

Case study

Voriconazole associated hypertension: A Case report

Abstract

The present study report a case of a young female with serological evidence of past candida tropicalis and candida krusei infection who developed severe hypertension after she had repeated received voriconazole for few days. Voriconazole is a triazole antifungal agent with a broad spectrum of antifungal activity. A 23-year-old female presented with a 20-days history of left flank pain, vomiting, malaise, dysuria, urinary frequency, urgency, cloudy urine and malodorous urine. the symptoms such as hypertension and blurred vision were observed during the three hospitalizations, but the mechanism of the medicine still need to be verified by further examination such as hormone detection, blood mass spectrometry and so on.

Key Words

Triazole antifungal agent; Hypertension; Voriconazole

Introduction

Voriconazole is a triazole antifungal agent with a broad spectrum of antifungal activity. The most common side effects of voriconazole include dizziness, headache, diarrhea, and fatigue^{1,2}. Patients very rarely can

Comment [PBAS1]: (L1) The abstract does not mention research objectives, types of research, research methods, as well as research results, and conclusions, please correct it immediately

Comment [PBAS2]: (L6) In the introduction there is no explanation of the purpose of the study

Comment [PBAS3]: (L5) In the introduction no efforts have been made to overcome the problem that causes hypertension

Comment [PBAS4]: (L4) In the introduction there is no explanation about what causes hypertension

Comment [PBAS5]: (L3) In the introduction there is no mention of previous research

develop thrombocytopenia and hepatic damage. Although other anti-infective drugs with activity against bacteria such as levofloxacin and piperacillin tazobactam have been associated with drug induced hypertension³, the incidence rate of azole is very low. Here, we report a case of a young female with serological evidence of past candida tropicalis and candida krusei infection who developed severe hypertension after she had repeated received voriconazole for few days. This is case report of voriconazole-induced hypertension.

Comment [PBAS6]: (L2) In the introduction there is no reference

Case presentation

A 23-year-old female presented with a 20-days history of left flank pain, vomiting, malaise, dysuria, urinary frequency, urgency, cloudy urine and malodorous urine. She denied fever, chills, rigor, or abdominal pain. She had the horseshoe kidney for which she underwent surgical separation for 9 years. Three years ago, she was diagnosed with pyelic lithiasis, hydronephrosis and recurrent UTIs for which she was treated with extracorporeal shock wave lithotripsy and anti-infective drug. At the time of admission, the physical examination revealed anemic appearance without costovertebral angle tenderness and lower extremity edema. Urine analysis showed 109 WBCs and 227 RBCs per high power field / micro liter. The urine culture indicated 10*5 colony-forming units (cfu)/ml bacterial concentrations in specimen. Furthermore, candida krusei was

detected in different urine specimens (at least 3 times), which was resistant to fluconazole (MIC=64ug/ml), sensitive to voriconazole (MIC≤0.25ug/ml), amphotericin B (MIC≤0.25ug/ml). Abdominal KUB showed left urinary system double-J tube and left kidney stones. What's more, Abdominal ultrasonography revealed bilateral hydronephrosis and left kidney stones. A chest computed tomography (CT) scan and other routine laboratory test were unremarkable. The first clinical diagnosis indicated recurrent complex urinary tract infections and hydronephrosis. Because of the acute kidney injury (Serum creatinine 255μmol/L), we chooses voriconazole 300mg q12h for antifungal treatment.

Despite without history of hypertension, the patient occurred increased blood pressure (140-160/90-100mmHg) on the second day of taking voriconazole. These may be related to primary disease or drugs. In this regard, we closely monitored the changes of blood pressure instead of antihypertensive drugs. (Fig.1) Five days after taking voriconazole, the patient developed fatigue, anorexia, dizziness and blurred vision, accompanied by persistent hypertension (165/100mmHg). Transient loss of consciousness and syncope occurred on day 8, when blood pressure was markedly elevated at 175/95 mmHg. Further, 24h dynamic electrocardiogram results showed that blood pressure was significantly higher than before (average blood pressure was 140/89mmHg and the highest blood pressure was 165/105mmHg).

Comment [PBAS7]: (L9) In this article, it is necessary to explain what factors cause hypertension, and what efforts are being made to reduce hypertension

Comment [PBAS8]: (L8) In this article, are kidney disorders caused by taking hypertension medication, or are there other factors that cause kidney problems?

Comment [PBAS9]: (L7) In this article, the topic of the problem is not clear, whether it is hypertension or kidney problems. Decide what issues to discuss

Comment [PBAS10]: (L10) In this article, it is necessary to explain the side effects of taking hypertension drugs for a long time

Considering the variety causes of syncope, including cerebral events, metabolic disturbances, psychogenic patterns and intoxication, cranial computer tomography, serum hormone index and other form of laboratory examination were completed. Nevertheless, the results of ACTH, cortisol, catecholamine and cranial CT were within the normal range. <Tab.1> Consider that CYP2C19 is the major drug metabolizing enzyme of voriconazole, we also detected that the metabolic pattern of CYP2C19⁶ of the patient was moderate. Voriconazole was discontinued at day 15 considering of the sufficiency treatment and the improved urinary irritation symptoms. Ten days following cessation of voriconazole therapy her blood pressure returned to normal, and the patient was discharged from the hospital with an improved general condition.

Four months later, the patient was subsequently admitted to our department again for the recurrent UTIs, for which presented urinary tract irritation, fever, chill, and flank pain. Urine analysis showed 3159 WBCs per micro liter. The urine culture indicated 10^5 colony-forming units (cfu)/ml *Candida tropicalis* concentrations in specimen. She was restarted on voriconazole tablets (200mg q12h) in an attempt to treat recurrent UTIs. A markedly elevated blood pressure and dizziness were also observed on the second day after medication. (Fig.2) The valsartan was temporarily used to control the hypertension when the blood pressure above 150/90 mmHg. However, the blood pressure was still poorly controlled. Fifteen

days later, on discussion with the patient it was decided to withhold antifungal therapy and repeat laboratory testing. Then three days following cessation of voriconazole therapy her blood pressure returned to normal. Furthermore, head CT, electrocardiogram, blood routine, liver function, and hormones (ACTH, cortisol, catecholamines) was normalized.

Comment [PBAS11]: (L11) In an article, each paragraph must include a reference

Discussion

Relevance evaluation of voriconazole induced hypertension.

In this case, the patient was admitted to the hospital due to complicated urinary tract fungal infection, and was received voriconazole 200mg q12h . However, although without history of hypertension, a significant increase in blood pressure (141/85 mmHg) was observed in the next day. The patient then had blurred vision and further increased blood pressure (165 / 95 mmHg). Furthermore, on the 8th day after voriconazole infusion, transient unconsciousness were found with blood pressure of 175 / 95 mmHg. The unconsciousness of the patient is regarded to be caused by neurovascular response to the sudden increase in blood pressure, after excluding craniocerebral, cardiogenic and hypovolemic. Then the patient's blood pressure returned to normal after stop taking the drug. 4 months later, the patient still had unexplained blood pressure rise after using voriconazole for the UTIs. Furthermore, the blood pressure accordingly decreased to normal after stop taking the drug.

Although the relevant symptoms such as hypertension and neurovascular syncope were not founded in the instructions of voriconazole, repeated increase in blood pressure was related to the time of administration of voriconazole, and the patients' performances such as hypertension and blurred vision improved after stopping the drug. Above all, according to the analysis of the judgment principle specified by the adverse drug reaction monitoring center of the ministry of health^{4,7}, the newly appearing blurred vision, hypertension and neurovascular syncope were related to the using of voriconazole.

Dosage of voriconazole and related problems.

For complicated urinary tract infections, the voriconazole therapy (200mg q12h) is recommended according to The UAA-AAUS Guidelines for Urinary Tract Infections⁸. Voriconazole is a kind of triazole antifungal agent, which can selectively inhibits demethylation of 14 α -wool sterol mediated by fungal cytochrome P450 enzyme, delays biosynthesis of ergosterol, and against *Candida albicans*, *Candida paraplantatus*, *Candida tropicalis*⁹. The patient was hospitalized due to the complicated urinary tract infection. What's more, the voriconazole was used for the treatment of *enterococcus faecium* and *Candida tropicalis* which were cultured in clean midstream urine. The dosage and frequency of voriconazole were reasonable. Due to the genetic polymorphism of CYP2C19, Weiss J et al.¹⁰ found that 15% - 20% of the Asian population belongs to the slow

metabolism type, which can lead to the abnormal increase of plasma concentration of triazole antifungal drugs and the aggravation of its hepatotoxicity. However, we also detected that the metabolic pattern of CYP2C19 of the patient was moderate. Therefore, it is unlikely that excessive intake or slow metabolism of voriconazole leads the increased blood concentration and hypertension.

Analysis of the mechanism of hypertension induced by voriconazole.

Cardiac output and peripheral vascular resistance were crucial for the formation of blood pressure. When cardiac output is increased, blood pressure increases accordingly. Furthermore, cardiac output is also affected by cardiac systolic and diastolic function, heart rate and blood volume. In the routine examination, the patient's cardiac function examination including blood routine, myocardial enzyme spectrum, liver and kidney function, cardiac ultrasound, chest CT were generally normal. What is the mechanism of azole antifungal drugs leading to elevated blood pressure?

For example, another antifungal drug, posaconazole, has been reported to increase the level of aldosterone in the blood by activating renin-angiotensin-aldosterone-system (RAAS) pathway¹¹⁻¹³, so that it save the sodium and excrete potassium, resulting in typical hypertension and hypokalemia. Stopping posaconazole for 2 weeks, the patient's blood

pressure returned to normal. We doubt that whether voriconazole has the same mechanism as posaconazole in causing blood pressure to rise. However, in this case report, we monitored serum Renin-Aldosterone-Angiotensin II and serum potassium in the early stage of the hypertension period (1 week after the acute risen of blood pressure), which showed that there was no obvious abnormality. It may suggest that the hypertension in this case may not be caused by the activation of RAAS pathway. <Tab.1>

Nevertheless, on the one hand, aldosterone elevation is a chronic procedure. According to the literature reports¹⁴, the elevation of aldosterone in the patient with hypertension induced by posaconazole was detected at 4 days after the increase in blood pressure¹⁵. However, the serum 11-deoxycortisol level in this case only to be detected at the first week after admitted to the hospital, which is controversial for the real mechanism. Therefore, it cannot be ruled out whether the increase of blood pressure is caused by the activation of RAAS pathway. On the other hand, the blood concentration of voriconazole in this case was not detected. Above all, the mechanism of voriconazole causing the hypertension is still unknown.

Impact on follow-up medication

In conclusion, it is the first time that the acute increased hypertension

has been detected in a patient with the normal dosage of voriconazole. In this paper, the symptoms such as hypertension and blurred vision were observed during the three hospitalizations, but the mechanism of the medicine still need to be verified by further examination such as hormone detection, blood mass spectrometry and so on. The relevant cases should be collected in the follow-up clinical work for statistical analysis and mechanism investigation, in that to expanding the indications and adverse effects of antifungal drugs.

Above all, although posaconazole has been reported to cause hypertension in the past, there is no report of hypertension caused by voriconazole, which should be paid attention to by clinicians.

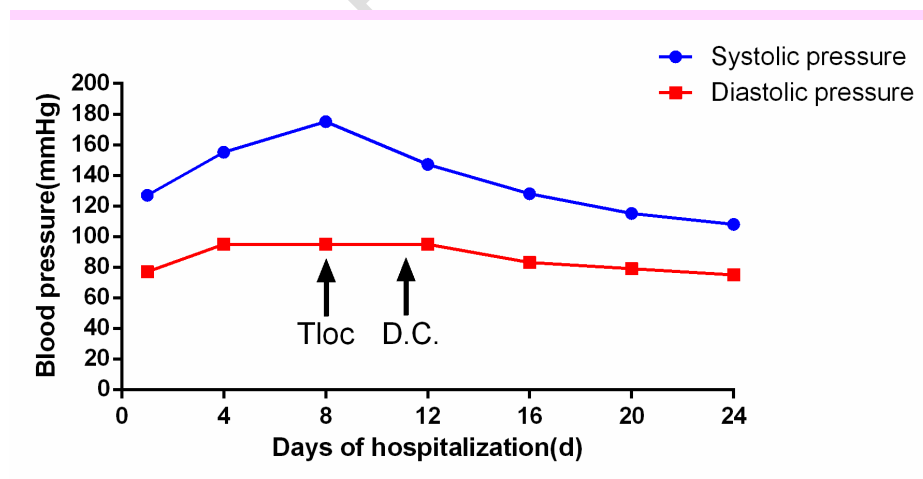


Figure 1. Fluctuation of blood pressure after voriconazole administration.

(Tloc, Transient loss of consciousness; D.C.: Discontinue)

The day after admitted (days)	Potassium (mmol/L)	Renin (pg/ml)	Aldosterone (pg/ml)	Angiotensin II (pg/ml)
0	3.7	4.44	101.44	121.75
3	4.0	9.04	120.33.	135.65
6	3.9	10.84	89.35	101.15

Table 1. Serum potassium and Renin-Aldosterone-Angiotensin II level association with the voriconazole administration.

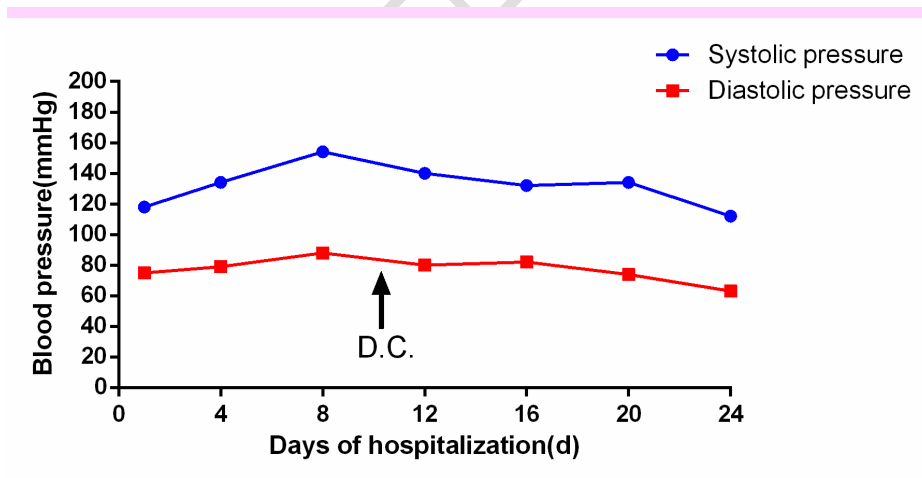


Figure 2. Fluctuation of blood pressure after voriconazole administration.

(D.C.: Discontinue)

References:

Comment [PBAS12]: (L12) In an article, each discussion should be compared with previous research and include references

Comment [PBAS13]: (L13) An article, there must include a conclusion

-
1. Levine, M. T. & Chandrasekar, P. H. Adverse effects of voriconazole: Over a decade of use. *Clin Transplant* **30**, 1377–1386 (2016).
 2. Hedrick, J. & Droz, N. Voriconazole-Induced Periostitis. *N Engl J Med* **381**, e30 (2019).
 3. Kaye, K. S. *et al.* Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection: The TANGO I Randomized Clinical Trial. *JAMA* **319**, 788–799 (2018).
 4. Benitez, L. L. & Carver, P. L. Adverse Effects Associated with Long-Term Administration of Azole Antifungal Agents. *Drugs* **79**, 833–853 (2019).
 5. World Health Organization (WHO). WHO draft guidelines for adverse event reporting and learning systems Geneva, Switzerland: The Organization; 2005.
 6. Moriyama, B. *et al.* Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C19 and Voriconazole Therapy. *Clin Pharmacol Ther* **102**, 45–51 (2017).
 7. McConachie, S. M., Volgyi, D., Moore, H. & Giuliano, C. A. Evaluation of adverse drug reaction formatting in drug information databases. *J Med Libr Assoc* **108**, 598–604 (2020).
 8. Choe, H.-S. *et al.* Summary of the UAA-AAUS guidelines for urinary tract infections. *Int J Urol* **25**, 175–185 (2018).

-
9. Govindarajan, A., Bistas, K. G., Ingold, C. J. & Aboeed, A. Fluconazole. in *StatPearls* (StatPearls Publishing, 2021).
 10. Mikus, G., Scholz, I. M. & Weiss, J. Pharmacogenomics of the triazole antifungal agent voriconazole. *Pharmacogenomics* **12**, 861–872 (2011).
 11. Nguyen, M.-V. H. *et al.* Posaconazole Serum Drug Levels Associated With Pseudohyperaldosteronism. *Clin Infect Dis* **70**, 2593–2598 (2020).
 12. Inderbinen, S. G., Zogg, M., Kley, M., Smieško, M. & Odermatt, A. Species-specific differences in the inhibition of 11 β -hydroxysteroid dehydrogenase 2 by itraconazole and posaconazole. *Toxicol Appl Pharmacol* **412**, 115387 (2021).
 13. Beck, K. R., Thompson, G. R. & Odermatt, A. Drug-induced endocrine blood pressure elevation. *Pharmacol Res* **154**, 104311 (2020).
 14. Sanchez-Niño, M. D. & Ortiz, A. Unravelling drug-induced hypertension: molecular mechanisms of aldosterone-independent mineralocorticoid receptor activation by posaconazole. *Clin Kidney J* **11**, 688–690 (2018).
 15. In Vivo 11 β -Hydroxysteroid Dehydrogenase Inhibition in Posaconazole-Induced Hypertension and Hypokalemia - PubMed. <https://pubmed.ncbi.nlm.nih.gov/28533238/>.

Comment [PBAS14]: (L14) In articles, the bibliography must be arranged alphabetically not by number, and using the Mendeley program