renin-angiotensin-aldosterone system inhibitors were associated. We found that dronedarone might have increased the voriconazole level in the second episode. At that time, severe hypercalcemia was concurrent, which improved with acute hemodialysis and eliminating dronedarone. Finally, severe hyperkalemia recurred without concurrent medications known to interact with voriconazole. Upon switching from voriconazole to itraconazole, the hyperkalemia was resolved. Drug level monitoring is necessary when voriconazole is used. Genetic susceptibility, such as through CYP2C19 polymorphism, may be investigated for 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 for 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 have been described as voriconazole use has 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 be- tween medications undergoing hepatic metabolism by the cytochrome P450 system. A causal relationship between voriconazole and hyperkalemia was concluded because hyperkalemia was recurrently provoked by voriconazole
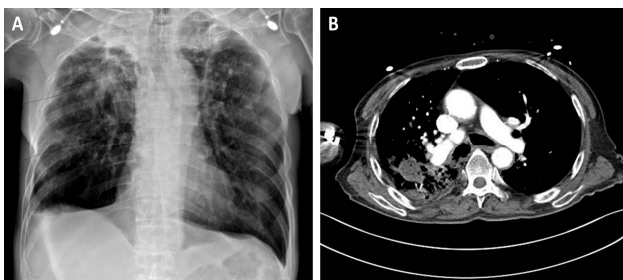
administration and was resolved by discontinuing the offending agent. We discuss a potential mechanism by which hyperkalemia could be induced by drug interactions between voriconazole and cardiovascular medications.
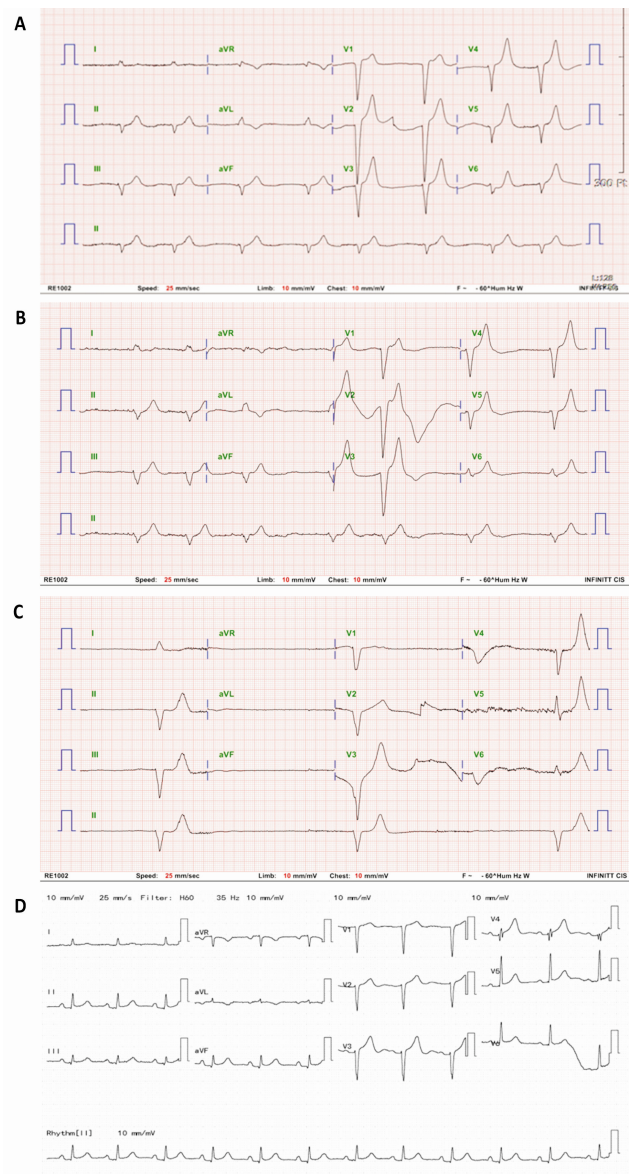
CASE REPORT

A 69-year-old male was admitted due to quadriparesis *via* the 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 with 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 was 5.5 mmol/L, and creatinine was 0.91 mg/dL. Figure 1 shows the chest radiographic findings.

At admission, the patient's blood pressure was 124/52 mmHg, and no focal neurologic deficit was noted on physical examination. Serum sodium was 133 mmol/L, potassium was 8.0 mmol/L, calcium was 9.3 mg/dL, phosphorus was 4.7 mg/dL, and creatinine was 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 was corrected by administration of intravenous

insulin lispro and calcium polystyrene sulfonate. His proteinuria was persistent, reaching 1,131 mg/d in a 24 h urine collection. Urinalysis showed a specific gravity of 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 electrophoresis, a kidney biopsy was performed. Light microscopic examination revealed two global scleroses among

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**).

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.
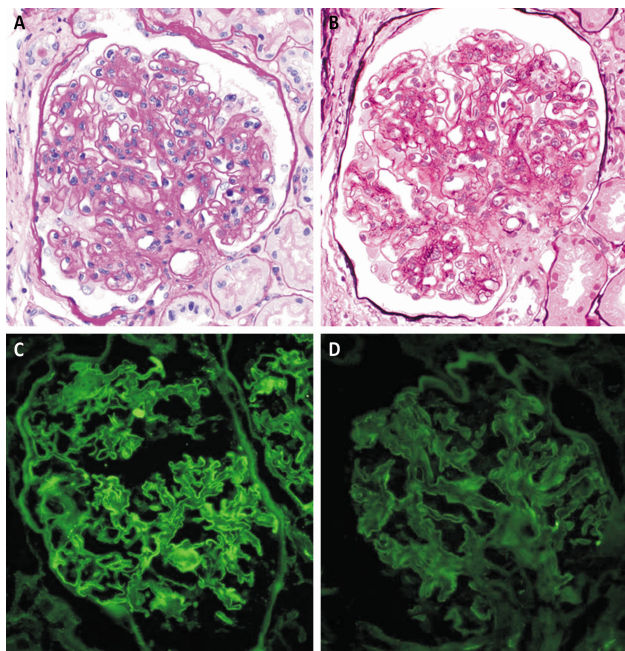
17 glomeruli sampled and showed marked mesangial expansion with mesangial hypercellularity and global thickening of the glomerular capillary walls. Immunofluorescence revealed lambda light chain-restricted glomerular mesangial and linear capillary loop staining (Fig. 3). Electron microscopic evaluation 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 chains were IgG and λ, respectively. However, no osteolytic lesions were found, and the bone marrow was normocellular. Thus, he was discharged without specific treatment while maintaining voriconazole.

Nine days later, the patient was readmitted because of gait disturbance and dysarthria. 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

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**).

was 127 mmol/L, potassium was 19 mmol/L, chloride was 125 mmol/L, creatinine was 36 mg/dL, and osmolality was 372 mOsm/kg H_2O. The transtubular potassium gradient (TTKG) was calculated to be 2.02, and arterial blood gas analysis showed a pH of 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; therefore, voriconazole was discontinued. Because the follow-up ECG showed the atrial fibrillation was resolved, dronedarone was discontinued. At discharge, his serum sodium was 135 mmol/L, potassium was 4.1 mmol/L, calcium was 9.5 mg/dL, phosphorus was 3.7 mg/dL, protein was 7.5 g/dL, albumin was 3.1 g/dL, and creatinine was 0.69 mg/dL.

Approximately one month later, the patient was readmitted because of massive hemoptysis and required bronchial artery embolization. The pulmonologist prescribed itraconazole to treat pulmonary aspergillosis. One week later, however, itraconazole was switched to a reduced dose (100 mg twice a day) of voriconazole. In the meantime, antihypertensives were switched to manidipine and propranolol.
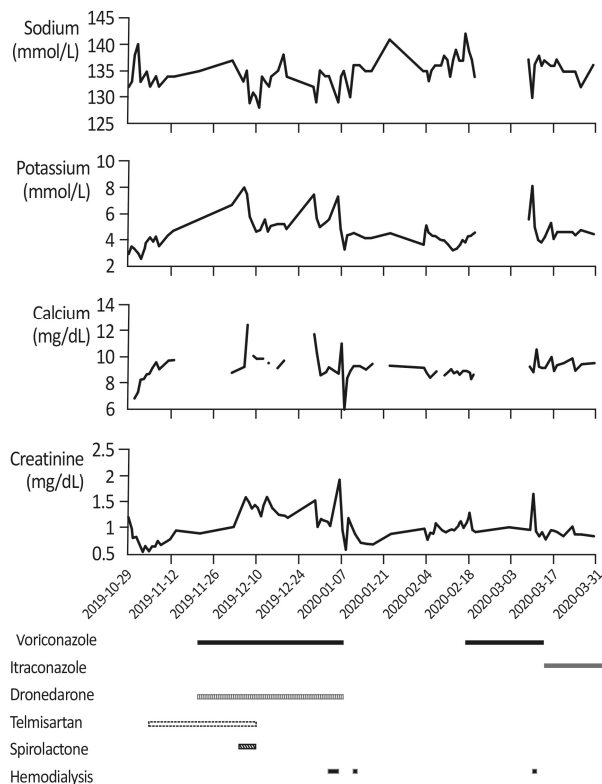
Sixteen days after voriconazole had been resumed, serum potassium had increased to 5.7 mmol/L, and one day later, the patient again visited the ER because of chest tightness. His serum sodium was 130 mmol/L, potassium was 8.0 mmol/L, calcium was 8.9 mg/dL, phosphorus was 5.8 mg/dL, and creatinine was 1.63 mg/dL. An ECG suggested complete atrioventricular block (Fig. 2C), and he recovered normal sinus rhythm after acute hemodialysis (Fig. 2D). Once again, voriconazole was replaced with itraconazole (200 mg once a day). Manidipine was discontinued 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

Figure 4 summarizes the laboratory findings at each episode of acute severe hyperkalemia and medications that we suspect caused hyperkalemia. In the first episode, hyperkalemia was thought to be induced by the combined use of an angiotensin II receptor blocker (telmisartan) and

Fig. 4. Changes in serum levels of sodium, potassium, calcium, and creatinine. Hyperkalemia appears to be induced by voriconazole administration and precipitated by concomitant medications. Although acute hemodialysis was required for emergency treatment, hyperkalemia was resolved by discontinuing voriconazole. Hyponatremia and azotemia were also associated with voriconazole toxicity.

a mineralocorticoid receptor antagonist (spironolactone). During 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 in the second episode of acute severe hyperkalemia. Although serum creatinine was elevated to 1.53 mg/dL, the decline in kidney function was not sufficient to explain the hyperkalemia. We had excluded the possibility of hyporeninemic hypoaldosteronism during the previous admission. Voriconazole-associated electrolyte disturbances have been described in only a few reports[4,6,7], and no previous studies found that hyperkalemia was induced by voriconazole alone (Table 1).

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

Triazole antifungals that include fluconazole, itraconazole, posaconazole, and voriconazole are not equivalent 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]. A plausible mechanism is inhibition of 11β-hydroxysteroid dehydrogenase 2, with resultant apparent mineralocorticoid

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.

excess[11]. It is interesting that serum potassium could be increased or decreased depending on the particular triazole antifungal agent.

Another enigma with 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 add to an 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 did not find any report of dronedarone-associated hypercalcemia, hypercalcemia was described in a patient using amiodarone, the prototype of a class III antiarrhythmic[14].

Previous reports of voriconazole-associated hyperkalemia similarly concerned patients with concurrent medications inhibiting cytochrome P450 such as calcineurin inhibitors[6,7]. Only in the second episode of severe hyperkalemia, were we aware of the potential drug-drug interaction between dronedarone and voriconazole. However, the third episode of severe hyperkalemia was encountered without dronedarone being administered. Thus, we conclude that voriconazole may itself induce hyperkalemia. Voriconazole was replaced with intraconazole after the second episode, but it was resumed by the pulmonologist because of its effectiveness.

In 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 continue its use. It was unfortunate that therapeutic drug monitoring was unavailable for voriconazole.

Another possibility of raising the voriconazole level is

genetic polymorphism of the isoenzyme CYP 2C19[4]. A CYP 2C19 is found in 15 to 20% of Asians[15], but we did not obtain this result from our patient. Hepatic dysfunction is another factor that can affect the voriconazole level, but it was not thought to be applicable in 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 (Fig. 4). The latter features were rapidly reversible, and it is unclear whether they were caused by voriconazole. Voriconazole is not nephrotoxic, and oral formulation without dosage adjustment can be safely employed in patients with renal failure[1]. In summary, adverse effects including hyperkalemia, hyponatremia, and nephrotoxicity should be of concern when the trough voriconazole concentration is 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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