

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

*Sile F Molloy<sup>1\*</sup>, John Bradley<sup>2\*</sup>, Natasha Karunaharan<sup>1</sup>, Muhammad Mputu<sup>3</sup>, Neil Stone<sup>1</sup>, Jacob Phulusa<sup>4</sup>, Chimwemwe Chawinga<sup>4</sup>, Kate Gaskell<sup>5</sup>, Dalitso Segula<sup>5</sup>, Damien Ming<sup>5</sup>, Mary Peirse<sup>5</sup>, Duncan Chanda<sup>3</sup>, Shabir Lakhi<sup>3</sup>, Angela Loyse<sup>1</sup>, Cecilia Kanyama<sup>4</sup>, Robert S Heyderman<sup>5,6</sup> and Thomas S Harrison<sup>1</sup>.*

Corresponding Author: Sile Frances Molloy, Ph.D.

St George's, University of London

London, UNITED KINGDOM E-mail:- [smolloy@sgul.ac.uk](mailto:smolloy@sgul.ac.uk)

*\*Joint first authors*

1 Centre for Global Health, Institute for Infection and Immunity, St. George's University of London, London, UK

2 MRC Tropical Epidemiology Group, London School of Hygiene and Tropical Medicine, London, UK

3 University Teaching Hospital, Lusaka Apex Medical University, Zambia

4 University of North Carolina Project–Malawi, Kamuzu Central Hospital, Lilongwe, Malawi

5 Malawi–Liverpool–Wellcome Trust Clinical Research Programme, College of Medicine, University of Malawi, Malawi

6 University College London, London, UK

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 ( $\geq 500$ ms) 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.

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**Conflicts of interest**

There are no conflicts of interest

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## References

1. Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, et al. **Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america.** *Clinical Infectious Diseases* 2010; **50**(3):291-322.
2. Southern African HIV Clinicians Society. **Guideline for the prevention, diagnosis and management of cryptococcal meningitis among HIV-infected persons: 2013 update.** *Southern African Journal of HIV Medicine* 2013; **14**(2):76.
3. **WHO Guidelines Approved by the Guidelines Review Committee.** In: *Rapid Advice: Diagnosis, Prevention and Management of Cryptococcal Disease in HIV-Infected Adults, Adolescents and Children.* Geneva: World Health Organization; 2011.
4. Manosuthi W, Sungkanuparph S, Anekthananon T, Supparatpinoy K, Nolen TL, Zimmer LO, et al. **Effect of high-dose fluconazole on QT interval in patients with human immunodeficiency virus (HIV)-associated cryptococcal meningitis.** *International Journal of Antimicrobial Agents* 2009; **34**(5):494-496.
5. Takemasa H, Nagatomo T, Abe H, Kawakami K, Igarashi T, Tsurugi T, et al. **Coexistence of hERG current block and disruption of protein trafficking in ketoconazole-induced long QT syndrome.** *British journal of pharmacology* 2008; **153**(3):439-447.
6. Straus SM, Kors JA, De Bruin ML, van der Hooft CS, Hofman A, Heeringa J, et al. **Prolonged QTc interval and risk of sudden cardiac death in a population of older adults.** *Journal of the American College of Cardiology* 2006; **47**(2):362-367.
7. Molloy SF, Kanyama C, Heyderman RS, Loyse A, Kouanfack C, Chanda D, et al. **Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa.** *New England Journal of Medicine* 2018; **378**(11):1004-1017.
8. Lalloo UG, Larsen R, Aberg J, Hogg E, Komarow L, Clifford DB, Pillay S, Deborah Langat D, Bukuru A, Mave V, Supparatpinoy K, Samaneka W. **Higher high dose fluconazole for the treatment of cryptococcal meningitis.** *CROI, Boston March 2018. Abstract Number: 35*  
<http://www.croiwebcasts.org/p/2018croi/35>

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

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

<sup>1</sup> ANCOVA analysis adjusting for baseline QTc

<sup>2</sup> Fishers exact test

<sup>3</sup> t-test