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Study to compare blood levels of ceftriaxone given by suppository or injection

Submission date 22/11/2022	**Recruitment status** Suspended	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 06/12/2022	**Overall study status** Suspended	
Last Edited 29/09/2025	**Condition category** Other	

Plain English summary of protocol

Background and study aims
In remote areas, babies born at home who become sick from infections during the first week of life need to be referred to a hospital that may be several hours or days journey away. If there was a medicine that was as effective as the injectable treatment given in the hospital that could be given in the rural health post this might improve their chance of recovery. Ceftriaxone is an intravenous antibiotic that treats infection effectively. Researchers have developed two test formulations (one capsule and one tablet) of a well-known antibiotic called ceftriaxone as suppositories which could be given to sick babies. Before this is done, they need to show that they deliver enough medicine to the body to treat severe infections and that they are safe. This study is the first step. The researchers will compare how much medicine gets into the blood after giving the new suppositories compared to giving a standard injection of ceftriaxone and check for any side effects of the suppository in healthy adults.

Who can participate?
Healthy non-pregnant Thai adults aged 18-46 years

What does the study involve?
The following will be evaluated in a random order in all participants.
1. Ceftriaxone (Roche®) 500 mg (slow intravenous injection)
2. Ceftriaxone rectal dosage form test formulation 1- hard-shell gelatin capsule (1 x 500 mg)
3. Ceftriaxone rectal dosage form test formulation 2 - rectodispersible mannitol-based tablet (1 x 500 mg)
Each participant will receive a single treatment dose of each of the three formulations in an order pre-determined by a computer-generated randomisation list. This will ensure approximately balanced proportions for all six schedules (either 6 or 7 participants per schedule). There will be a 7-28 days washout period between doses. The last follow-up visit is 28 (+ 2) days after the final dose. Participants lost to follow-up or unevaluable for any reason before completion of blood sampling after the final dose will be replaced at the discretion of the investigators with another participant of the same population, if either the sample size or completeness of the dataset is compromised.

What are the possible benefits and risks of participating?
There are no anticipated direct benefits for participating in this study. Knowledge gained from this study may assist with the development of a rectal dosage form of ceftriaxone which could be used to treat children with severe infections in the community in the region in the future.
There may be minor bruising, local tenderness or pre-syncopal symptoms (the feeling that you are about to faint) associated with blood samples. This risk will be minimised by having the procedure performed by trained nurses.
As with any antibiotic, unexpected serious adverse events, including severe allergic reactions may occur. In order to mitigate this risk, participants will be treated in an in-patient clinical area where Advanced Life Support trained physicians, equipment and drugs are immediately available for the management of any immediate post-dose serious adverse reactions. Participants will be observed closely for at least 30 minutes following the administration of any dose of study medication.
Ceftriaxone is usually very well tolerated. Doses exceeding 2 g have been associated with 'pseudocholelithiasis' (sludging in the gall bladder) in sick patients some of whom have been on parenteral nutrition. Ultrasound evidence of sludging in the gall bladder may be seen in up to 50% of patients but 9% of patients may be symptomatic. This side effect is unlikely to occur in a healthy population dosed once.
Cephalosporins may cause mild maculopapular rashes (<2%), loose stools (<3%), and transient increases in creatinine (1%) and liver enzymes (<3%).
The active pharmaceutical ingredient is the same so the risks of rectal formulations of ceftriaxone are the same as those described above for parenteral ceftriaxone. In addition, participants may experience adverse events at the site of administration such as tenesmus (the feeling that you need to pass stools), proctalgia (rectal pain) or proctitis (rectal inflammation).

Where is the study run from?
Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University (Thailand)

When is the study starting and how long is it expected to run for?
March 2019 to August 2026

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Prof. Elizabeth A Ashley (Principal Investigator), Elizabeth.Ashley@tropmedres.ac

Contact information

Type(s)
Principal investigator

Contact name
Prof Elizabeth A Ashley

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
NCT03895567

Protocol serial number
BAC18003

Study information

Scientific Title
A randomised crossover study of the pharmacokinetics, safety and tolerability of two rectal formulations of ceftriaxone compared to parenteral ceftriaxone, in healthy Thai adults

Acronym
CefREC

Study objectives
Is the bioavailability of ceftriaxone administered by suppository (in two new formulations) greater than or equal to 15%?

Ethics approval required
Ethics approval required

Ethics approval(s)
1. approved 20/04/2023, Oxford Tropical Research Ethics Committee (University of Oxford, University Offices, Wellington Square, Oxford, OX1 2JD, United Kingdom; +44 (0) 1865 (2)82106; oxtrec@admin.ox.ac.uk), ref: 10-19

2. approved 07/03/2023, Faculty of Tropical Medicine Ethics Committee (Mahidol University, , Bangkok, 10400, Thailand; +66 (0)2 3549100; tmectropmed@mahidol.ac.th), ref: TMEC 22-083

Study design
Randomized open-label single-centre Phase I crossover study

Primary study design
Interventional

Study type(s)

Treatment

Health condition(s) or problem(s) studied
Healthy volunteers

Interventions
Current interventions as of 07/03/2023:
The following regimens will be evaluated in random order in all participants:
1. Ceftriaxone (Roche ®) 500mg (slow intravenous injection)
2. Ceftriaxone rectal dosage form test formulation 1 - hard-shell gelatin capsule (1 x 500 mg)
3. Ceftriaxone rectal dosage form test formulation 2 - rectodispersible mannitol-based tablet (1 x 500 mg)

Possible schedules: ABC, ACB, BAC, BCA, CAB, CBA.

Each recipient will receive a single treatment dose of each of the three formulations in an order pre-determined by a computer-generated randomisation list. This will be a constrained randomisation which ensures approximately balanced proportions for all six schedules (either 6 or 7 participants per schedule). There will be a 7-28 days washout period between doses. The last follow-up visit is 28 (+ 2) days after the final dose. Participants lost to follow-up or unevaluable for any reason before completion of pharmacokinetic sampling after the final dose will be replaced at the discretion of the investigators with another participant of the same population, if either sample size or completeness of the dataset is compromised.

Previous interventions:
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1. Ceftriaxone (Roche ®) 500mg (slow intravenous injection)
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Possible schedules: ABC, ACB, BAC, BCA, CAB, CBA.

Each recipient will receive a single treatment dose of each of the three formulations in an order pre-determined by a computer-generated randomisation list. This will be a constrained randomisation which ensures approximately balanced proportions for all six schedules (either 6 or 7 participants per schedule). There will be a minimum 7-day washout period between doses. The last follow-up visit is 28 (+ 2) days after the final dose. Participants lost to follow-up or unevaluable for any reason before completion of pharmacokinetic sampling after the final dose will be replaced at the discretion of the investigators with another participant of the same population, if either sample size or completeness of the dataset is compromised.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)

Ceftriaxone (Roche ®) 500 mg (slow intravenous injection), ceftriaxone rectal dosage form test formulation 1 - hard-shell gelatin capsule (1 x 500 mg), ceftriaxone rectal dosage form test formulation 2 - rectodispersible mannitol-based tablet (1 x 500 mg)

Primary outcome(s)
Bioavailability of rectal formulations estimated from the pharmacokinetic data obtained following administration of parenteral and rectal formulations for each participant.

Key secondary outcome(s))
Current secondary outcome measures as of 07/03/2023:
1. Description of other key pharmacokinetic parameters measured using a validated LC-MS/MS bioanalytical method:
1.1. Exposure (AUC0-∞)
1.2. Peak concentration (Cmax)
1.3. Absorption rate (Tmax)
1.4. Time above a plasma concentration of 1 µg/ml (this concentration is above the MIC90 for major neonatal pathogens (Streptococcus agalactiae, Klebsiella spp., Escherichia coli, methicillin-sensitive Staphylococcus aureus) and is the lower limit of detection of the assay)
2. Safety and tolerability:
2.1. Occurrence of serious adverse events (SAEs) from the date of the first dose to 28 days after the final dose, according to the MedDRA classification
2.2. Occurrence of all adverse events from the date of the first dose to 28 days after the final dose, according to the MedDRA classification

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2.2. Occurrence of all adverse events from the date of the first dose to 28 days after the final dose, according to the MedRA classification

Completion date
01/08/2026

Eligibility

Key inclusion criteria
1. Healthy male or non-pregnant female, aged 18 to 46 years (inclusive)
2. Willing and able to give informed consent to participate in the trial
3. Able, in the investigator's opinion, and willing to comply with the study requirements and follow-up

Participant type(s)

Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
46 years

Sex
All

Key exclusion criteria
Current participant exclusion criteria as of 07/03/2023:
1. Female participant who is pregnant, lactating or planning pregnancy during the course of the study
2. Presence of any condition which in the judgment of the investigator would affect the absorption of the rectal formulation e.g. previous surgery, haemorrhoids, inflammatory bowel disease
3. Irritable bowel syndrome (IBS) or diarrhoea in the 24 hours prior to the study drug administration
4. Presence of any condition which in the judgment of the investigator would place the participant at undue risk or interfere with the results of the study (e.g. serious underlying cardiac, renal, hepatic or neurological disease; severe malnutrition; congenital defects or febrile condition)
5. Seropositive for HIV at screening
6. Hepatitis B surface antigen (HBsAg) detected in serum at screening
7. Seropositive for hepatitis C virus (antibodies to HCV) at screening
8. Participation in a clinical trial and/or has received a drug or a new chemical entity within 30 days or 5 half-lives, or twice the duration of the biological effect of any drug (whichever is longer) prior to the first dose of study medication and throughout the study period
9. Any medical condition that in the judgment of the investigator would make the administration of the study treatments unsafe
10. Use of medications known to have a potentially clinically significant interaction with ceftriaxone or with sodium chenodeoxycholate (Na-CDC) in the 28 days prior to the first dose and throughout the study period. This includes aluminium-containing antacids, colestipol, phenobarbital and the combined oral contraceptive pill.
11. Known 27-hydroxylase deficiency (presenting as cerebrotendinous xanthomatosis)
12. History of anaphylaxis and/or hypotension, laryngeal oedema, wheezing, angioedema or urticarial rash following treatment with ceftriaxone, another cephalosporin or any beta-lactam (e.g. penicillin)
13. History of any other clinically significant reaction to ceftriaxone, another cephalosporin or beta-lactam e.g. drug-induced nephritis, hepatitis, erythema multiforme that, in the opinion of the investigator, contraindicates participation in the study.
14. Serious chronic illness.
15. Abnormal baseline laboratory screening test as defined below:

15.1. AST > 2 x upper normal limit
15.2. ALT > 2 x upper normal limit
15.3. Anaemia (Hb < 11 g/dL for female and Hb < 12 g/dL for male)
15.4. Platelets < 150,000
15.5. Total bilirubin > 2 x upper normal limit
16. Hepatomegaly, right upper quadrant abdominal pain or tenderness.
17. Body Mass Index> 35
18. History of alcohol or substance abuse or dependence during the 6 months before study participation: History of regular alcohol consumption averaging >7 drinks/week for women or >14 drinks/week for men. One drink is equivalent to 12 g alcohol = 5 oz (150 ml) of wine or 12 oz (360 ml) of beer or 1.5 oz (45 ml) of 80-proof distilled spirits.

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1. Female participant who is pregnant, lactating or planning pregnancy during the course of the study
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Date of first enrolment
01/09/2025

Date of final enrolment
31/05/2026

Locations

Countries of recruitment
Thailand

Study participating centre
Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University
420/6 Ratchawithi Rd
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Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

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

Individual participant data (IPD) sharing plan
The 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?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes