

The pharmacology of azithromycin in severe malaria bacterial co-infection in African children

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| Submission date 24/10/2017 | Recruitment status No longer recruiting | <input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol |
| Registration date 27/10/2017 | Overall study status Completed | <input checked="" type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results |
| Last Edited 07/11/2024 | Condition category Infections and Infestations | <input type="checkbox"/> Individual participant data |

Plain English summary of protocol

Background and study aims

Malaria is a tropical disease spread by mosquitoes that causes high temperature, sweats and chills, headaches, vomiting, muscle pains and diarrhea. Severe malaria killed an estimated 475,000 African children in 2013. Fast-acting effective antimalarial drugs are now used in most hospitals, but a large number of children still die (around one in every ten). To reduce this number, there is a need to find better ways to manage these sick children. Some children with severe malaria infection also have a higher chance of also having infections caused by bacteria (bugs) at the same time. These bacterial infections increase the risk of children with severe malaria dying in hospital even more (to around a one in four chance). Around one-third of all severe malaria deaths in African children are thought to be due to these bacterial infections. The problem is that most African hospitals are not able to grow the bacteria from blood to work out which children really have these bacterial infections. So there are two options: no one gets antibiotics, or everyone gets antibiotics. The problem with giving all these children antibiotics is that most of them don't need them, and using antibiotics for all children can increase the risk of resistance in the community (meaning antibiotics stop working for people who really need them). There is no agreement on which antibiotics, at what dose or for how long, they should be used in children with severe malaria. The main bacteria responsible for these infections come from the gut, because the gut becomes 'leaky' in severe malaria so these bugs can cross over into the blood. These bacteria are frequently resistant to, or are not treated by, currently recommended and commonly available antimicrobials. The aim of this study is to examine one of the antibiotics that can be given by mouth (specifically azithromycin) which has the potential to treat most common causes of infections and to find out what is the correct dose to give (to treat infections) in order to progress to the next step which will be a larger trial comparing different types of antibiotics to improve both short term and longer term outcomes.

Who can participate?

Children aged six months to 12 years old who are admitted to the hospital with malaria.

What does the study involve?

Participants are randomly allocated to one of three groups. Those in the first group receive a 10 mg/kg dose of azithromycin. Those in the second group receive a 15 mg/kg dose of azithromycin. Those in the last group receive the 20 mg/kg dose of azithromycin. The medication is taken

once daily over five days. Participants are followed up at day seven, day 28 and day 90 to assess their treatment and how well the medication is working.

What are the possible benefits and risks of participating?

Participants may benefit from regular assessment of by doctors/nurses to enable carers to make important changes to your child's treatment in hospital, if these are needed. Researchers help supply routine medical supplies and treatments for participants to the hospital, so that carers will not have to buy any treatments. This means that there will be no delay to starting treatment. The medical tests performed during this illness are also paid for by the study. Participants are asked back for follow up visit(s), therefore transport from hospital to your home and back to the clinic are paid for. During the follow up visit(s), we will treat any illnesses we find, or arrange referral to appropriate hospital. The trial will be recruiting patients with severe illness and likely a high mortality rate. At the start of the trial, all sites will receive emergency care training, including triage of those at highest risk. All patients will be closely monitored so that clinical deteriorations can be identified at the earliest opportunity. GCP-compliant adverse event data collection and reporting procedures will be adopted. Azithromycin is an approved drug for use in children and risk is therefore very low.

Where is the study run from?

Mbale Regional Referral Hospital (Uganda)

When is the study starting and how long is it expected to run for?

July 2017 to November 2019

Who is funding the study?

Medical Research Council (UK)

Who is the main contact?

Professor Kathryn Maitland

Contact information

Type(s)

Scientific

Contact name

Prof Kathryn Maitland

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers

WMNP_P66265

Study information

Scientific Title

Pharmacokinetics and pharmacodynamics of azithromycin in severe malaria bacterial co-infection in African children

Acronym

TABS-PKPD

Study objectives

Hypotheses:

1. Azithromycin (an antibiotic) given to children once-daily for 5 days in addition to standard treatment of severe malaria (including anti-malarials) can provide adequate dosing in children admitted to hospital with severe malaria
2. Children severe malaria with culture-proven bacteraemia can be accurately identified using clinical criteria alone or in combination with a rapid diagnostic biomarker tests, in comparison with a control cohort of children hospitalized with severe malaria but not meeting Teule criteria, at low risk of bacterial co-infection

Ethics approval required

Old ethics approval format

Ethics approval(s)

1. Imperial College Research Ethics Committee (ICREC), 10/11/2017, ref: 17IC3965
2. Mbale Regional Referral Hospital Research Ethics Committee, Mbale Uganda Preliminary, 27/10/2017

Study design

Phase I/II trial randomised single centre study

Primary study design

Interventional

Secondary study design

Randomised parallel trial

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet

See study outputs table

Health condition(s) or problem(s) studied

Severe Malaria

Interventions

Children are randomised (1:1:1) to compare three doses of azithromycin: 10, 15 and 20 mg/kg (based on weight-bands) taken orally once daily over five days in order to optimize dose and study pharmacokinetics and their relation with treatment outcome.

Randomisation lists are generated and kept at the MRC CTU at UCL, London. The randomisation envelopes are prepared before the trial at the Clinical trials facility, KWTRP, Kilifi. These contain the actual allocation visible only once opened. Children are randomised (1:1:1) to receive 10, 15 or 20 mg/kg azithromycin (based on weight-bands). The cards will be numbered consecutively and opened in numerical order.

Children are followed up at day seven, day 28 and day 90 to study the medication pharmacokinetics and their relation with treatment outcome.

Intervention Type

Drug

Phase

Phase I/II

Drug/device/biological/vaccine name(s)

Azithromycin

Primary outcome measure

Sepsis markers are measured using the c-reactive protein tests using blood samples at baseline to 72 hours (continuous) and microbiological cure (7-day).

Secondary outcome measures

1. Mortality is measured using dedicated case report forms at clinical visit or telephone interviews at 48 days and 90 days
2. Length of hospital stay is measured using dedicated case report forms
3. Re-hospitalisation measured using parental interview using case report forms at follow up visits on Day 7, Day 28 and Day 90
4. Adverse events is measured using dedicated serious adverse event forms during hospital admission and follow up visits on Day 7, Day 28 and Day 90

Overall study start date

01/07/2017

Completion date

30/12/2022

Eligibility

Key inclusion criteria

1. Children aged 6 months to 12 years at admission to hospital with Plasmodium falciparum malaria (on either blood film or ParacheckTM rapid diagnostic test)
2. Axillary temperature >38°C or <36°C
3. 'Teule' severity criteria: any one of the following: prostration; respiratory distress; severe anaemia (haemoglobin <5g/dL) or HIV infection
4. Parents willing/able to provide consent

Participant type(s)

Patient

Age group

Child

Lower age limit

6 Months

Upper age limit

12 Years

Sex

Both

Target number of participants

105

Total final enrolment

105

Key exclusion criteria

1. Major contraindications to azithromycin, eg strong existing clinical diagnosis of QT-prolongation
2. Concomitant use of interacting drugs: drugs that may cause QT-prolongation or drugs that may cause a pharmacokinetic interaction with azithromycin, like strong CYP3A/P-GP inducers and concomitantly administered antacids

Date of first enrolment

01/09/2020

Date of final enrolment

01/04/2022

Locations

Countries of recruitment

Uganda

Study participating centre
Mbale Regional Referral Hospital
Mbale Clinical Research Institute
Mbale
Uganda
PO Box 92

Sponsor information

Organisation
Imperial College, London

Sponsor details
Joint Research Compliance Office
Room 221
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Sponsor type
University/education

ROR
<https://ror.org/041kmwe10>

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

United Kingdom

Results and Publications

Publication and dissemination plan

We plan to communicate with the following audience groups: national policymakers (Ministry of Health, child health services); international policymakers (WHO, Medicine for Malaria Venture); nursing and paediatric associations; academics working in related fields; and the community where the trial is taking place. In addition, we will promote the value of existing online open-access educational courses (MOOC) in antibiotic stewardship (the judicious use of antibiotics) both locally and nationally. Education is widely recognized as one of the cornerstones of successful antimicrobial stewardship programmes. E-learning is progressively being used in Africa as a means for training/education. Engagement with peers, medical education establishments and national policy makers provides an opportunity to highlight that inappropriate and excessive use of antimicrobials is a prime contributor to the rise of antimicrobial resistance and reinforces the key message that antimicrobial stewardship is a global concern.

The Pathways to Impact section gives details on how this will maximise this study's impact. At that stage since the data generated from the study will not be able to inform treatment guidelines rather it will generate new data, which will help inform the design of a larger Phase III trial. The studies trial results will be disseminated through face-to-face meetings; open access peer-reviewed publication; presentation at international conferences; lay summaries; and websites.

Public engagement: Results from this trial will be disseminated locally through community meetings and national meetings with the wider healthcare professional community. These systems have been developed for dissemination of MRC FEAST trial results, and we plan to extend these with the ongoing TRACT trial.

National policymakers: The country PIs have already been in discussion with their Ministry of Health about the proposed trial. A summary or briefs will be produced to highlight the trial results and next steps required to inform rationale evidence-based guidelines.

International policymakers: We will seek meetings with WHO, UNICEF and other international policy makers to discuss the results and subsequent trial plans.

Communication to academic audiences will be through presentation at national and international conferences, partially related to malaria; and publication in prestigious, open access peer-reviewed journals. The country PIs will take leading roles in communicating with national audiences in the countries in which they are based.

We will be happy to share both the study protocol and SAP once this has received ethics approval and when the SAP is developed.

Intention to publish date

01/12/2020

Individual participant data (IPD) sharing plan

The current data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|-------------|--------------|------------|----------------|-----------------|
| Protocol article | version 1.0 | 10/01/2023 | 31/07/2023 | Yes | No |
| Statistical Analysis Plan | | 20/05/2021 | 26/02/2024 | No | No |
| Results article | | 06/11/2024 | 07/11/2024 | Yes | No |