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Effect of high-dose fluconazole on QT interval in patients with human immunodeficiency virus (HIV)-associated cryptococcal meningitis[☆]

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Sir,

Azoles may cause prolongation of the QT interval either directly or by inhibiting the hepatic metabolism of other QT-prolonging agents. Ketoconazole is known to block the human ether-a-go-go-related gene (hERG) product and thereby inhibit the potassium I_{K_r} current in the heart [1]. Whether fluconazole also inhibits hERG is currently unknown.

The BAMSG 3-01 study was a Phase II trial for the treatment of cryptococcal meningitis in acquired immune deficiency syndrome (AIDS) patients [2]. Patients were randomly assigned to receive amphotericin B (0.7 mg/kg/day) either alone or plus fluconazole (400 mg/day or 800 mg/day) for the first 14 days. Patients' QT intervals were assessed at baseline to identify those at risk of QT prolongation as well as after 7 days of therapy to determine whether the daily fluconazole dose or Day 14 trough serum concentration (C_{min}) (24 h after dosing) was

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Ethical approval: The protocol was approved by each site's institutional review board or ethics committee.

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associated with QT prolongation. Serum concentration results were obtained using gas–liquid chromatography [3]. To calculate the corrected QT (QTc) interval, Fridericia's formula was used ($QTcF = QT/RR^{0.33}$) as it is more accurate than Bazett's formula ($QTcB = QT/RR^{0.50}$) in patients with altered heart rate [4]. Patients with a baseline QTcF > 500 ms were excluded; at Day 7, subjects with a QTcF > 500 ms or a QTcF prolongation (>60 ms above baseline) were discontinued. Details on the study design have been described previously [2].

P-values comparing all treatment arms were obtained by analysis of covariance (ANCOVA) and Mantel–Haenszel χ^2 test. The percentages of subjects with QTc > 500 ms or QTc prolongation were compared. ANCOVA models were constructed to identify baseline characteristics associated with baseline QTc intervals, Day 7 parameters associated with Day 7 QTc intervals, and baseline characteristics predictive of Day 7 QTc intervals. Models with an outcome of Day 7 QTc interval were adjusted for baseline QTc interval. The relationship of Day 7 QTcF interval change from baseline and Day 14 C_{min} was assessed by calculating the Spearman rank correlation coefficient.

In total, 141 subjects received therapy, with 139 and 127 subjects having baseline and Day 7 electrocardiogram (ECG) assessments performed, respectively. All baseline ECG measures except QTcF interval were comparable between arms ($P > 0.05$). The mean $\pm$ standard deviation (S.D.) baseline QTcF intervals for the amphotericin B (AmB), amphotericin B plus fluconazole 400 mg (AmB+Fluc400) and amphotericin B plus fluconazole 800 mg (AmB+Fluc800) arms were 395.5 ± 24.67 , 406.8 ± 22.16 and 407.9 ± 24.88 ms, respectively ($P = 0.033$). At Day 7, all ECG measures except percent of subjects experiencing abnormalities were similar among arms ($P > 0.05$). However, the percent of patients experiencing clinically significant abnormalities was comparable ($P = 0.829$). After adjusting for baseline QTc, the Day 7 QTc interval adjusted means for each of the combination therapy arms were comparable with the AmB arm ($P > 0.10$). However, Day 7 median and adjusted mean change from baseline to Day 7 estimates were higher in the AmB+Fluc800 arm compared with the AmB arm (Fig. 1). Based on multivariate models, lower baseline Karnofsky scales were associated with higher baseline QTcF and QTcB intervals; lower Day 7 potassium levels were associated with higher Day 7 QTcF intervals; and no Day 7 characteristics were associated with QTcB intervals ($P < 0.05$). For predictive factors, higher baseline cerebrospinal fluid (CSF) opening pressure and Karnofsky scales were predictive of higher Day 7 QTcF intervals; and higher baseline CSF opening pressure, potassium, age and lower CD4⁺ count were predictive of higher Day 7 QTcB intervals ($P < 0.05$).

Fluconazole concentration samples were only obtained for a subset of subjects; specifically, 47 patients had ECG and non-zero Day 14 fluconazole measurements (36 received AmB+Fluc800, 9 AmB+Fluc400 and 2 AmB). The mean $\pm$ S.D. QTcF interval at baseline was 407.6 ± 24.5 ms and at Day 7 was 410.8 ± 27.2 ms ($P = 0.504$, paired *t*-test). The geometric mean Day 14 C_{min} was 35.6 mg/L (range 4.2–84.1 mg/L). The Spearman rank correlation for QTcF interval change from baseline and Day 14 C_{min} was 0.282 ($P = 0.074$). Based on the linear regression model, the predicted Day 14 C_{min} (90% confidence interval for the mean) associated with Day 7 QTcF interval change from baseline of 30 was 42.0 (33.7–52.2) and of 60 was 49.2 (34.6–69.8) ($P = 0.065$).

No comparative trial evaluating the direct effect of high-dose oral fluconazole on the QT interval has previously been conducted. We show that AmB+Fluc800 was not associated with increased risk of either QTcB or QTcF interval prolongation compared with AmB+Fluc400 and AmB treatment. Percentages of subjects experiencing Day 7 QTc > 500 ms or prolongation were similar. However, patients receiving AmB+Fluc800 had a slight increase in QTc compared with baseline. High trough concentrations appear to be associated with a trend towards increased risk of QTc prolongation at Day 7, although the sample size for the number

of subjects with both ECG and non-zero Day 14 fluconazole measurements was relatively small.

Thus, ECG monitoring of high-dose fluconazole should be conducted and physicians should be aware of other potential risk factors for prolongation, particularly hypokalaemia. A larger-scale study is required to clarify the correlation between QT prolongation and high-dose fluconazole.

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Fig. 1.

(A) QTc intervals at Day 7 among three treatment arms [with the percentage of patients experiencing high QTc interval values (>500 ms)] and (B) QTc intervals change from baseline to Day 7 among three treatment arms [with the percentage of patients experiencing QTc interval prolongation (>60 ms)]. Adjusted means (dots) and associated 90% confidence intervals (lines) for each treatment arm were obtained from an analysis of covariance (ANCOVA) model that adjusted for baseline QTc values, country and baseline opening pressure category. Median values (dashes) by treatment arm are also presented. *P*-values from the ANCOVA model comparing each combination therapy arm with amphotericin B alone group are shown. AmB, amphotericin B alone; AmB+Fluc400, amphotericin B plus fluconazole 400 mg; AmB

+Fluc800, amphotericin B plus fluconazole 800 mg; QTcF, Fridericia-corrected QT interval; QTcB, Bazett-corrected QT interval.