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Clinical investigation of in-vivo susceptibility of Plasmodium falciparum to artesunate in Western Cambodia (study 2)

Submission date	Recruitment status	[_] Prospectively registered
14/05/2008	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
16/05/2008	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
19/06/2015	Infections and Infestations	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
BKMAL0801; 077166

Study information

Scientific Title
Clinical investigation of in-vivo susceptibility of Plasmodium falciparum to artesunate in Western Cambodia (study 2)

Study objectives
There are worrying signs from Western Cambodia that parasitological responses to artesunate and artemether containing treatment regimens for uncomplicated falciparum malaria are slower than elsewhere in the world. Both delayed parasite clearance and unusually high failure rates with artesunate-mefloquine and artemether-lumefantrine have been reported. Although occasional poor responses to artesunate have been described previously the current reports suggest a consistent problem.

In pooled data from 12,553 patients receiving artemisinin derivatives, 17% had parasite clearance times (PCTs) over 48 hours and 5% had PCTs over 72 hours. As the rate of parasite clearance is a good pharmacodynamic measure of efficacy of the artemisinin related compounds, slow parasite clearance could indicate the emergence of significant resistance. These antimalarials are central to current treatment strategies, and so spread of significant resistance outside this area would be a disaster. Radical containment measures might be needed. In this context there is an urgent need to proceed quickly to investigate the level of resistance to artemisinin derivatives in Western Cambodia to provide a definitive assessment so that if necessary containment plans can be developed in 2007/2008.

A group of malaria investigators from Cambodia and Thailand have joined together to address this urgent question as quickly and effectively as possible. The trial described here proposes to assess the current recommended doses given in the normal way, and if necessary a higher dose of artesunate. There is no known dose related toxicity with artesunate, and doses up to 10 mg/kg /day have been given (by us) without any adverse effects. The two features of this study which differ from normal studies in uncomplicated malaria are the repeated blood sampling and the seven-day in-patient stay. If responses to artesunate are poor it is essential to have characterised the blood concentration profile as well as the parasitological response to differentiate resistance from abnormal pharmacokinetics.

As of 22/02/2010 this record has been updated to include an extended sample size due to the inclusion of a site in Thailand as well as the original site in Cambodia. The target number of participants has been updated to reflect this; the initial target number of participants was 40 (planned end of recruitment = 31/12/2008). The overall trial end date was also extended; the initial overall trial end date was 31/03/2009.

Ethics approval required
Old ethics approval format

Ethics approval(s)

1. Oxford Tropical Medicine Research Ethics Committee (sponsor ethics approval), 13/12/2007, ref: OXTREC [015/07]
2. National Ethics Committee for Health Research (Cambodia), 07/12/2007, for the site: Pailin Hospital

Study design
Multicentre randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Acute falciparum malaria

Interventions
Current interventions as of 22/02/2010:
Arm 1 (N = 40): receive artesunate alone at a dose of 6 mg/kg/day for seven days
Arm 2 (N = 40): receive artesunate alone at a dose of 6 mg/kg/day in two divided doses for seven days
Arm 3 (N = 40): receive artesunate at a dose of 8 mg/kg/day for three days, plus mefloquine at a dose of 15 mg/kg on day three and 10 mg/kg on day four
Arm 4 (N = 40): receive artesunate at a dose of 8 mg/kg/day in two divided doses for three days, plus mefloquine at a dose of 15 mg/kg on day three and 10 mg/kg on day four

Follow up duration for all arms: 63 days

Initial information at time of registration:
Arm 1 (N = 10): receive artesunate alone at a dose of 6 mg/kg/day for seven days
Arm 2 (N = 10): receive artesunate alone at a dose of 6 mg/kg/day in two divided doses for seven days
Arm 3 (N = 10): receive artesunate at a dose of 8 mg/kg/day for three days, plus mefloquine at a dose of 15 mg/kg on day three and 10 mg/kg on day four
Arm 4 (N = 10): receive artesunate at a dose of 8 mg/kg/day in two divided doses for three days, plus mefloquine at a dose of 15 mg/kg on day three and 10 mg/kg on day four

Follow up duration for all arms: 63 days

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Artesunate, mefloquine

Primary outcome measure
Parasite clearance times in relation to artesunate/dihydroartemisinin (DHA) plasma concentration (PK/PD) (time point: 63 days).

Secondary outcome measures
1. Cure rates (time point: 63 days)
2. In vitro sensitivity of P. falciparum to artesunate measured prior to treatment (time point not applicable)
3. Molecular markers of drug resistance measured prior to treatment (time point not applicable)

Overall study start date
01/04/2008

Completion date
01/12/2010

Eligibility

Key inclusion criteria
Children greater than 6 years old and adults (either sex) presenting with acute falciparum malaria will be eligible for this study provided that:
1. They or their parents/guardians give fully informed consent
2. They have not received antimalarial drugs in the previous 48 hours
3. Plasmodium falciparum parasitaemia exceeds 10,000 /uL
4. They agree to seven days of hospitalisation

Participant type(s)
Patient

Age group
Mixed

Sex
Both

Target number of participants
160

Key exclusion criteria

1. Pregnancy
2. Microscopy indicates a mixed infection
3. History of allergy to artesunate or mefloquine

Date of first enrolment
01/04/2008

Date of final enrolment
31/10/2010

Locations

Countries of recruitment
Cambodia

Thailand

Study participating centre
Mahidol-Oxford Research Unit
Bangkok
Thailand
10400

Sponsor information

Organisation
University of Oxford (UK)

Sponsor details
Manor House
John Radcliffe Hospital
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Oxford
England
United Kingdom
OX3 9DU

Sponsor type
University/education

Website
http://www.ox.ac.uk/

ROR

https://ror.org/052gg0110

Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust (UK) (grant ref: 077166)

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Funder Name
Bill and Melinda Gates Foundation (USA) (grant ref: 48821)

Alternative Name(s)
Bill & Melinda Gates Foundation, Gates Foundation, BMGF, B&MGF, GF

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United States of America

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/05/2010		Yes	No