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Tolerability of long-term fluconazole therapy

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Background: Fluconazole is a commonly prescribed first-generation triazole antifungal. Although the toxicity profile of fluconazole has been evaluated in clinical trials, there are scant data regarding its tolerability with long-term therapy. Treatment guidelines for coccidioidomycosis recommend fluconazole therapy and severe or disseminated infections can require lifelong treatment.

Objectives: To assess the prevalence of long-term fluconazole adverse effects, their consequences for antifungal therapy, time to adverse effects and the association between dosing regimen or fluconazole serum level and adverse effect status.

Methods: We conducted a single-centre, retrospective study of adult patients (≥18 years) with proven or probable coccidioidomycosis receiving long-term fluconazole therapy for an intended duration of ≥28 days.

Results: Out of 124 patients included, 64 (51.6%) experienced adverse effects. The most common adverse effects were xerosis (16.9%), alopecia (16.1%) and fatigue (11.3%). Of the 64 patients experiencing adverse effects, 42 (65.6%) required a therapeutic intervention such as dose reduction, discontinuation or switch to a new antifungal. Patients experiencing adverse effects were prescribed higher total daily fluconazole doses (6.7 versus 5.7 mg/kg; $P < 0.01$). The median therapeutic drug levels did not differ significantly between patients who experienced adverse effects and those who did not (36.1 versus 28.1 mg/L; $P = 0.35$).

Conclusions: A significant number of patients receiving long-term fluconazole therapy for coccidioidomycosis experienced adverse effects. Of these, around two-thirds required a therapeutic change. We believe these findings are representative of the adverse effect profile of long-term fluconazole therapy as it is used in clinical practice for coccidioidomycosis as opposed to use in clinical trials.

Introduction

Invasive fungal infections continue to increase yearly and represent a significant cause of morbidity and mortality worldwide.[1–6] Fluconazole is a first-generation triazole antifungal used in the treatment of several fungal infections. Treatment courses of fluconazole are often short, ranging from 1 day to 3 weeks for many indications.[7,8] However, there are fungal diseases, such as coccidioidomycosis, that can require fluconazole therapy for considerably longer treatment durations.

Coccidioidomycosis is caused by the dimorphic fungi *Coccidioides immitis* and *Coccidioides posadasii*. It is an ongoing concern in highly endemic areas, including the south-western USA and South America, as it can cause up to 30% of community-acquired pneumonia cases within these regions,[1,9] and the number of cases continues to increase yearly.[10]

Treatment guidelines for coccidioidomycosis recommend high doses of fluconazole (at least 400 mg daily) and in some cases prolonged treatment courses can extend to lifelong therapy depending on disease burden, clinical response and host immune factors.[11] In our experience, long-term courses of fluconazole therapy are associated with frequent adverse effects. These range from the relatively benign, such as nausea, to severe and life-threatening hepatitis.[12–14]

The toxicity profile of fluconazole has been primarily characterized in short-term clinical trials, typically <4 weeks in duration, and the adverse effects experienced by patients requiring prolonged therapy have yet to be studied.[7] The characterization of the adverse effect profile of prolonged fluconazole therapy can aid healthcare providers in prompt recognition and the use of alternative treatment strategies when necessary. In this study, we describe the occurrence and type of adverse effects of long-term

fluconazole therapy during treatment of coccidioidomycosis. Our primary objectives were to (i) characterize the occurrence and types of adverse effects of long-term fluconazole therapy, and (ii) evaluate the need for therapeutic interventions for these adverse effects. Our secondary objectives were to (i) compare the mg/kg daily dose and fluconazole serum levels (obtained at random) between patients who experienced adverse effects and those who did not, and (ii) assess the time to adverse effects.

Methods

The University of California, Davis Health system is located in Sacramento, CA, USA and serves as a tertiary care referral for nearby counties in highly endemic regions with annual coccidioidomycosis case rates of up to 251.7 cases per 100000 persons.[15] One hundred and fifty consecutive patients with coccidioidomycosis receiving fluconazole for >28 days were reviewed using ICD-9 and ICD-10 codes with either primary or secondary diagnoses for all forms of coccidioidomycosis (acute pulmonary coccidioidomycosis, chronic pulmonary coccidioidomycosis, unspecified pulmonary coccidioidomycosis, cutaneous coccidioidomycosis, coccidioidomycosis meningitis, disseminated coccidioidomycosis, other forms of coccidioidomycosis or unspecified coccidioidomycosis) cross-referenced with the hospital pharmacy database.

Manual chart review confirmed the diagnosis of coccidioidomycosis and the receipt of fluconazole for >28 days and at least two patient visits were required for inclusion. Adverse effects, or an appreciably harmful or undesired reaction,[16] attributed to fluconazole therapy were documented by the original treating physician. Therapeutic interventions were defined as fluconazole discontinuation, dose reduction or change to an alternative antifungal agent. In patients who experienced fatigue, headache, rash or arthralgia on treatment, we assessed for resolution or improvement of these symptoms after therapeutic intervention to distinguish between symptoms of coccidioidomycosis disease and adverse effects from fluconazole.

Patient baseline demographics (age, sex, ethnicity and comorbidities that may have impacted fluconazole clearance) and medication records were abstracted from patient charts. We additionally compared the total daily dose in mg/kg per day between patients who experienced adverse effects and those who did not. Fluconazole serum concentrations, when available, were also compared against patient adverse effect status. The time to adverse effect from the date of fluconazole initiation to the date of the first reported adverse effect was also abstracted.

We performed statistical analyses using STATA version 13.1 IC (StataCorp, College Station, TX, USA) and used a 5% significance level. Descriptive statistics were performed to characterize the occurrence and type of adverse effects as well as their effect on therapeutic course. Continuous variables were assessed for normality and homoscedasticity and analysed by the *t*-test or Mann–Whitney *U*-test, and for categorical variables we employed Pearson's χ^2 or Fisher's exact test where appropriate.

Results

We identified 137 adults with coccidioidomycosis and a fluconazole prescription for at least 28 days with at least two clinical visits. Thirteen patients were excluded (8 without diagnosed coccidioidomycosis and 5 for inadequate documentation on follow-up visits to evaluate fluconazole), leaving 124 patients in the final sample for analysis. The patients were predominantly male (76.6%) with a median age of 46.1 years and 66 patients (53.2%) experiencing pulmonary disease. Additional patient characteristics can be found in Table S1 (available as Supplementary data at *JAC* Online). Fluconazole therapy lasted for a median duration of 147 days (IQR 59.5–399 days) with the most frequently prescribed dose being 400 mg daily (range 100–1600 mg).

Table 1. Occurrences of adverse effects and their need for a therapeutic intervention

Adverse effect[a]	Occurrence, *n* (%)	Therapeutic intervention[b], *n* (%[c])
Any	64 (51.6)	42 (65.6)
Xerosis	21 (16.9)	8 (38.1)
Alopecia	20 (16.1)	11 (55)
Fatigue	14 (11.3)	13 (92.9)
Nausea and vomiting	12 (9.7)	10 (83.3)
Anorexia	8 (6.5)	7 (87.5)
Headache	8 (6.5)	6 (75)
Arthralgia	7 (5.6)	5 (71.4)
Transaminitis	7 (5.6)	0 (0)
Cheilitis or dry lips	6 (4.8)	4 (66.7)
Xerostomia	4 (3.2)	2 (50)
Dizziness	3 (2.4)	3 (100)
Neuropathy	3 (2.4)	2 (66.7)
Abdominal discomfort	2 (1.6)	2 (100)
ALP elevation	2 (1.6)	2 (100)
Drug–drug interaction[d]	2 (1.6)	2 (100)
Dysgeusia	2 (1.6)	0 (0)
Other[e]	8 (6.5)	4 (50)

ALP, alkaline phosphatase.
[a]A patient could experience more than one adverse effect.
[b]Required therapeutic intervention consisting of discontinuation, change to alternative azole or dose reduction.
[c]Percentage is based on the frequency of that respective adverse effect.
[d]Two documented drug–drug interactions that resulted in hospital admission (hypotension due to fluconazole and amlodipine; and hypotension and bradycardia due to fluconazole, amiodarone and amlodipine).
[e]One patient each: hypotension, impotence, anxiety, seizure, brittle nails, unspecified hepatotoxicity, weakness and aphthous ulcers.

Sixty-four patients (51.6%) experienced an adverse effect that was directly attributed to fluconazole by their treating physician during their course of therapy (Table 1). The most common adverse effects experienced were xerosis in 21 patients (16.9%), alopecia in 20 patients (16.1%) and fatigue in 14 patients (11.3%). Of the 64 patients with an adverse effect, 42 (65.6%) required a therapeutic intervention (Table S2). Of the 16 patients experiencing adverse effects similar to symptoms of coccidioidomycosis (arthralgia, fatigue, rash or headache) who required a therapeutic intervention, 15 had documented resolution or improvement in these adverse effects after therapeutic intervention. Notably, no patients included in our study experienced provider-documented QTc prolongation or haematopoietic abnormalities.

The median time to adverse effect was 119 days (Figure 1), at which point most patients are expected to have shown significant symptomatic improvement.[17] Patients experiencing adverse effects received higher total daily doses of fluconazole than those that did not (6.7 versus 5.7 mg/kg; $P < 0.01$). Fluconazole serum levels obtained at random were available for 37 different fluconazole regimens from 36 patients (Table S3). There was no statistically significant difference in median fluconazole serum levels

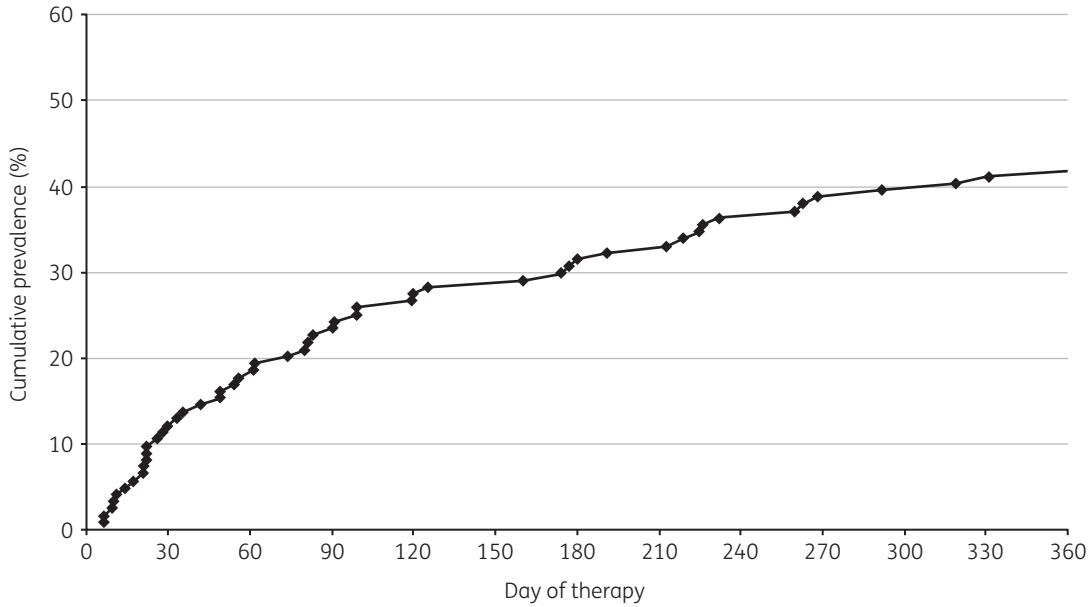

Figure 1. Time to fluconazole adverse effects.

between patients who did and did not experience an adverse effect (36.1 versus 28.1 mg/L; $P = 0.35$), which could be explained by the relatively small number of levels available for analysis. Women were more likely to experience an adverse effect than men ($P < 0.01$, Table S1).

Discussion

Fluconazole remains one of the most commonly prescribed antifungal agents in the treatment of coccidioidomycosis, and long-term therapy is frequently required. Despite its frequent use, no prior study has sought to characterize the tolerability of long-term fluconazole therapy in coccidioidomycosis.

In our study, approximately half of patients experienced adverse effects while on long-term fluconazole therapy for coccidioidomycosis and nearly two-thirds of these patients required a therapeutic intervention. The prevalence of adverse effects in our study was higher than that found in a prior report.[18] These differences may represent a decreased willingness of patients and providers to tolerate adverse effects of fluconazole given the availability of alternative antifungal agents. The median time to adverse events was ∼4 months, which falls within the typical duration of therapy (3–6 months).[11]

We found a statistically significant difference in total daily dose in patients experiencing adverse effects, suggesting adverse effects are likely dose dependent. Women were more likely to experience adverse effects than men, which could be owing to relatively higher mg/kg doses or differences in pharmacokinetics of fluconazole between sexes. There were no other patient characteristics significantly associated with adverse effect status, although there was a trend towards higher median age and a greater proportion of baseline renal dysfunction in patients experiencing adverse effects.

The most frequent adverse events noted in our study (xerosis, alopecia, fatigue, etc.) are generally benign and reassurance can be offered to patients. However, the availability over the past decade of alternative triazoles with reduced and differing toxicity profiles appears to have decreased patient and physician tolerance of possible medication-induced adverse effects. These alternative options can be utilized when necessary, and have had favourable therapeutic outcomes.[19]

This study has several limitations. It was a retrospective study dependent on thorough documentation in the electronic medical record for accuracy and thus adverse events may have been underestimated. Additionally, it is possible adverse effects of fluconazole and symptoms of coccidioidomycosis were conflated; however, we attempted to control for this by assessing whether adverse effects that could be mistaken for common symptoms of coccidioidomycosis subsided after therapeutic interventions. Furthermore, symptoms of coccidioidomycosis abate over time, rather than appearing >3 months after the initiation of treatment.[17]

We were unable to detect a statistically significant difference in fluconazole serum levels in patients who experienced adverse effects versus those who did not. We believe this assessment could have been underpowered to detect a difference owing to the few fluconazole levels available as it is not routine clinical practice to monitor fluconazole serum levels, and there may have been a bias towards ordering fluconazole levels in patients suspected of having an adverse event. Furthermore, levels that were collected were random levels and not troughs, which could have impacted our findings.

Conclusions

Our findings suggest that a significant number of patients receiving long-term fluconazole therapy for coccidioidomycosis experience adverse effects. Of these, around two-thirds required a therapeutic change. We believe these findings are representative of the adverse effect profile of fluconazole as it is used in clinical practice as opposed to use in clinical trials. Although our cohort consisted of

patients with coccidioidomycosis, we believe the adverse effects are likely to be seen in patients on long-term fluconazole for the treatment of other diseases. Providers should be vigilant in monitoring for these adverse effects and consider dose adjustments or therapeutic alternatives where appropriate.

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Author contributions

M. R. D., M. H. N., M. A. D. and G. R. T.: conception and design; analysis and interpretation of data; drafting the article; and final approval.

Supplementary data

Tables S1–S3 are available as Supplementary data at *JAC* Online.

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