

Title: Lack of Allergic Cross-Reactivity between Fluconazole and Voriconazole

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TO THE EDITOR- We report a patient with cerebral cryptococcosis who developed a systemic allergic reaction to fluconazole and was successfully challenged with voriconazole. This allergic reaction is likely to have a different pathologic mechanism to hepatotoxicity without allergy where others have reported a lack of cross-reaction between, and successful challenge with, fluconazole and voriconazole [1], and voriconazole and posaconazole [2].

A 65 year old immunocompetent, HIV-negative male developed confusion, right sided weakness and neglect. MRI imaging demonstrated two lesions in the left frontal lobe and left parietal region. Brain biopsy confirmed *Cryptococcus gattii*. He commenced therapy with fluconazole 400mg daily. Other medications included phenytoin 300mg nocte, paracetamol 1g qid, ranitidine 150mg bd and dexamethasone 4mg bd on a weaning schedule over 16 days. Liver function tests were normal. In the third week of treatment, the patient noted an itchy erythematous maculopapular rash involving his buttocks. The phenytoin was ceased and the rash initially improved. Two weeks later the rash recurred, this time involving his abdomen, torso, legs and arms, and was associated with periorbital oedema and right arm oedema. There were no other features of anaphylaxis such as hypotension, dyspnoea or wheeze. The fluconazole was ceased and antihistamines were commenced. Over the next week the patient developed an asymptomatic increase in his liver enzyme levels. His GGT and ALT became elevated, reaching peaks of 626 U/L and 58U/L, respectively (figure 1). There was concurrent eosinophilia with a peak of $2.5 \times 10^9/L$ (figure 1). Skin biopsy showed an inflammatory cell infiltrate with the presence of eosinophils, consistent with a drug reaction. After resolution of the eosinophilia and liver function abnormalities, three options were considered. A desensitisation to fluconazole was thought to be unacceptable given the severity of the systemic reaction, presence of oedema and eosinophilia. Use of a non-azole class of antifungals such as amphotericin would have necessitated long term intravenous access and

was not practical for the patient who was keen to resume work as soon as possible. So due to the availability of an oral preparation, he underwent a supervised graded challenge with oral voriconazole, starting at a dose of 25mg daily on day 1, 75mg bd on day 2, 150mg bd on day 3, 300mg daily on day 4 then 200mg bd thereafter. There was no recurrence of symptoms, liver enzyme elevation or eosinophilia.

The patient's cerebral cryptococcosis has continued to improve clinically and radiologically. At the time of writing, the patient was followed up for a period of eight months. In this case, the absence of pre-existing liver disease, presence of eosinophilia, rash and periorbital oedema supports an immunoallergic reaction to fluconazole.

While cutaneous side effects from fluconazole are common, hypersensitivity reactions are rare [3]. There are three reports of severe systemic hypersensitivity reactions involving rash, oedema, hepatotoxicity or eosinophilia [4, 5, 6], including an attempted rapid desensitisation for a presumed IgE-mediated reaction [6]. Only one of these documented the presence of eosinophilia [4]. None describes successful challenge with another azole. To our knowledge there is one report of angio-oedema as a side effect of voriconazole, however this was tolerable and did not require cessation of therapy [7]. Other reports have documented the absence of cross-reactivity among azole derivatives, where itraconazole was used successfully in place of fluconazole in a patient with maculopapular rash diagnosed by oral challenge test [8].

We conclude from our experience with this case and review of the literature, that severe hypersensitivity reactions to fluconazole can occur and that voriconazole can be successfully introduced without cross-sensitisation occurring. In addition to documenting a systemic

allergic reaction to fluconazole, our case demonstrates successful challenge with another azole. Hence in situations of azole hypersensitivity, clinicians could consider cautious use of another azole before choosing another class of antifungal agent.

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Figure 1. Changes in liver function test values and eosinophil count after initiation of antifungal therapy. GGT, γ -glutamyl transpeptidase; ALT, alanine transaminase.

