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Efficacy and safety of artemisinin-piperaquine (Artequick) compared to dihydroartemisinin-piperaquine (Artekin) in uncomplicated falciparum malaria in adults

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A hospital-based, randomized controlled study was done at No. 1 MH (1000 Bedded), Mingaladon, No. 1 MH (700 Bedded), PyinOoLwin and No. 9 MH (100 Bedded), Lashio, on a total of 64 uncomplicated falciparum malaria patients from January to September 2007, to determine the therapeutic efficacy, safety and tolerability of artemisinin-piperaquine (Artequick) tablet in comparison with dihydroartemisinin-piperaquine (Artekin) for the treatment of 30 uncomplicated falciparum malaria patients in adults. Artequick 2 tabs was given at 0 and 24 hours in one group and Artekin 2 tabs was given at 0, 6, 24 and 32 hours in the control group. Initial parasitaemia/μl were 16471.88±38755.1 and 13528.9±1909.3. Fever clearance times (FCT) were 43.23±17.35 and 12.4±13.1 hours, and Parasite clearance times (PCT) were 57.6±21.88 and 46.8±22.1 hours, respectively, in Artequick and Artekin groups. In Artequick group, there were four late treatment failures (LTF) that adequate clinical and parasitological response (ACPR) was 94% compared to 100% ACPR in Artekin group. There were no serious side effects. Artequick is as safe as Artekin but with lower ACPR in this study. Further dose finding studies will be needed to establish its efficacy in the treatment of uncomplicated falciparum malaria in adults.

INTRODUCTION

To combat the development and spread of resistance to drugs in *P. falciparum* infection, WHO has recommended the use of artemisinin combination therapy (ACT) and, if possible, the preparations should be formulated in a single tablet to enhance the compliance. Artequick (artemisinin-piperaquine) and Artekin (dihydroartemisinin-piperaquine) are among these artemisinin combination therapy. Clinical studies on the Artekin (dihydroartemisinin-piperaquine) have been carried out in several countries including Thailand, Vietnam, Cambodia and Myanmar and are reported to be safe and effective [1].

Artequick (artemisinin-piperaquine) is an improved fixed dose Artemisinin combination therapy. Phase I, II and III clinical studies on Artequick have been completed and reported [2]. Primary evaluation of Artequick on 1025 malaria patients in clinical trial (phase II and III) at 7 hospitals in 4 countries indicated that it was well tolerated, highly efficacious, quick acting and with low toxicity. Over 6000 people treated with Artequick in Kampong Speu of Cambodia also showed that it was very well tolerated and with a low cost. This new excellent ACT is thus expected to enter the public sector in a large scale in the near future [2].

A hospital-based, randomized controlled study of Artekin compound tablet (40 mg dihydroartemisinin and 320 mg piperaquine phosphate, the dosage of 2 tabs given at 0, 6, 24 and 32 hours) comparing with Artequin™ (fixed dose combination pack of artesunate – mefloquine, 2 tablets daily for 3 days course)

was done at the Defense Services General Hospital (DSGH), Mingaladon in 2006. The sensitivity was 100% for this combination. Then, randomized control trial of Artekin and Larimal fixed dose combination (Blister) pack of artesunate 50 mg and 153.1 mg amodiaquine (dosage of 2 tablets BD for 3 days) gave 100% sensitivity in 2007 at DSGH.

Hence, this study on the clinical efficacy and safety of a fixed dose combination tablet of Artequick® will provide useful information for future evidence-based guidelines in the treatment of falciparum malaria in adults in Myanmar.

Aim

- To find out the efficacy, safety and tolerability of Artequick (artemisinin-piperaquine) compound tablet in uncomplicated falciparum malaria in Myanmar

Objectives

- To measure the clinical and parasitological efficacy of Artequick in uncomplicated falciparum malaria
- To evaluate the frequency, severity and duration of adverse clinical, haematological, biochemical and ECG features

PATIENTS AND METHODS

Study design

An open label, randomized hospital-based clinical study.

Study sites

Clinical Research Unit (Malaria), No.1 DSGH (1000 Bedded), Mingaladon, No. 1 MH (700 Bedded), PyinOoLwin and No.9 MH (100 Bedded), Lashio.

Study period

March 2007 to September 2007

Acute symptomatic uncomplicated falciparum malaria patients admitted to the above hospitals were recruited. Patients were categorized as symptomatic if they were febrile or with one of the following symptoms: Feeling ill, headache, aches and pains, nausea or vomiting.

Inclusion criteria

- Both sexes
- The age group between 12-60 years
- Positive peripheral blood film for trophozoite forms of pure *Plasmodium falciparum* with the count ranging from 2000/µl up to 200,000/µl
- Axillary temperature ≥37.5°C or history of fever during the previous 24 hours
- Patients who have no evidence of severe and complicated falciparum malaria
- Patients who have not been treated with any artemisinin derivatives or mefloquine within the past 14 days
- Patients who are willing to give informed consent for treatment and able to remain hospitalized for 28 days

Exclusion criteria

- Presence of any feature of severe or complicated malaria
- Presence of mixed infection (e.g. vivax or malariae)
- Patients with fever due to causes other than malaria e.g. TB, etc.
- Patients with other concomitant diseases like diabetes mellitus, etc.
- Pregnant women in the first trimester of pregnancy
- Contraindications to antimalarial drugs

Withdrawal criteria

- Patient's request
- Any serious adverse effects to drugs
- Serious or repeated non-compliance with protocol specifications

Sample size

Artequick

Sixty-four adults (24 patients from No.1 MH Mingaladon, 20 patients from No.1 MH PyinOoLwin and 20 patients from No.9 MH Lashio)

Artekin

Thirty adults (10 patients each from above three hospitals)

Study drug

Artequick® (fixed dose combination artemisinin-piperaquine, expiry date 07–2009, produced from Artepharm Co. Ltd, Guangzhou, China, Batch No. 20060801). Each tablet contains artemisinin (AMS) 62.5mg and piperaquine (PPQ) 375mg.

Dose=2 tabs at 0 hour and 2 tabs at 24 hours (Total dosage=4 tabs).

Control drug

Artekin (compound dihydroartemisinin-piperaquine, produced from Holleykin Pharmaceutical Co. Ltd., Guangzhou, China, Batch No. 20030302). Each tablet contains 40 mg dihydroartemisinin and 320 mg piperaquine phosphate.

Dose=2 tabs at 0, 8, 24, 32 hours.
(Total dosage=8 tabs)

Procedure

Eligible patients were subjected to the following procedure.

Routine history taking, clinical examination and relevant investigations were done. Randomization was done by lottery procedure. Data were recorded in the standard proforma by the assigned medical officer, under the supervision of the medical specialist in charge of the trial.

Assessments

Clinical

Symptoms review, adverse effect review (according to the check-list format), and physical examination were made on Day 0, 1, 2, 3, 4, 7, 14 and 28. Body temperatures were taken 4 hourly until normal for 24 hours, then daily up to Day 28.

Parasitology

Giemsa-stained thick and thin blood smears were examined by the trained technician and parasite counts performed 6 hourly until negative for 24 hours and daily up to 3 consecutive negatives, then weekly up to Day 14 whenever it was indicated (e.g., reappearance of fever).

Haematology

Haemoglobin %, total and differential count were carried out on day 0, 3, 7, 14 and 28.

Biochemistry

Blood urea and sugar were examined on day 0, 3, 7, 14 & 28.

ECG

Haematology, biochemistry and ECG were monitored on day 0, 1, 3, 7, 14 & 28 to the patients admitted to DSGH only and not in other hospitals.

Drug tolerance and safety

Frequency, severity and duration of adverse clinical, haematological, biochemical and therapeutic response were assessed according to WHO criteria as ETF, LTF, ACPR.

Definitions (WHO 2003)

Early treatment failure (ETF)

- Development of danger signs or severe malaria on Day 1, Day 2, or Day 3 in the presence of parasitaemia.
- Parasitaemia on Day 2 higher than Day 0 count, irrespective of axillary temperature.
- Parasitaemia on Day 3, with axillary temperature ≥37.5 ^{o}C.
- Parasitaemia on Day 3 ≥25% of count on Day 0.

Late treatment failure (LTF)

It is divided into late clinical failure (LCF) and late parasitological failure (LPF).

Late clinical failure (LCF)

- Development of danger signs or severe malaria after Day 3 in the presence of parasitaemia, without previously meeting any of the criteria of early treatment failure
- Presence of parasitaemia and axillary temperature ≥37.5^{o}C on any day from Day 4 to Day 28, without previously meeting any of the criteria of early treatment failure.

Late parasitological failure (LPF)

- Presence of parasitaemia on Day 28 and axillary temperature <37.5°C, without previously meeting any of the criteria of early treatment failure or late clinical failure

Adequate clinical and parasitological response (ACPR)

- Absence of parasitaemia on Day 28, irrespective of axillary temperature, without previously meeting any of the criteria of early treatment failure, late clinical failure or late parasitological failure

Efficacy

- Indicators include ETF, LTF, ACPR

PCT (Parasite clearance time)

- The time from initiation of therapy to the first negative blood film that remained negative for 48 hours

% PC_{24h} and % PC_{48h}

- Percentage clearance of parasitaemia at 24 and 48 hours

FCT (Fever clearance time)

- The time from initiation of therapy to time the temperature reached normal (37°C) and remained so for 24 hours

Retreatment of failure

- ETF and LTF cases were retreated with standard antimalarial treatment (according to the national guidelines). All cases were recovered.

Data analysis

All data in the proforma were checked for completeness, errors and inconsistencies (by the assigned investigators) prior to entry of the raw data into the constructed data-base sheet (Microsoft Office Excel). Statistical analyses were done by computer using EPI-INFO software at CRU (Malaria), DSGH.

Ethical considerations

The protocol was submitted to Ethical Committee (Research & Development Committee), Ministry of Defence for approval. Informed written consents were obtained from all the patients.

RESULTS

There were four late treatment failure cases out of 64 cases completed to study with Artequick, but there was no treatment failure case in Artekin group, out of 30 cases studied.

Table 1. Baseline characteristics of two groups

Parameters	Regimens		<p>
	Artequick (n=64)	Artekin (n=30)	
Age (years)	28.14±10.3	32.5 ±11.3	0.898
Body weight (kg)	60.00± 4.9	53.9 ± 7.3	0.965
Height (ins)	174.53± 8.4	163.9 ± 7.9	0.128
Initial temp (°C)	38.20 ± 1.4	38.2 ± 1.1	0.937
Initial parasitaemia/µl (range)	400-200,000	800-200,000	0.939

Plus-minus values are shown in mean±SD

Table 2. Response of fever and parasitaemia in two groups

Response	Regimen		<p>
	Artequick (n=64)	Artekin (n=30)	
Fever clearance time FCT (Hours)	43.23±17.35	12.4±13.1	0.088
Parasite clearance time PCT (Hours)	57.60±21.88	46.8±22.1	0.091

Data are shown in mean±SD

Table 3. Serial laboratory (biochemical) parameters in two groups

Parameters	Day 0	Day 7	Day 14	Day 21	Day 28
Artequick					
Blood urea (mg%)	26.5 ±7.2	23.0 ±7.8	23.6 ±5.0	23.0 ±2.6	21.0 ±5.0
Blood sugar (mg%)	102.0 ±10.2	98.0 ±6.9	95.9 ±5.6	95.2 ±4.5	95.3 ±7.8
Artekin					
Blood urea (mg%)	26.3 ±7.4	24.7 ±6.3	22.5 ±1.7	22.2 ±2.6	23.1 ±5.8
Blood sugar (mg%)	96.4 ±21.5	102.1 ±10.1	99.1 ±9.1	99.6 ±5.5	101.8 ±7.2

Data are shown in mean±SD

There were no adverse events like dizziness, headache, nausea, vomiting, palpitations, pruritus and abnormal ECG finding in two groups.

Table 4. Serial laboratory (haematological) parameters in two groups

Parameters	Day 0	Day 7	Day 14	Day 21	Day 28
Artequick					
Hb(g/dl)	11.3 ±1.7	12.8 ±1.4	11.7 ±1.1	12.0 ±1.4	11.7 ±1.4
Total WBC ($x10^3$/l)	5.0 ±1.2	5.6 ±0.8	4.9 ±0.9	5.0 ±1.1	5.3 ±1.0
Differential Polymorph (%)	62.6 ±3.3	65.0 ±3.9	64.3 ±2.3	64.8 ±3.1	63.6 ±3.1
Lymphocyte (%)	33.3 ±2.6	30.0 ±3.2	33.3 ±3.7	31.1 ±3.1	31.6 ±3.0
Monocyte (%)	1.9 ±0.5	3.0 ±0.5	2.0 ±0.6	2.2 ±0.6	2.1 ±0.4
Eosinophil (%)	2.1 ±0.4	2.0 ±0.5	1.96 ±0.5	1.9 ±0.6	1.9 ±0.6
Artekin					
Hb (g/dl)	10.8 ±2.7	10.4 ±2.1	11.3 ±1.6	11.5 ±1.5	11.6 ±1.4
Total WBC ($x10^3$/l)	4.7 ±0.9	4.7 ±0.7	5.0 ±0.7	5.0 ±1.5	5.1 ±1.0
Differential polymorph (%)	63.2 ±3.3	63.1 ±3.1	62.0 ±4.2	63.4 ±3.3	64.0 ±3.1
Lymphocyte (%)	32.3 ±3.7	33.3 ±2.9	33.3 ±3.9	32.3 ±3.4	31.8 ±3.0
Monocyte (%)	2.1 ±0.0	1.9 ±0.5	1.7 ±0.5	2.0 ±0.4	1.8 ±0.4
Eosinophil (%)	2.2 ±0.4	2.3 ±0.4	2.2 ±0.5	2.3 ±0.5	2.2 ±0.6

Data are shown in mean±SD

DISCUSSION

Southeast Asia region has the most resistant malaria parasite in the world limiting the treatment option. It is generally accepted that to combat drug resistance, combination of antimalarial drugs that include an artemisinin derivative should be used and, if possible, these should be formulated in a single tablet. RCT trials of Artekin have been done in many countries and showed good efficacy and tolerability. Present study shows that the drug Artequick has 4 LTF cases, having 94% ACPR. None of our patients develops severe side effects. Cinical trials of Artequick in Thailand [6] reported the cure rate of 72% at the same dosage as in our study.

But the cure rate was improved to 98% with higher dose of 2 tabs at 0, 24, 48 hours. Our study showed that Artequick is as safe as Artekin but with lower ACPR in this study. Further dose finding studies will be needed to establish its efficacy in the treatment of uncomplicated falciparum malaria in adults.

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