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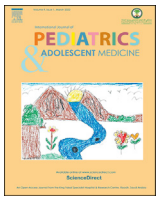

Case report

Voriconazole- induced severe hypokalemic rhabdomyolysis: A case report

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ABSTRACT

We report a child who presented with lower limb weakness and inability to walk, laboratory confirmed severe hypokalemia with typical electrocardiogram changes, and evidence of rhabdomyolysis while on voriconazole treatment for *Pseudallescheria boydii* soft tissue infection. Although voriconazole is a well-tolerated antifungal agent, hypokalemia is a well-known, yet uncommon side effect associated with its use. Furthermore, hypokalemic-rhabdomyolysis has not been reported with voriconazole use alone. Maintaining the clinical suspicion about the potential association between voriconazole and hypokalemic-rhabdomyolysis can lead to prompt recognition and intervention.

1. Introduction

Voriconazole is a broad-spectrum triazole antifungal agent that is generally well tolerated. Hypokalemia is not a common side effect of voriconazole [1]. Rhabdomyolysis has been reported with the use of voriconazole in conjunction with other medications, but not when used alone [2–4]. In this review, we report a child with soft tissue fungal infection who developed severe hypokalemia that led to rhabdomyolysis after voriconazole treatment. Recognition of such an association can drive prompt diagnosis and earlier intervention to optimize patient care.

2. Case summary

Our patient is a nine-year-old otherwise healthy girl, diagnosed with *Pseudallescheria boydii* traumatic soft tissue infection and started on oral voriconazole therapy (8 mg/kg/dose twice daily) following surgical debridement and a ten-day course of intravenous liposomal amphotericin B (Ambisome®) (5 mg/kg/day). On the eighth day of voriconazole treatment, she developed bilateral leg pain after exertion, when in a play area. Two days later, she developed bilateral lower limb weakness, difficulty in walking, and subsequently developed complete inability to walk. There was no history of fever, respiratory symptoms, abdominal complaints, joint problems or any CNS manifestations. She also denied any urinary symptoms or skin rash and no history of trauma was recorded. She did not consume any herbs or medications other than voriconazole.

Physical examination demonstrated an ill-looking, but conscious, oriented, and alert girl. Her vital signs were stable. Examination of the extremities revealed bilateral calf tenderness on palpation, but there was no hotness, redness or swelling. Muscle power was 5/5 in all extremities. No other sensory abnormalities were detected and the rest of her physical examination was recorded to be normal.

Her urine dipstick showed RBC +4. Laboratory workup revealed low serum potassium of 2.2 mmol/l. Muscle enzymes were abnormally high that included creatine kinase of 13006 U/L, lactate dehydrogenase of 1213 U/L, aspartate aminotransferase of 516 U/L, and serum myoglobin of 274 mmol/l. The values of sodium, chloride, phosphate, and calcium were all within normal range. Hence,

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voriconazole was discontinued immediately. She was managed with fluid hydration and potassium intravenous boluses. Her potassium level continued to decline (to 1.7 mmol/l) that reflected on her electrocardiogram; showing inverted T-wave and abnormal U-wave. She was shifted to the intensive care unit for cardiac monitoring and was given fluid hydration, and continuous potassium infusion and boluses. Clinically, her calf muscles became more tender, warm, and swollen. She developed muscle stiffness that resulted in painful flexion of the bilateral proximal interphalangeal joints and subsequent extension of the wrist. The patient was unable to stand without support. The level of creatine kinase increased to 44,644 U/L, whereas further investigations showed negative EBV and CMV serology, negative blood and urine culture results, and normal abdominal ultrasound. On the sixth day at the hospital, subsequent clinical improvement was noted. She returned home on the 14th hospital day with a serum potassium level of 4 mmol/l. She was fully ambulatory with no residual weakness or pain. Voriconazole drug level was not available.

3. Discussion

To our knowledge, this is the first case of serious rhabdomyolysis caused by the use of voriconazole and no other myotoxic drugs in a child. Fatal and life-threatening rhabdomyolysis was reported in people using voriconazole in combination with other medications like statins [2–4]. The development of myotoxicity could be associated with the use of some medications such as corticosteroids, amiodarone, colchicine, cyclosporine, zidovudine, and vincristine [5] among others, none of which was consumed by our patient. We calculated a score of 6 on the Naranjo adverse drug reaction probability scale which indicates propable causality for the use of voriconazole and the development of rhabdomyelesis. Had voriconazole drug level been done, it would have only increased the Naranjo Scale Score to 7, still a propable causality.

The mechanism by which voriconazole can cause rhabdomyolysis is poorly understood. Hypokalemia, induced by voriconazole, can trigger rhabdomyolysis. Severe potassium depletion (serum potassium less than 2.5 meq/L) can lead to muscle cramps, muscle weakness, rhabdomyolysis, myoglobinuria [6], ECG abnormalities, and quadriplegia [7]. Decreased potassium release resulting from profound hypokalemia can diminish blood flow to muscles during exertion, and it leads to ischemic rhabdomyolysis [8]. Out of 227 adverse events related to the use of voriconazole in 187 patients, hypokalemia constituted for only two events [1]. Compared to amphotericin B, the prevalence of voriconazole induced hypokalemia is 16.4%, and only 2.4% have potassium levels below 2.5 mmol/l [9]. Severe hyperkalemia occurs secondary to massive muscle breakdown, leading to cardiac dysrhythmias and possible cardiac arrest [7,10]. Our patient suffered from severe hypokalemia and required cardiac monitoring in the intensive care unit because of electrocardiogram changes. During the course of her illness she did not have hyperkalemia that suggests primary rhabdomyolysis.

Amphotericin B can cause hypokalemia [9] and hypokalemic-rhabdomyolysis [11]. Our patient received liposomal amphotericin B (Ambisome®) for 10 days in the hospital. Before discharge, her serum potassium and renal function tests were normal. The mean half-life of amphotericin B is long [12] and after using it, renal impairment can persist up to 6 months [13]. Hypokalemia was reported to last up to one-month after the discontinuation of amphotericin B [14]. In these reports, hypokalemia and/or renal impairment developed when amphotericin B was received and it persisted thereafter. Our literature search did not reveal any reports of hypokalemia development after the discontinuation of amphotericin B treatment.

4. Conclusion

Severe hypokalemia, induced by the use of voriconazole alone, leading to rhabdomyolysis is a rare adverse event. This condition is possibly under-recognized and results from the scarcity of publications. We recommend baseline screening of potassium level to be performed when considering voriconazole treatment and close monitoring of potassium levels after treatment initiation. Special attention must be paid when using other medications that can affect the potassium level. It is important to recognize this potential association between voriconazole and hypokalemic-rhabdomyolysis and to include it in the working diagnosis of patients presented with compatible symptoms.

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Ethical statement

Consent was taken from the parent of the child.

Authors contributions

Abdulsalam Alawfi: Conceptualization, Literature review, Writing - original draft (case summary and discussion)

Abdullah Algarni: Conceptualization, Literature review

Jocelyn Donesa: Data curation, Writing - original draft (introduction)

Motasem Abuelreish: Project administration, Supervision, Writing - review and editing

Declaration of competing interest

None.

References

[1] Eiden C, Peyrière H, Cociglio M, Djezzar S, Hansel S, Blayac JP, et al. Adverse effects of voriconazole: analysis of the French Pharmacovigilance Database. Ann Pharmacother 2007 May;41(5):755–63.
[2] Doran E, Ledema J, Ryan L, Coombes I. Fatal rhabdomyolysis following voriconazole and simvastatin. Aust Prescr 2012 Jun;35(3):88–9. https://doi.org/10.18773/austprescr.2012.040.
[3] Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. Ann Pharmacother 2002 Feb;36(2):288–95. https://doi.org/10.1345/aph.1A289.
[4] McKelvie PA, Dennett X. Myopathy associated with HMG-CoA reductase inhibitors (statins): a series of 10 patients and review of the literature. J Clin Neuromuscul Dis 2002 Jun;3(4):143–8. https://doi.org/10.1097/00131402-200206000-00002.
[5] Mor A, Wortmann RL, Mitnick HJ, Pillinger MH. Drugs causing muscle disease. Rheum Dis Clin N Am 2011 May;37(2):219–31. https://doi.org/10.1016/j.rdc.2011.01.005.
[6] Shintani S, Shiigai T, Tsukagoshi H. Marked hypokalemic rhabdomyolysis with myoglobinuria due to diuretic treatment. Eur Neurol 1991;31(6):396–8. https://doi.org/10.1159/000116702.
[7] Dubey AP, Viswanath S, Suhag V, Pathak A, Rathore A, Kapoor A. Oral voriconazole causing severe hypokalemia, acute quadriplegia and prolonged QT interval: a rare case report. WJPMR 2016;2(2):60–2.
[8] Knochel JP, Schlein EM. On the mechanism of rhabdomyolysis in potassium depletion. J Clin Invest 1972 Jul;51(7):1750–8. https://doi.org/10.1172/JCI106976.
[9] Walsh TJ, Pappas P, Winston DJ, Lazarus HM, Petersen F, Raffalli J, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med 2002 Jan 24;346(4):225–34. https://doi.org/10.1056/NEJM200201243460403.
[10] Efstratiadis G, Voulgaridou A, Nikiforou D, Kyventidis A, Kourkouni E, Vergoulas G. Rhabdomyolysis updated. Hippokratia 2007 Jul;11(3):129–37.
[11] Marking U, den Boer M, Das AK, Ahmed EM, Rollason V, Ahmed BN, et al. Hypokalaemia-induced rhabdomyolysis after treatment of post-Kala-azar dermal leishmaniasis (PKDL) with high-dose AmBisome in Bangladesh - a

case report. PLoS Neglected Trop Dis 2014 Jun 12;8(6):e2864. https://doi.org/10.1371/journal.pntd.0002864.
[12] Heinemann V, Bosse D, Jehn U, Kähny BR, Wachholz K, Debus A, et al. Pharmacokinetics of liposomal amphotericin B (Ambisome) in critically ill patients. Antimicrob Agents Chemother 1997 Jun;41(6):1275–80. https://doi.org/10.1128/AAC.41.6.1275.
[13] Deray G. Amphotericin B nephrotoxicity. J Antimicrob Chemother 2002 Feb;49(Suppl 1):37–41. https://doi.org/10.1093/jac/49.suppl_1.37.
[14] Ali A, Aziz SA, Khan A, Gelani S. Persistent hypokalemia in an acute lymphoblastic leukemia patient. Indian J Med Paediatr Oncol 2009 Jul;30(3):103–4. https://doi.org/10.4103/0971-5851.64255.