



Case Report

Cross-reactivity between voriconazole, fluconazole and itraconazole

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SUMMARY

What is known and objective: Hypersensitivity to triazoles is a rare occurrence and cross-reactivity between agents is unknown. We present a successful voriconazole challenge in a patient allergic to fluconazole and itraconazole.

Case summary: A 41-year-old immunocompetent male with coccidioidomycosis developed fever, eosinophilia and maculopapular rash from fluconazole. Switching to itraconazole resulted in worsening of the rash and skin sloughing over 25% of his body. He was given an oral-graded challenge of voriconazole which he tolerated without incident.

What is new and conclusion: This is the first report of a lack of cross-reactivity between itraconazole and voriconazole.

WHAT IS KNOWN AND OBJECTIVES

The rate of hypersensitivity reactions and cross-reactivity within the triazole antifungal class remains poorly described. Although there are a number of cases in the literature concerning triazole allergic reactions, the rate of cross-reactivity between triazole agents remains unknown and poses a significant challenge to healthcare providers managing patients who develop an allergy to an azole, but who require continued azole therapy.^{1–4} In 2009, Pinto and Chan described a successful supervised graded challenge with oral voriconazole in a patient who developed a systemic allergic reaction to fluconazole, thus implying that no cross-reactivity exists between fluconazole and voriconazole.⁵ Since that time, however, there have been no other additional accounts to confirm lack of cross-reactivity between fluconazole and voriconazole, nor any reports of success or failure with a voriconazole challenge with an azole allergy other than fluconazole.⁶ We report successful use of Pinto and Chan's voriconazole challenge in a patient who had allergic reactions to both fluconazole and itraconazole. To our knowledge, this is also the first case to show a lack of cross-reactivity between voriconazole and itraconazole.

DETAILS OF THE CASES

The patient was a 41-year-old immunocompetent, human immunodeficiency virus-negative male who presented with positive coccidioidomycosis (Cocci) serology titres, positive *C. immitis* sputum and bronchioalveolar lavage cultures, and was without

eosinophilia (1.6–3.3%). He was discharged on metformin, lisinopril and fluconazole. At follow-up, seventeen days later, he had mild rash covering his arms and trunk, abdominal pain and nausea with vomiting. He was admitted to the hospital, medications were held and he was treated for acute renal failure. At this time, his eosinophil count was 22.0%. His kidney function improved and he was restarted on fluconazole at 400 mg twice daily. Fluconazole was discontinued after 3 days due to persistent fever (Tmax 103.0 F) and worsening maculopapular rash that progressed to cover his entire body. Two days later, after the rash had improved and vitals stabilized, the patient was started on voriconazole (fluconazole Naranjo score = 8, probable allergic reaction). He received a total of four voriconazole doses without incident before being discharged. He was unable to obtain voriconazole upon discharge due to insurance issues and 3 days later was started on itraconazole. He was readmitted 2 days later for subjectively worsening maculopapular rash on the arms and trunk which now included skin sloughing over 25% of his body. Itraconazole was discontinued (itraconazole Naranjo score = 4, possible allergic reaction). He was transitioned to outpatient lipid-based amphotericin B and tolerated treatment for 5 months before being re-challenged on oral therapy with voriconazole. A graded challenge was completed as outlined by Pinto and Chan (25 mg daily on day one followed by 75 mg b.i.d., 150 mg b.i.d. and 300 mg daily on each subsequent day and then 200 mg b.i.d. thereafter).⁵ No signs or symptoms of allergic reaction were observed during the voriconazole challenge. Eosinophilia persisted for a total of 2 months. The patient tolerated more than 2 years of voriconazole therapy before being lost to follow-up.

WHAT IS NEW AND CONCLUSION

Allergic reactions to triazoles are rare and cross-reactivity between members in the class remains unknown. To our knowledge, this is the first report of a lack of cross-reactivity between itraconazole and voriconazole. This case supports previously described cross-reactivity between fluconazole and itraconazole, and a lack of cross-reactivity between fluconazole and voriconazole and stands in opposition with DiLeo and colleagues who found a lack of cross-reactivity between fluconazole and itraconazole.^{2,5,7}

CONFLICT OF INTERESTS

The authors report no conflict of interests.

DISCLOSURE

The authors have nothing to disclose, and the presented case report occurred during the routine care of patients at our facility.

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