Effect of oral fluconazole 1200mg/day on QT interval in African adults with HIV-associated cryptococcal meningitis

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Fluconazole remains in routine use as an induction regimen for the treatment of Cryptococcal meningitis (CM) in many low and middle income countries (LMICs), either alone, or in combination with amphotericin B. Guidelines recommend dosages of 800mg/day to 1200mg/day [1-3]. However, it has been previously suggested that fluconazole may prolong the QT interval, either directly, or by inhibiting the hepatic metabolism of other QT-prolonging agents [4, 5]. A lengthened corrected QT interval (QTc) is a biomarker for ventricular tachyarrhythmias such as *torsades de pointes* and is a risk factor for sudden death, particularly in older patients [6]. In a prior study of CM, patients receiving amphotericin B plus fluconazole (800mg/day) had a slight increase in QTc compared with baseline (mean change from baseline: 6.6ms [95%CI: -3.2ms to 16.4ms]) [4]. However, overall, day 7 QTc intervals for those treated with amphotericin B plus fluconazole (800mg/day) were similar compared with patients treated with amphotericin B in combination with fluconazole, at the lower dose of 400mg/day, and amphotericin B alone; and there was no suggestion of an increase in the risk of clinically significant QTc prolongation (>500ms) [4].

We assessed the effect of a fluconazole dose of 1200mg/day, on QTc interval in a cohort of patients enrolled in the ACTA trial. This was a Phase III trial for the treatment of HIV-associated CM in Africa testing 5 different treatment regimens, 3 of which contained fluconazole at 1200mg/day dosage [7]. Electrocardiograms (ECGs) to measure the heart rate corrected QT (QTc – using Bazett's formula) were

performed for all participants at baseline and 1 week after enrolment, for the first 22 months of the study, until the Data Monitoring Committee recommended to discontinue routine ECG monitoring on the basis that the clinical risk did not warrant routine ECG monitoring in this context.

QTc results from patients randomised to regimens including fluconazole, 1200mg/day (oral treatment of fluconazole plus flucytosine for 2 weeks; amphotericin B plus fluconazole for 1 week, and amphotericin B plus fluconazole for 2 weeks, 2/3 of those enrolled in the trial) were compared to those randomised to non-fluconazole containing regimens (amphotericin B plus flucytosine for 1 week and amphotericin B plus flucytosine for 2 weeks, 1/3 of those enrolled). Mean QTc length in each of the 2 groups at day 7 was compared by analysis of covariance (ANCOVA), adjusting for baseline QTc measurement. Mean change in QTc length from baseline to day 7 was analysed using a t-test and the proportion of patients with long QTc (≥500ms) in each group was compared at day 7 using Fishers exact test. Analyses were performed using Stata version 14.1.

A total of 150 patients had QTc results recorded at baseline with 104 (69.33%) randomised to a high dose fluconazole treatment regimen. As expected there was no significant difference in mean QTc length for patients randomized to fluconazole treatment compared to those randomised to no fluconazole at baseline (412.9ms and 414.2ms, respectively, p=0.88). At baseline, 15 patients (10%) had Grade 1 (450-480ms), 6 patients (4%) had Grade 2 (480-490ms) and 7 patients (4.67%) had Grade 3 QTc (>500ms) at baseline. Of the patients with Grade 3 QTc at baseline, 6 resolved (<450ms) by day 7 with electrolyte replacement and avoidance of known QT prolonging concomitant drugs. Fluconazole was withheld temporarily for 2 patients. One patient with severe CM and sepsis died prior to a follow-up ECG.

Following commencement of antifungal treatment, QTc was recorded for 125 patients at day 7 with 84 (67.2%) randomised to high dose fluconazole. Sixteen patients (12.8%) had Grade 1 (450-480ms), 8 patients (6.4%) had a Grade 2 (480-490ms) and 1 patient (0.8%) had a Grade 3 QTc (>500ms) at day 7. The patient with Grade 3 QTc had a normal QTc at baseline (437ms) that increased at day 7 to 505ms and this patient was randomised to a fluconazole containing treatment regimen. The patient was well on discharge at day 14 of the study and completed 10-week follow-up without further adverse events. Overall mean QTc length at day 7 was 415.8ms (IQR: 390.0 to 444.0). The mean change in QTc length from baseline was 2.9ms (IQR: -30 to 37): 10.1ms (IQR: -28 to 46) in the fluconazole containing treatment group compared to -12.6ms (IQR: -39 to 13.5) in those not taking fluconazole (p=0.04) (Table 1). There was evidence for a difference in mean QTc length for patients taking fluconazole treatment compared to those not taking fluconazole (422.5ms and 402.1ms, respectively, p=0.01), adjusting for baseline QTc length. However, there was no evidence for a difference in the number of patients with long QTc (>500ms) between the 2 groups at day 7 (1 patient had a long QTc in the fluconazole group compared to none in the non-fluconazole group, p=1.0) (Table 1).

A small increase in mean QTc length for patients taking high dose fluconazole (1200mg/day) was observed in this study, as shown previously for doses of 800mg/day [4]. As in the prior study, there was no evidence for an increase in the proportion of patients developing a clinically significant prolonged QT interval. Since our study was conducted, preliminary results of a phase II trial using even higher fluconazole doses (1600mg/day and 2000mg/day) have been reported, without, as yet, details of QT interval effects but with no mention of serious concerns over QT interval prolongation [8].

Our study suggests that a fluconazole dose of 1200mg/day does not lead to clinically significant lengthening of the QTc interval and that ECG monitoring need not be mandatory in this population, treated at this dose for short periods. However, it is important to emphasize, as with all drugs with the potential to prolong QT interval, that it remains important to monitor and correct any electrolyte imbalance and to avoid, where possible, concomitant drugs that may also raise QTc prolongation.

Acknowledgements
The main clinical trial was supported by grants from the Medical Research Council, United Kingdom (100504) and the French Agency for Research on AIDS and Viral Hepatitis (ANRS) (ANRS12275). We would like to thank the patients involved in this study, as well as the staff at each site and the data and safety monitoring committee: Andrew Nunn, Halima Dawood, Andrew Kitua, and William Powderly.

Conflicts of interest
There are no conflicts of interest

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Table 1: QTc measurements at baseline and Day 7 by treatment group

	Day 7 (n=113)	(n=125)	Mean change from baseline to day 7 (n=113)
Treatment group	**Mean QTc, ms (IQR)**	**Long QTc, ms n (%)**	**Mean change, ms (IQR)**
Fluconazole	422.5 (401 to 448.5)	1 (1.0%)	10.1 (-28 to 46)
No fluconazole	402.1 (385 to 443)	0	-12.6 (-39 to 13.5)
p-value	0.01[1]	1.0[2]	0.04[3]
Overall	415.8 (390.0 to 440.0)	1 (0.8%)	2.9 (-30 to 37)

[1] *ANCOVA analysis adjusting for baseline QTc*
[2] *Fishers exact test*
[3] *t-test*