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

Submission date
24/10/2017

Recruitment status
No longer recruiting

Registration date
27/10/2017

Overall study status
Completed

Last Edited
07/11/2024

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] 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
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Protocol serial number
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

Study type(s)
Treatment

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

Key secondary outcome(s))
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

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 >380C or <360C
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

Healthy volunteers allowed
No

Age group
Child

Lower age limit
6 months

Upper age limit
12 years

Sex
All

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

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, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

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?
Results article		06/11/2024	07/11/2024	Yes	No
Protocol article		10/01/2023	31/07/2023	Yes	No
Statistical Analysis Plan	version 1.0	20/05/2021	26/02/2024	No	No