


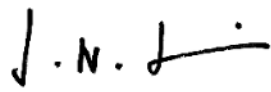


Work Practice Document: 18

ECG

Title of study	High Dose AMBISOME® on a Fluconazole Backbone for Cryptococcal Meningitis Induction Therapy in sub-Saharan Africa: A Phase III Randomized Controlled Non-inferiority Trial		
Acronym	Ambition-cm – AMBIsome Therapy Induction OptimizatiON		
ISRCTN No.:	ISRCTN72509687		
WPD Current version	Version 1.0, 20/07/2017		
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Revision History:		
Version Number	Effective Date	Reason for Change
1.0		First version

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Purpose

This document outlines the protocol for ECGs for study patients.

References

1. AMBITION Protocol
2. Division of AIDS (DAIDS), National Institute of Allergy and Infectious Disease/National Institutes of Health Toxicity Tables, DAIDS Toxicity criteria version 2.1, March 2017
3. Oxford Handbook of Clinical Medicine, 8th Edition, Oxford University Press, April 2010
4. Manosuthi et al, Effect of high-dose fluconazole on QT interval in patients with human immunodeficiency virus (HIV)-associated cryptococcal meningitis, Int J Antimicrob Agents. 2009 November; 34(5): 494–496.

Scope

This WPD applies to study patient ECGs and the calculation of the QTc interval

Materials

WPD 3: Patient enrolment and follow up

Cardiovascular physiology concepts: <http://www.cvphysiology.com/Arrhythmias/A009.htm>

Fluconazole may cause prolongation of the QT interval either directly or by inhibiting the hepatic metabolism of other QT-prolonging agents but thousands of patients have now received high-dose fluconazole in cryptococcal treatment trials with no evidence of cardiac complications due to QT prolongation. A lengthened QT interval is a biomarker for ventricular tachyarrhythmias such as torsades de pointes and a risk factor for sudden death.

The Q-T interval represents the time for both ventricular depolarization and repolarization to occur.

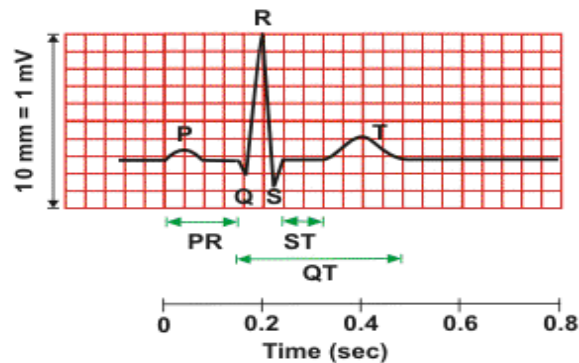
This interval can range from 0.2 to 0.45 seconds depending upon heart rate.

In practice, the Q-T interval is expressed as a "corrected Q-T (QTc)" by taking the Q-T interval and dividing it by the square root of the R-R interval (interval between ventricular depolarizations). This allows an assessment of the Q-T interval that is independent of heart rate.

- Normal corrected Q-Tc intervals are:
- Men ≤ 0.45 seconds
- Women ≤ 0.46 seconds

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CALCULATING THE QT INTERVAL



P wave (0.08 - 0.10 s) QRS (0.06 - 0.10 s)
P-R interval (0.12 - 0.20 s) Q-T_c interval (≤ 0.44 s)*
*QT_c = $\frac{QT}{\sqrt{RR}}$

The ECG is recorded at a speed of 25 mm/sec, and the voltages are calibrated so that 1 mV = 10 mm in the vertical direction. Therefore, each small 1-mm square represents 0.04 sec (40 msec) in time and 0.1 mV in voltage. Each large square represents 0.2 seconds.

1. Count the number of small boxes between the start of the Q wave and end of the T wave. Multiply number of boxes by 0.04.
2. Calculate the R-R interval
3. Divide QT interval by square root of the RR

NB Variations in QTc values up to 0.07 seconds can be observed in the normal range. A prolonged corrected QT interval must exceed the upper threshold of normal by gender to be considered abnormal.

Drugs causing a prolonged QTc interval should be avoided in combination with fluconazole if possible. Drug classes that may cause a prolonged QTc interval include the following:

- Antibiotics (quinolones (ciprofloxacin), macrolides (clarithromycin, azithromycin), pentamidine)
- Psychiatric drugs (cisapride, citalopram, haloperidol, chlorpromazine)
- Antiemetics (domperidone)
- Antiarrhythmics (amiodarone, procainamide)

Hypomagnesaemia and hypokalaemia can contribute to QT prolongation and should be corrected if QT prolongation discovered. For management of electrolyte replacement, refer to WPD 9, Toxicity management.

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There will not be baseline ECGs for patient enrolled onto AMBITION. In the event a patient's clinical condition warrants an ECG and a prolonged QTc is identified please refer to the below table for guidance on further management:

Actions to take if evidence of QT prolongation on ECG;

GRADE	DEFINITION	ACTION
1	Mild QTc prolongation: 0.45 to 0.47 seconds	Fluconazole should continue without interruption, at the discretion of the site investigator. Stop non-essential medication which is known to prolong the QTc.
2	Moderate QTc prolongation: 0.47 to 0.50 seconds	Fluconazole should continue without interruption, at the discretion of the site investigator. A repeat ECG should be considered 1 week later Stop non-essential medication which is known to prolong the QTc.
3	Severe QTc prolongation: >0.50 seconds OR ≥ 0.06 seconds above baseline	Fluconazole should be interrupted with the agreement of the site investigator. If the QTc prolongation resolves to Grade ≤ 1 within 3 days, the investigator should consider re-starting fluconazole at the usual dose and repeating ECGs at weekly intervals. If the QTc prolongation does not resolve to Grade ≤ 1 within 3 days, fluconazole should be discontinued. Alternative treatment must be discussed with the PI Stop non-essential medication which is known to prolong the QTc.
4	Life-threatening signs or symptoms (e.g., arrhythmia associated with CHF, hypotension, shock, syncope); torsades de pointes COMPLETE SAE eCRF WITHIN 24 HOURS	Participants should permanently discontinue fluconazole. Alternative treatment must be discussed with the PI. Stop non-essential medication which is known to prolong the QTc.

Grades from DAIDS Version 2.1 March 2017

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Training

Each staff member receives or has direct access to applicable Working Practice Documents (WPDs).

Each staff member reviews the applicable WPDs once a year.

All WPD training is documented and tracked in the WPD training logbook located in the Project Coordinator's office.

New staff is trained on applicable WPDs within 30 days of employment and all WPDs within 90 days of employment.

Staff members whose duties fall within this WPD scope are retrained within 14 days of the approval of each WPD revision.

