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Fluoride Excess in Coccidioidomycosis Patients Receiving Long-Term Antifungal Therapy: an Assessment of Currently Available Triazoles

George R. Thompson III,[a,b] Derek Bays,[a] Stuart H. Cohen,[b] and Demosthenes Pappagianis[a]

Department of Medical Microbiology and Immunology, Coccidioidomycosis Serology Laboratory, University of California—Davis, Davis, California, USA,[a] and Department of Internal Medicine, Division of Infectious Diseases, University of California Davis Medical Center, Sacramento, California, USA[b]

The use of voriconazole, a trifluorinated antifungal, has been associated with the development of fluoride excess and periostitis/exostoses. We evaluated a cohort of patients on long-term triazole therapy and found that other fluorinated triazoles (fluconazole and posaconazole) conferred no risk for the development of hyperfluorosis and its complications in our cohort.

A total of 3 to 5% of patients with coccidioidomycosis have disseminated disease or chronic pulmonary infection requiring long-term suppressive antifungal therapy with a triazole. Concerns regarding the potential toxicity of long-term triazole therapy have been raised, and recent observations have presented compelling evidence for the causal role of long-term voriconazole, a trifluorinated antifungal, as a risk factor for the development of fluoride excess and subsequent painful periostitis and exostoses in posttransplant patients (1, 2, 5). However, the safety and potential toxicity of fluconazole and posaconazole (difluorinated triazoles) have not been assessed, nor has hyperfluorosis been reported for nontransplant patients. We have subsequently sought to determine if fluoride excess is common and if clinical sequalae consistent with hyperfluorosis are present in our cohort of chronic coccidioidomycosis patients receiving long-term antifungal therapy.

This is a cohort study designed to test whether patients receiving long-term antifungal therapy (>6 months' duration) with different triazoles were at risk for hyperfluoremia and/or the clinical development of periostitis or exostoses. This study was approved by the Institutional Review Board of the University of California—Davis.

Patients referred to the University of California—Davis Medical Center for chronic pulmonary, disseminated, or meningeal coccidioidomycosis as defined by existing European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria (3) who were also receiving a fluorinated triazole (fluconazole, posaconazole, or voriconazole) for greater than 6 months were included. All patient samples were collected over a 60-day enrollment period. Patients taking long-term itraconazole (a nonfluorinated triazole) were included as a control group.

All patients were assessed for clinical symptoms suggestive of coccidioidal osteomyelitis or arthritis and periostitis or exostoses, and radiographic studies were obtained if suggestive symptoms were present. Demographic and laboratory data were abstracted from patient medical records, and serum fluoride levels were determined using an Accumet pH/ion meter equipped with a fluoride-specific electrode. Serum samples were buffered with TISAB prior to analysis.

Analysis of variance (ANOVA) between groups with Tukey's posttest analysis was used to compare demographic characteristics, clinical factors, and laboratory values between groups. Then using the residuals from each model, Q-Q plots and Shapiro-Wilk's testing was performed to assess normality of the residuals. For variables found to depart significantly from normality, Kruskal-Wallis testing was performed. For all analyses, 2-tailed P values of <0.05 were considered to be statistically significant.

Twenty-nine patients with chronic coccidioidomycosis receiving chronic triazole therapy were identified (itraconazole, $n = 6$; fluconazole, $n = 9$; posaconazole, $n = 5$; voriconazole, $n = 9$) (Table 1). The patients were predominantly male (23/29) and ranged in age from 18 to 65 years, although these differences were not statistically significant between groups ($P = 0.29$).

The duration of therapy varied widely between groups, and those receiving itraconazole were treated significantly longer than those in other groups ($P = 0.047$). Patients treated with itraconazole had the lowest mean serum fluoride levels (1.74 μmol/liter; range, 1.13 to 2.34 μmol/liter), while those treated with fluconazole and posaconazole had slightly higher, but statistically insignificant, mean serum concentrations (2.98 μmol/liter [range, 0.97 to 4.53 μmol/liter] and 4.06 μmol/liter [range, 3.00 to 5.34 μmol/liter], respectively) compared to itraconazole. Mean serum fluoride levels in the voriconazole group (9.17 μmol/liter; range, 1.83 to 21.0 μmol/liter) were greater than those treated with either itraconazole or fluconazole ($P = 0.002$) but did not significantly differ from those treated with posaconazole ($P = 0.24$). No relationship between triazole dosing, duration of therapy, or serum drug concentrations and serum fluoride level was found. Additionally, no differences were found in serum creatinine levels ($P = 0.63$). Alkaline phosphatase levels differed significantly between the voriconazole-treated group and all other groups ($P = 0.027$), although this difference was driven almost entirely by one patient with a serum alkaline phosphatase level of 956 U/liter. Two patients in the voriconazole-treated group had serum fluoride levels of >20 μmol/liter, although the alkaline phosphatase level of both of these patients was within normal limits, and serum creatinine levels were 0.97 and 1.62 mg/dl.

Interestingly, despite the frequent use of radiographic imaging for evaluation of potential coccidioidal osteomyelitis/arthritis (12

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Address correspondence to George R. Thompson III, grthompson@ucdavis.edu.

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TABLE 1 Clinical and laboratory characteristics of coccidioidomycosis patients receiving long-term triazole (>6 months) therapy

Characteristic	Value[a]			
	Itraconazole ($n = 6$)	Fluconazole ($n = 9$)	Posaconazole ($n = 5$)	Voriconazole ($n = 9$)
Age, yr (±SD)	46 (±13.8)	43 (±14.6)	50 (±7.5)	34 (±21.4)
No. (%) of males	6 (100)	7 (78)	3 (60)	7 (78)
Median duration of therapy in mo (range)	64 (7–125)	8 (6–58)	30 (30–51)	24 (8–50)
Plasma fluoride (range) (μmol/liter)	1.74 (1.13–2.34)	2.98 (0.97–4.53)	4.06 (3.00–5.34)	9.17 (1.83–21.0)
Serum creatinine (range) (mg/dl)	1.05 (0.9–1.2)	1.11 (0.7–1.5)	1.88 (1.1–1.3)	2.01 (0.8–6.2)
Serum alkaline phosphatase (range) (U/liter)	79.3 (60–95)	59.6 (49–70)	84.5 (68–110)	214.1 (69–956)
No. of patients with radiographic imaging of symptomatic area	2	3	2	5
No. of patients with periostitis or exostoses	0	0	0	0

[a] All values are expressed as means except where otherwise noted.

total patients), no patient in our study had radiographically apparent periostitis or exostoses.

Interest in the potential side effects of long-term triazole therapy has recently increased following reports of cutaneous malignancy with long-term voriconazole (4) and more recent evidence illustrating the development of hyperfluorosis, periostitis, and exostoses (5). Previous reports describing osseous complications of chronic therapy have been limited to solid-organ transplantation patients and have not evaluated the possibility of hyperfluorosis developing in patients chronically exposed to other fluorinated triazoles (fluconazole or posaconazole) (1, 2, 5).

Exogenous fluoride is absorbed in the stomach and small intestine, and up to 25 to 33% of all absorbed fluoride is taken up into calcified tissues, with the amount increasing over an individuals' lifetime. The remainder of absorbed fluoride is excreted in the urine, yet neither serum creatinine level nor the estimated glomerular filtration rate has been found predictive of serum fluoride levels in prior reports or in our study (5, 6).

Intuitively, fluorinated triazole serum drug concentrations could predict patient serum fluoride levels; however, prior reports and our results do not support this notion. In fact, the patient in our study with the highest serum fluoride level (21.0 μmol/liter) had a modest serum voriconazole level of 3.3 mg/liter, and the patient with the highest fluoride level observed in the posaconazole-treated group (5.34 μmol/liter) had a serum posaconazole level of only 0.8 mg/liter. Although these findings are based on a limited sample size, it suggests that patient-specific differences in fluoride metabolism may be responsible for the development of hyperfluorosis.

Our results comparing the nonfluorinated triazole itraconazole to the fluorinated triazoles suggest that among patients chronically exposed to fluconazole or posaconazole, serum fluoride levels are elevated compared to the accepted normal ranges (1 to 4 μmol/liter), although only minimally. Additionally, no fluconazole or posaconazole patient in our study developed clinically apparent periostitis or exostoses, although larger adequately powered studies will need to be performed to determine the absolute risk with these agents. Although our small sample size was similar to that described by Wermers et al. (5),serum fluoride levels in our voriconazole-treated group did not significantly differ from theirs ($P > 0.10$), and no patient was found to have evidence of periostitis or exostoses in our group. Despite Wermers et al.'s finding of osseous abnormalities attributed to hyperfluorosis in 50% of voriconazole-treated patients, their results should not be interpreted as a true incidence given their case-control study design.

In conclusion, our results further support the association of voriconazole with the development of hyperfluorosis and demonstrate that fluconazole and posaconazole pose a significantly lower risk for the development of elevated serum fluoride levels. Although osseous complications of long-term voriconazole may occur, the incidence of these complications of long-term voriconazole therapy will need to be determined in future studies.

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