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Study of resistance to artesunate of malaria parasite

Submission date	Recruitment status	[_] Prospectively registered
22/01/2008	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
25/01/2008	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
21/03/2013	Infections and Infestations	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
Version 12 Dec 2007

Study information

Scientific Title
Clinical investigation of in-vivo and in vitro susceptibility of P. falciparum to artesunate in Western Thailand

Study objectives
Has the resistance to artemisinins in P. falciparum emerged in Thailand?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics approval received from Mahidol University Ethical Committee on the 20th December 2007 (ref: MUTM 2007-130).

Study design
Pharmacokinetic and dynamic study of artesunate in two randomly assigned treatment groups.

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Malaria/uncomplicated/resistance

Interventions
Patients will be randomised in blocks of 10 to receive either:
1. Artesunate (Guilin Pharmaceutical Company, PRC) orally (po) 2 mg/kg/day for 7 days
2. Artesunate (Guilin Pharmaceutical Company, PRC) po 4 mg/kg/day for 3 days plus mefloquine 15 mg/kg on day 3 and 10 mg/kg on day 4

On enrolment a detailed history and full clinical examination will be performed and recorded on a standard Case Report Form (CRF). The patient will then be weighed. A Teflon® heparinised sampling catheter will be inserted in a forearm vein.

Baseline blood samples will be taken as described below. Part of the blood sample will be taken at baseline for immediate culture (for an in-vitro susceptibility test) and also storage of parasites (cryopreserved in liquid nitrogen), parasite deoxyribonucleic acid [DNA] and messenger ribonucleic acid [mRNA]. On admission 5 ml blood will be collected for parasite count (thin and thick films stained by Giemsa's method), and routine biochemistry (sodium, potassium, chloride, calcium, blood urea nitrogen, creatinine, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin, total protein, glucose and total carbon dioxide) and haematology (haematocrit, haemoglobin, white blood cell count with differentiation, platelets). An additional 5 ml of blood will be collected in a sterile heparinised tube for parasite culture and cryopreservation, and 2 ml for assessment of drug levels (artesunate and mefloquine).

The total amount of blood taken for study purposes will be 12 ml on admission and about 10 to 20 ml during follow-up (dependent on the parasite clearance time; blood collection for parasitaemia during hospitalisation will stop when the patient is parasite negative).

Sampling (2 ml):
1. Parasite counts: 0, 4, 8, 12, 18, 24 hours then 6 hourly until parasite clearance
2. Drug levels: plasma samples will be taken. Most are fixed times but for artesunate there is a

population PK component so random times within time-bins are proposed. In children capillary whole blood sampling for mefloquine may need to be substituted.

Patients will remain in hospital for 7 days or longer if parasites have not cleared. They will then be followed up to Day 63 and at each weekly visit will have a haematocrit and parasite count checked.

Intervention Type
Drug

Phase
Not Specified

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

Primary outcome(s)
A population based pharmacokinetic-pharmacodynamic modelling approach will be used to describe the antimalarial effect of artesunate in patients with acute falciparum malaria. The objective of the modelling exercise is to characterise the relationship between pharmacokinetic variables (areas under curve [AUC], Cmax) and parasite clearance measures (parasite clearance time [PCT], parasite reduction ratio [PRR]), completed with in vitro susceptibility and molecular markers of resistance.

Key secondary outcome(s))
Parasitological efficacy

Completion date
01/06/2008

Eligibility

Key inclusion criteria
1. 40 patients with uncomplicated falciparum malaria
2. Aged greater than or equal to 15 years, either sex
3. Symptomatic of malaria infection, i.e., history of fever or presence of fever greater than 37.5°C
4. Microscopic confirmation of asexual stages of P. falciparum with parasitaemia greater than 10,000/ml
5. Written informed consent to participate in trial

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex

All

Key exclusion criteria
1. Pregnancy or lactation (urine test for beta-human chorionic gonadotropin [β-HCG] to be performed on any woman of child bearing age unless menstruating)
2. P. falciparum asexual stage parasitaemia greater than or equal to 4% red blood cells (175,000 /µl)
3. History of treatment with antimalarials (except chloroquine [CQ] or sulfadoxine-pyrimethamine [SP]) in the previous 48 hours
4. Microscopy indicates a mixed infection
5. Signs or symptoms indicative of severe malaria:
5.1. Impaired consciousness (Glasgow Coma Scale [GCS] less than 15)
5.2. Bleeding disorder (severe nosebleed, bleeding gums, frank haematuria, bleeding from venepuncture sites)
5.3. Respiratory distress (deep breathing or respiratory rate [RR] greater than 30)
5.4. Shock (circulatory collapse with systolic blood pressure [SBP] less than 80 mmHg)
5.5. Hyperparasitaemia (see above)
5.6. Acidosis (bicarbonate [HCO3-] less than 15 mmol/L)
5.7. Renal insufficiency (creatinine greater than 3 mg/dL)
5.8. Severe jaundice (total bilirubin greater than 2.5 mg/dL)
5.9. Severe anaemia (haematocrit [Hct] less than 20% in adults or less than 15% in children)
5.10. Severe hypoglycaemia (glucose less than 40 mg/dL)
6. Known hypersensitivity to artemisinin derivatives or mefloquine
7. History of convulsions or neuropsychiatric disorder
8. History of splenectomy

Date of first enrolment
01/01/2008

Date of final enrolment
01/06/2008

Locations

Countries of recruitment
Thailand

Study participating centre
Shoklo Malaria Research Unit (SMRU)
Mae Sot
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63110

Sponsor information

Organisation

University of Oxford (UK)

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Charity

Funder Name
The Wellcome Trust South-East Asia (SEA) Programme (Thailand)

Results and Publications

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	30/07/2009		Yes	No