CASE REPORT

Case Report: Voriconazole induced refractory hyperkalemia and adrenal insufficiency [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Voriconazole, an azole drug, inhibits cytochrome P450 dependent lanosterol 14-alpha-demethylase. It is a potent anti-fungal agent. Adverse effects include neurotoxicity, cardiac arrhythmias, electrolyte disturbances and adrenal insufficiency. Hyperkalemia is a rare adverse effect that has been described, but is not well reported, in the literature.

We present a case of intractable hyperkalemia resulting from voriconazole use. A 47-year-old male presented with worsening shortness of breath, requiring mechanical ventilation within 24 hours of presentation. Diagnosis of acute respiratory distress syndrome was made. Empirical treatment with broad-spectrum antibacterial coverage resulted in no improvement. Voriconazole was added for anti-fungal coverage, causing treatment resistant hyperkalemia necessitating continuous renal replacement therapy (CRRT). Renal function remained normal. Stopping voriconazole restored normal potassium levels. CRRT was discontinued.

Hyperkalemia caused by voriconazole occurs in less than 2% of cases. It is a potentially life-threatening side effect. Physicians should be aware of this association and seek alternative treatment when necessary.

Keywords

Voriconazole, Hyperkalemia. Adrenal Insufficiency, Fungal infection, Adverse effects.

Open Peer Review

Approval Status

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Any reports and responses or comments on the article can be found at the end of the article.

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Introduction

Voriconazole is a second-generation azole anti-fungal drug. One side effect of Voriconazole is interference with CYP 450 as it is a potent inhibitor of CYP 450. This can cause interactions with other drugs. Other adverse effects documented, include hormonal, cardiac, neurotoxic effects, and electrolyte imbalance^{1,2}. In our literature review we found a case report of adrenal insufficiency due to concomitant use of voriconazole and glucocorticoids³, a case series of hyponatremia associated with voriconazole use² and a case of iatrogenic Cushing syndrome associated with concomitant use of voriconazole and budesonide⁴. Hyperkalemia, in the light of the literature review is a rare side effect associated with voriconazole. Our case is noteworthy as in our patient the adrenal insufficiency and hyperkalemia manifested in absence of use of any other accompanying drug that could cause hyperkalemia. We present a case of hyperkalemia caused by voriconazole in a hospitalized patient. The likely cause of hyperkalemia in our patient is adrenal deficiency due to inhibition of adrenal enzymes.

Case presentation

A 47-year-old white male, retired trailer driver by occupation, with known Crohn's disease and hypertension presented with productive cough and worsening shortness of breath over three weeks in August 2020. On physical exam, patient was febrile with a temperature of 100-degree F, slightly tachypneic, with a respiratory rate of 24 per minute; blood pressure was 96/89 and he had right lower zone bronchial breathing on auscultation. The patient was admitted and initially started on piperacillin-tazobactam 4.5 gm. IV q6 hr, azithromycin 500 mg IV daily, vancomycin 1gm IV BID, and oseltamivir 75 mg BID. However, his respiratory status worsened over the first

48 hours and required transfer to the intensive care unit on the second day of hospitalization with septic shock and acute respiratory distress syndrome. The patient was intubated and mechanically ventilated and therapeutic paralysis induced. The patient was administered rocuronium IV at the dose of 8mcg/kg/min. Patient was supported by ventilator with volume assisted control. He required two vasopressors, epinephrine (0.3 mcg/kg/min) and nor-epinephrine (12 mcg/kg/min) as IV infusion to maintain his blood pressure. The patient failed to show improvement, therefore, voriconazole 240 mg IV BID was added on the fifth day of hospitalization. Following this, the patient started developing electrolyte abnormalities with rising potassium (Figure 1 and Table 1), and falling sodium (Figure 2 and Table 2). While the patient's creatinine remained stable (Figure 3 and Table 3).

For the rising potassium, immediate medical management with intravenous furosemide 80mg, rectal sodium polystyrene sulfonate 60 gm., and intravenous regular insulin 7 units were given, with 50 ml of 50% dextrose, continuous albuterol 2.5 mcg nebulization, and intravenous sodium bicarbonate 50 mEq intravenous push. However, this failed to improve the hyperkalemia. His urine output during this period was within normal range. Due to the intractable hyperkalemia, continuous renal replacement therapy (CRRT) was initiated. The patient was also started on intravenous hydrocortisone 60 mg every six hours and fludrocortisone 0.2 mg. The voriconazole was discontinued, the patient's electrolyte abnormalities normalized and the CRRT was stopped in less than 48 hours. Fludrocortisone was discontinued in 48 hours as well. The patient continued to improve and was extubated on day 11 of hospitalization. He was discharged to a specialist nursing facility on day 14. His follow

Figure 1. Trends in the serum potassium levels of patient during hospitalization. The patient serum potassium level was noted to increase following voriconazole addition to the drug regimen. Discontinuing voriconazole shows normalization of potassium levels, establishing that voriconazole was the offending agent.

Table 1. Potassium levels on corresponding days of hospitalization.

DAYS	POTASSIUM mmol/L
1	3.4
2	3.4
3	3.7
4	3.8
5	4.2
6	5.5
7	6
8	6.5
9	3
10	3.5
11	3.4
12	3.5
13	3
14	3.5
15	3.6
16	2.7

up chemistry showed Na^+ levels of 139 mEq/L (Normal range: 135 mEq/L– 145 mEq/L), K^+ levels of 4 mEq/L (Normal range: 3.5mEq/L–5.5mEq/L), HCO_3^- levels of 20 mEq/L (Normal range: 23mEq/L – 30mEq/L) , Creatinine level of 1.3 mg/dl (Normal range: 0.7– 1.5 mg/dL).

Discussion

Amphotericin B had been the drug of choice for mycosis up to the development of azole drugs. Azoles have the convenience of being administered orally and have a safer side effect profile compared to Amphotericin B⁵. Azoles are synthetic compounds and are further classified into two groups. The imidazole sub-group includes miconazole and ketoconazole. The triazole sub-group includes itraconazole, fluconazole, and voriconazole⁵.

Voriconazole has a potent antifungal effect. Voriconazole inhibits ergosterol synthesis in the fungal cell wall by inhibiting the 14- α demethylase enzymes hence causing eradication of fungal infection. Voriconazole leads to many drug-drug interactions because it causes inhibition of CYP 450 enzymes. Many drugs are metabolized by CYP450 enzymes hence voriconazole causes their level to increase in blood if used concomitantly.

Voriconazole is a relatively new, second-generation addition to the triazole anti-fungal family. It is both a substrate and an inhibitor of the enzymes of cytochrome P450 family, including CYP2C19, CYP2C9, and CYP3A4, thus leading to a number of adverse effects⁴.

Side effects in human, caused by inhibition of CYP 450 include decreased synthesis of many adrenal and gonadal

Figure 2. Trends in the serum sodium levels of patient during hospitalization. Hyponatremia trend shown after voriconazole administration; along with finding of hyperkalemia suggests voriconazole induced adrenal insufficiency.

Table 2. Sodium levels in patient on corresponding days of hospitalization.

DAYS	SODIUM mmol/L
3	135
6	132
9	135
12	150
15	132

enzymes. This can lead to adverse effects including gynecomastia and adrenal insufficiency⁵. Voriconazole also decreases enzyme function in the kidney and liver⁶.

Other adverse effects include liver toxicity; hormonal effects like alopecia, decreased libido, and impotence². Electrolyte imbalances like hyponatremia², hypokalemia, and adrenal insufficiency have been previously reported¹. Certain side effects associated with voriconazole itself include neurotoxicity, cardiac arrhythmias, pancreatitis phototoxic reactions, and periostitis¹.

Severe adverse effects due to drug interaction of steroids², and tacrolimus⁷ are noted with concomitant use of azole drugs.

Figure 3. Trends in the serum creatinine levels of the patient during hospitalization. The trends in creatinine levels were seen to be within normal range, reflecting adequate renal function.

Table 3. Creatinine levels on corresponding days of hospitalization.

DAYS	CREATININE mg/dL
1	1.36
2	1.2
3	1.15
4	1.06
5	1.125
6	1.1
7	1.125

DAYS	CREATININE mg/dL
8	1.05
9	0.7
10	1.25
11	1.25
12	1.05
13	0.98
14	0.85
15	1
16	1.3

The azole potentiates the drug effect by CYP 450 inhibition. There have been cases of increased steroid effect causing Cushing disease due to potentiated effect and later adrenal insufficiency due to hypothalamic-pituitary-adrenal (HPA) axis suppression^{3,4,8}. Due to inhibition of CYP 450 as a side effect of voriconazole, the metabolism of tacrolimus may be decreased, causing high levels of tacrolimus in blood which causes hyperkalemia⁸.

Our patient presented with shortness of breath, was diagnosed with acute respiratory distress syndrome and was treated with broad-spectrum antibiotics; he was also prescribed voriconazole for antifungal coverage. As voriconazole was initiated, the patient developed hyperkalemia and hyponatremia. Creatinine was noted to be within normal limits during hospitalization. The patient was treated on the lines of adrenal insufficiency. Voriconazole, when removed, resulted in clinical improvement. Sodium and potassium levels improved, establishing that the adrenal insufficiency had been due to an adverse reaction to voriconazole. In our case, adrenal insufficiency was treated on clinical suspicion. Voriconazole was confirmed as the causative agent because removing voriconazole relieved the patient's symptoms.

Voriconazole can cause adrenal insufficiency by directly inhibiting the adrenal enzymes. In case of concomitant use of steroids, HPA suppression can be the reason for adrenal insufficiency. The diagnosis of adrenal insufficiency is made by measuring ACTH level. The cortisone challenge test helps differentiate between primary and secondary adrenal insufficiency⁸.

Our case, has limitations as the diagnosis was made on clinical suspicion. However, in the absence of a history of steroid use, direct adrenal enzyme inhibition due to voriconazole is the most likely cause. The diagnosis is supported by the fact that removal of voriconazole resulted in an improvement in the patient's condition.

Conclusion

Hyperkalemia resulting from voriconazole use is an uncommon adverse effect occurring in less than 2% of cases but it is important because of the serious and potentially life-threatening consequences. It should be kept in mind whenever initiating treatment and an alternative treatment sought if deemed necessary. Moreover, electrolyte levels should be monitored when initiating voriconazole. Our case report underscores the need for case control studies to establish this association.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Consent

Written informed consent for publication of their clinical details was obtained from the patient.

Acknowledgements

The case has been previously reported as conference abstract at American Society of Nephrology (ASN), Kidney Week, San Diego, 2018. <https://www.asnonline.org/education/kidney-week/archives/>

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Open Peer Review

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The authors demonstrate a case of voriconazole-induced refractory hyperkalemia and adrenal insufficiency. The manuscript is well written. However, I still have some questions about the manuscript.

1. The patient was diagnosed by the authors with adrenal insufficiency. Please provide the diagnosis data for the patient (e.g. cortisol level, at what time in the day, and ACTH data) because the treatment of the underlying disease of Crohn's disease may require budesonide, the adrenal insufficiency may easily result from the Crohn's disease treatment related side effect. Please provide the long treatment regiment of Crohn's disease (at what dose and for how long).
2. Tables 1 to 3 and Figures 1 to 3 seem redundant. All these figures and tables may be integrated into one table or figure, marking the timing of insult of voriconazole.
3. The time course of voriconazole infusion with hyperkalemia is compatible. However, for the diagnosis of etiology of hyperkalemia, the workup is not yet completely presented in the manuscript. The authors should provide more data. For example, is there shifting in this patient (ex. rhabdo, hemolysis), what is the TTKG or urine fraction of excretion of potassium? Also, renin aldosterone levels had been associated with voriconazole-related hyperkalemia - is renin/ aldosterone data available in such a patient? I sincerely ask for a discussion in the manuscript. Additionally, acid-base status is required for making such a diagnosis, I suggest the authors make a table to integrate relevant data for the diagnosis etiology for hyperkalemia (including serum/urine/acid-base/endocrine data). It is difficult to convince the reader that hyperkalemia is mediated by inhibition of CYP450 if these data are not available. As previous reports have postulated inhibition of 11 β -hydroxysteroid dehydrogenase¹.

4. Also, a basic fluid status evaluation should be provided in the manuscript due to the setting of hyponatremia. Urine sodium and osmolality could be provided if available for better determination of etiology for critically ill patients.
5. In the discussion, paragraphs 2-4, the authors mentioned CYP450, is there any medication the patient used during ICU admission that would cause drug-drug interaction and enhance such effect?
6. In the conclusion section, they describe less than 2% of voriconazole use results in hyperkalemia. Please add references and consider adding them to the discussion section. The conclusion stretching out of the discussion and case part is not recommended.

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Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Nephrology, onco-nephrology, critical nephrology, acute kidney injury, electrolytes

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Reviewer Report 23 March 2021

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Taseen Syed

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It was a pleasure reviewing this interesting case report written by Tariq, EF *et. al* "Voriconazole induced refractory hyperkalemia and adrenal insufficiency". Authors have reported a rare side effect of refractory hyperkalemia secondary to Voriconazole. It was interesting to see the downward trend of potassium levels and resolution of adrenal insufficiency after stopping Voriconazole. Such case reports are important to be published as physicians should be aware of such rare side effects from these commonly used medications in the ICU setting.

Minor revisions:

- Authors can take out the date when patient presented.
- Tables and figures are essentially showing the same information. I would recommend authors use only graphs as these are showing exactly what happened with electrolyte abnormalities, and the downward trend after starting voriconazole.
- Following needs reference:
" Voriconazole has a potent antifungal effect. Voriconazole inhibits ergosterol synthesis in the fungal cell wall by inhibiting the 14-alpha demethylase enzymes hence causing eradication of fungal infection. Voriconazole leads to many drug-drug interactions because it causes inhibition of CYP 450 enzymes."

I hope these minor revision can be done by the authors to improve the content of the case report.

Thank you.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Gastroenterology and Transplant Hepatology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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