

A randomized open study to assess the efficacy and tolerability of dihydroartemisinin–piperaquine for the treatment of uncomplicated falciparum malaria in Cambodia

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Summary

OBJECTIVES To compare the efficacy and tolerability of dihydroartemisinin–piperaquine (DHA–PQP) with that of a 3-day regimen of mefloquine and artesunate (MAS3) for the treatment of uncomplicated falciparum malaria in Cambodia.

METHOD Randomized open-label non-inferiority study over 64 days.

RESULTS Four hundred and sixty-four patients were included in the study. The polymerase chain reaction genotyping-adjusted cure rates on day 63 were 97.5% (95% confidence interval, CI, 93.8–99.3) for DHA–PQP and 97.5% (95% CI, 93.8–99.3) for MAS3, $P = 1$. There were no serious adverse events, but significantly more episodes of vomiting ($P = 0.03$), dizziness ($P = 0.002$), palpitations ($P = 0.04$), and sleep disorders ($P = 0.03$) reported in the MAS3 treatment group, consistent with the side-effect profile of mefloquine.

CONCLUSIONS DHA–PQP was as efficacious as MAS3, but much better tolerated, making it more appropriate for use in a routine programme setting. This highly efficacious, safe and more affordable fixed-dose combination could become the treatment of choice for *Plasmodium falciparum* malaria in Cambodia.

keywords efficacy, tolerability, dihydroartemisinin–piperaquine, falciparum malaria

Introduction

Malaria remains one of the most important causes of morbidity and mortality in Cambodia with about 13% of the population living in areas of malaria transmission. Multidrug-resistant falciparum strains are common, particularly in the western provinces that share borders with Thailand (Price *et al.* 2004). In 2003, the Ministry of Health reported a total of 132 572 new cases of malaria, 82% of which were caused by *Plasmodium falciparum*. There were 492 malaria-related deaths (Chatterjee 2005). As a considerable proportion of malaria patients are treated in private clinics, these figures (confined to the public health system) underestimate the real prevalence and mortality of malaria.

Worldwide, antimalarial drug resistance is increasing and the latest malaria treatment guidelines published by

the World Health Organization (WHO) recommend artemisinin-based combination therapy (ACT) as first-line treatment for all patients with falciparum malaria (WHO 2006).

In Asia, artesunate and mefloquine has been the most widely used artemisinin-based antimalarial combination in areas of multidrug resistance (Nosten *et al.* 2000; WHO 2003). In 2001, the National Centre for Malaria Control in Cambodia changed the national protocol for the treatment of uncomplicated falciparum malaria to a 3-day regimen of mefloquine and artesunate (MAS3). However, in practice, patients may take one drug without the other. Use of mefloquine as monotherapy is likely to lead to an increase in mefloquine resistance. Yeung *et al.* (2004) described a survey in Cambodia which found that more than 80% of the patients with possible malaria sought treatment in the informal sector. Of the antimalarial

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treatments purchased, 37% contained an artemisinin derivative, but only 20% of these were taken in combination with mefloquine as recommended.

Poor tolerability of mefloquine is a cause for concern which has been well documented in Cambodia and explicitly mentioned in the 2002 National Malaria Treatment Guidelines of the Cambodian Ministry of Health. Previous studies have often designated the related adverse events as being self-limiting and graded them as mild to moderate, with a negligible overall impact on treatment adherence and efficacy (ter Kuile *et al.* 1995; Ezedinachi *et al.* 1999; Krudsood *et al.* 2002). Based on field experience in Cambodia and Thailand, we are inclined to believe that adverse effects such as vomiting, dizziness and sleep disturbances are frequent enough to threaten correct adherence to mefloquine-containing treatments. The fact that mefloquine and artesunate are not available in a fixed-dose combination also makes non-adherence and the emergence of resistance more likely.

Dihydroartemisinin–piperaquine (DHA–PQP), currently developed and produced in China, is among the most promising of new ACT regimens. Recent studies in Thailand found excellent efficacy and good tolerability (Ashley *et al.* 2004, 2005). The regimen is available as a fixed-dose formulation of both drugs, which makes it easier for self-administration and may have a favourable impact on adherence to treatment. The cost of the treatment, which at the time of this study was approximately 1.2 US Dollars (USD) per adult treatment, is considerably lower than the market price of MAS3 of about 3 USD. This large field-based study aimed to determine the efficacy and tolerability of this new combination antimalarial treatment when compared with MAS3.

Methods

Study setting and population

The study was conducted at two sites: Anlong Veng, in Oddar Meanchey province with a population of 13 578 inhabitants and Kvav, in Siem Reap province with a population of 8017 inhabitants. Malaria transmission in these two areas is low and seasonal. Médecins Sans Frontières (MSF) has supported health care delivery in both localities for several years, with a particular focus on improving the quality of diagnosis and treatment of malaria.

Between October 2002 and March 2003, patients were recruited from consultations conducted at the health centres or their outreach malaria clinics. These clinics are run by nurses of the Ministry of Health.

The sample size was calculated to be at least 217 cases in each treatment group to show non-inferiority in the therapeutic efficacy at 63 days of DHA–PQP *vs.* MAS3. This calculation was based on an estimated therapeutic efficacy in the MAS3 group of 98% and the capacity to detect a difference between the two groups of less than 5% (to remain above the 90% of efficacy recommended by the World Health Organization) with 90% power and a two-sided 5% significance level, taking into account 10% loss to follow-up and 20% of *vivax* appearance.

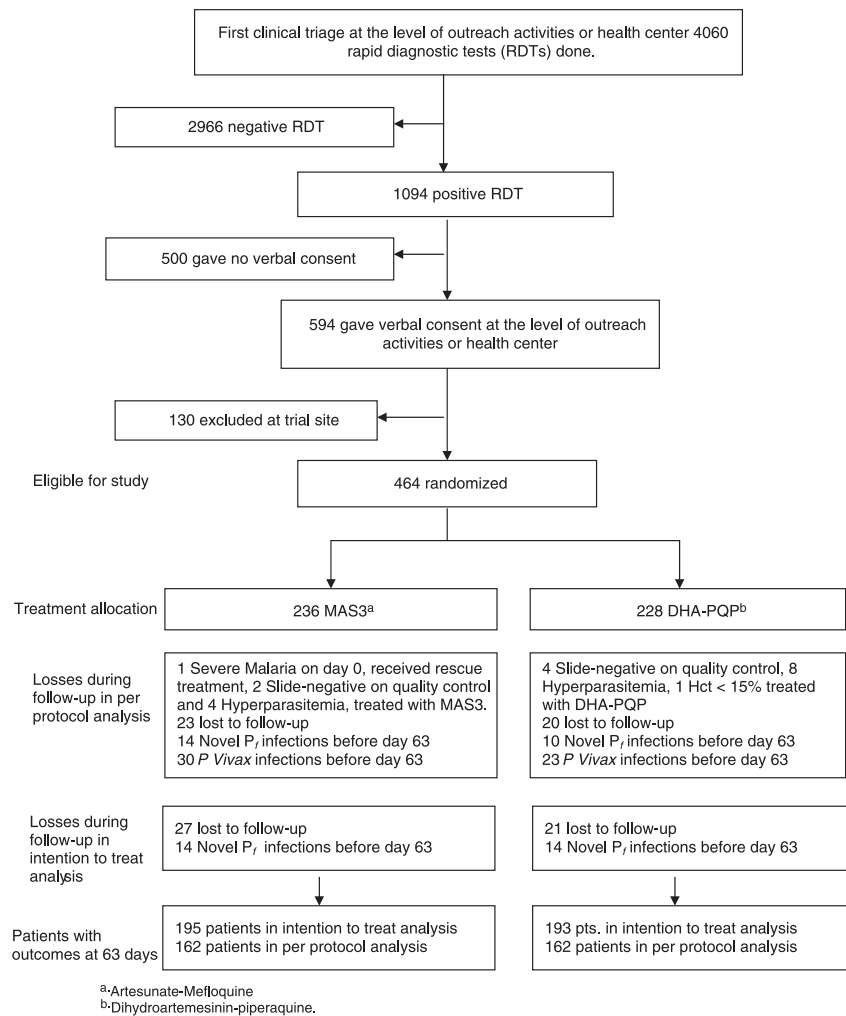
All individuals with signs and/or symptoms of uncomplicated malaria (fever at presentation or history of fever within the last 24 h), and biological confirmation by the rapid diagnostic test (Paracheck PFTM) were eligible for screening. The main criteria for study inclusion were: age greater than 1 year, history of fever or presence of fever (axillary temperature ≥ 37.5 °C), and written informed consent to participate in the study. Patients with mixed infection of *Plasmodium vivax* or *Plasmodium malariae* with *P. falciparum* were included. Excluded from the study were pregnant or lactating mothers, and anyone with the following: asexual stage parasitemia greater or equal to 4% red blood cells (approximately 175 000 parasites/ μ l), signs or symptoms of severe malaria, a history of convulsions or a neuropsychiatric disorder or a history of treatment with mefloquine in the past 60 days. Figure 1 illustrates the patient recruitment and flow in the trial.

The study received ethical clearance from the National Ethical Review Committee of the Ministry of Health in Cambodia and the ethical review board of MSF.

Drugs and treatment regimens

Patients were allocated randomly to receive one of the treatments using a computer-generated randomization (STATA version 8, StataCorp, college station, TX 77845, USA). Treatment allocations were concealed in sealed envelopes.

- Dihydroartemisinin–piperaquine (DHA–PQPTM; Holleykin Pharmaceutical Co. Ltd, Guangzhou, China). One tablet of DHA–PQP contains 40 mg of DHA and 320 mg PQP. An adult dose consisted of four doses of two tablets, given at 0, 8, 24 and 48 h. The approximate total adult dose was 6/48 mg/kg (DHA/PQP). For children, a dose of 1.6/12.8 mg/kg was given at the same time intervals; this dosage was obtained by suspension of a DHA–PQP tablet in 5 ml of water.
- Artesunate + mefloquine for 3 days, as pre-packed drugs (Ministry of Health, Cambodia). Artesunate (Guillin, China, 50 mg tablets) and mefloquine

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(Mepha, Switzerland, 250 mg tablets) All adults received a fixed regimen of 500 mg of mefloquine and 100 mg of artesunate twice daily on day 0 and 200 mg of artesunate once daily on day 1 and day 2. The target dose for children was 4 mg/kg body weight artesunate daily for 3 days and 25 mg/kg body weight mefloquine split into two doses at least 8 h apart on the first day. The exact dosage was calculated and given to the nearest quarter tablet. This was crushed and mixed with liquid for children who were unable to swallow tablets.

Both treatments were administered under direct observation. Each dose was repeated in full if vomiting occurred within 30 min of administration, or halved if vomiting occurred between 30 min and 1 h of drug administration.

Clinical and laboratory monitoring

Enrolled patients were admitted to the trial centre for the 3-day period of treatment. All subjects were given a unique code. Clinical and biological parameters were recorded, including axillary temperature, parasitemia and haematocrit (Hct). A blood spot was collected on Whatmann 3M chromatography paper for PCR genotyping in the event of parasite reappearance. Baseline symptoms were screened for actively on day 0 using a questionnaire with 20 possible symptoms. From day 1 to day 3, the clinical evaluation was repeated and the same symptom questionnaire was completed to record adverse events. These were defined as any new sign or symptom after the first dose of drug had been taken. Patients were monitored daily until fever clearance and by blood microscopy until parasite clearance. There-

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after, patients were seen weekly until 63 days of follow-up when axillary temperature was recorded, a symptom questionnaire was completed, a malaria smear examined and Hct measured. Medical officers of the MSF team conducted home visits for patients who did not attend a scheduled visit. Any additional medications taken during the trial period were documented.

In case of parasite reappearance, a new capillary blood sample was taken from the patient onto filter paper to perform PCR genotyping that tested for allelic variation in three loci: merozoite surface proteins (MSP-1 & MSP-2) and glutamate-rich protein in order to distinguish recrudescence from reinfection. Infections with the same three-locus genotype pre- and post-treatment with P (match) <0.05 , when compared with the prevalence of that genotype frequency in the parasite population from this area, were considered as recrudescence infections (Brockman *et al.* 1999).

Patients previously treated with DHA–PQP were treated with MAS3 if there was no contraindication. Patients who had received MAS3 were treated with artesunate 2 mg/kg and doxycycline 4 mg/kg daily for 7 days. Children under the age of 8 received 2 mg/kg artesunate daily for 7 days. Patients with a positive blood smear for *P. vivax*, *P. malariae* or both were given chloroquine (25 mg base per kg divided over 3 days) and follow-up was continued.

Statistical methods

Data were entered and analysed using EPI-INFO 6.4 (centres for Disease Control and Prevention, Atlanta Georgia, USA) and the STATA software (version no. 8 StataCorp, college station, TX 77845, USA). The primary end points were the PCR-adjusted cure rates at day 63. Following established guidelines (Piaggio *et al.* 2006), the cure rates were analysed in a per-protocol (PP) analysis and an intention-to-treat (ITT) analysis, where all randomized patients who had received treatment were included. Cases of indeterminate PCR were considered as recrudescence infections, adopting a worst-case scenario approach.

Overall, event-free survival distributions for both treatment groups were estimated using the Kaplan–Meier method and compared using the Cox–Mantel (log-rank) test. Patients who did not complete follow-up or had a new Plasmodium infection (*P. falciparum*, *P. vivax* or *P. malariae*) were censored at the time they were last seen for the primary outcome. With the same principle, cure rates in each treatment arm were also calculated as an incidence rate at each day of follow-up. In this approach, the difference of the cure rates at day 63 were calculated and the confidence intervals (CIs) of those differences

were calculated by the Score method (Newcombe 1998). This method allows comparing the difference between the incidence of treatment success for both treatments and the CI around this difference to demonstrate non-inferiority.

Baseline characteristics of patients were compared using the chi-squared or Fisher's exact test for categorical variables and by ANOVA or the Kruskal–Wallis test for continuous variables. All P values were two sided and the level of significance was set at $P = 0.05$ or less. 95% CIs were used throughout.

Safety and tolerability endpoints were the incidence of adverse events, in the first 3 days after the start of the treatment. Differences in proportions were compared using the two-sided chi-squared test.

Results

Characteristics of the study population

Four hundred and sixty-four patients were included in the two sites; of whom 236 were assigned to receive MAS3 and 228 to receive DHA–PQP (Figure 1).

Seven patients were excluded from the analysis: 6 (1.3%) were found to be smear negative after laboratory quality control confirmed by PCR and one patient developed signs of severe malaria and was given rescue therapy. Twelve patients (2.6%) were hyperparasitemic, and one patient had a Hct of less than 15%; these were excluded from the PP analysis. Forty-eight (10.3%) patients failed to complete the 9-week follow-up. One of these patients withdrew consent. The percentages of patients lost to follow-up were similar between the treatment groups ($P = 0.8$). Baseline characteristics of the study populations are summarized in Table 1. Both groups were comparable and there were no major differences noted between the patients recruited at each site.

Efficacy and treatment outcomes

Both treatments show very high cure rates. There were 43 reappearances of falciparum malaria during the follow-up period in the ITT analysis (38 in the PP analysis) (Table 2). The comparison of the parasite genome of these cases with the baseline PCR results identified 34 cases (in ITT, 30 in PP) to be novel infections and eight cases (in ITT, seven in PP) to be recrudescence infections (four (both analyses) in the DHA–PQP group and four (in ITT, three in PP) in the MAS3 group). For one infection, we were unable to define a three-locus genotype due to inability to amplify all three genes despite repeated attempts, this patient (MAS3 group) was considered to have a recrudescence infection. All

B. Janssens *et al.* DHA-PQP vs. MAS3 against malaria in Cambodia**Table 1** Baseline characteristics of all patients included in the trial

	MAS3 ^a	DHA-PQP ^b
Males, <i>n</i> (%)	163 (71.2)	150 (69.8)
Age (years), median (range)	21 (1–57)	21 (2–65)
Weight (kg), median (range)	48 (8–68)	47 (9–73)
Fever duration before admission (days), median (range)	3 (1–30)	3 (0–15)
Geometric mean parasitemia (per μ l) (range)	4786 (30–158256)	3311 (40–173328)
Haematocrit % mean (SD)	35.7 (6.7)	35.6 (6.9)
Total	229	215

^aArtesunate–Mefloquine.^bDihydroartemisinin–piperazine.**Table 2** Appearance of *Plasmodium falciparum*, differentiated by polymerase chain reaction (PCR) between novel and recrudescence infections

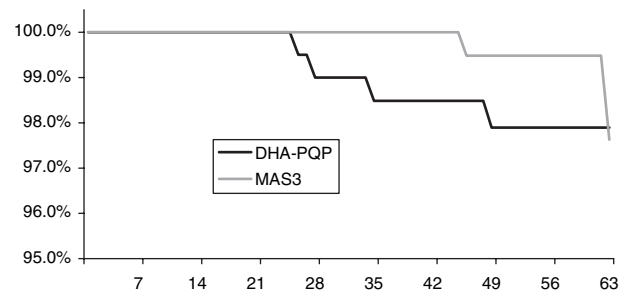
	No. of cases by day after treatment initiation									
	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56	Day 63	Total
<i>P. falciparum</i> novel infections										
DHA-PQP	–	–	–	1 (–)	3	3	2	5 (2)	4	18 (14)
MAS3	–	–	1	–	3	3	5	2	2	16 (16)
<i>P. falciparum</i> Novel + recrudescence										
DHA-PQP	–	–	–	1	1	–	1	–	–	3 (3)
MAS3	–	–	–	–	–	–	1	–	1	2 (2)
<i>P. falciparum</i> recrudescence infection										
DHA-PQP	–	–	–	1	–	–	–	–	–	1 (1)
MAS3	–	–	–	–	1	–	–	–	2†	3

DHA-PQP, dihydroartemisinin–piperazine; MAS, Artesunate–mefloquine.

†In one case, PCR results were indeterminate and this case was considered as recrudescence in the analysis.

Analysis presented for the ITT analysis and values in () for the PP analysis

recurrent infections appeared at day 21 or later. In the PP analysis at 63 days, the PCR-adjusted success rate was 97.5% (158/162) (95% CI, 93.8–99.3) in the DHA-PQP group and 97.5% (158/162) (95% CI, 93.8–99.3) in the MAS3 group (difference 0.0%, 95% CI, –4.0 to +4.0). A Kaplan–Meier survival analysis with log rank test for significance estimated similar cure rates: 98.0% (95% CI, 94.6–99.2) for DHA-PQP and 97.6% (95% CI, 93.8–99.1) for MAS3 ($P = 0.9$) (Figure 2). In the ITT analysis, the cure rate adjusted by the PCR results was 97.9% (189/193) (95% CI, 94.8–99.4) in the DHA-PQP group and

**Figure 2** Kaplan–Meier curve on a PP analysis of the PCR-adjusted cure rates for both treatment groups over the 63-day follow-up.

97.4% (190/195) (95% CI, 94.1–99.2) in the MAS3 group (difference +0.5%, 95% CI, –3.0 to +4.0). Kaplan–Meier survival analysis gave a cure rate of 98.1% (95% CI, 95.0–99.3) for DHA-PQP and 97.5% (95% CI, 94.1–99.0) for MAS3 ($P = 0.8$). In both, the ITT and PP analyses, the CI for differences were within the 5% limits to satisfy statistical criteria for non-inferiority of DHA-PQP to MAS3.

Mixed infections

At baseline, 21 patients had mixed infections, 19 with *P. vivax* and two with *P. malariae*. By day 3, all patients were free of *P. vivax* and *P. malariae*. During the course of the trial, infections with *P. vivax* malaria were detected in 86 patients (in ITT analysis, 80 in PP), 47 (in ITT, 44 in PP) in the MAS3 group and 39 (in ITT, 36 in PP) in the DHA-PQP group, in one patient an infection of *P. malariae* was detected. Table 3 describes the time of occurrence of these infections during the course of the trial.

Fever and parasite clearance

On day 0, the proportions of the patients with fever (axillary temperature ≥ 37.5 °C) were comparable between the MAS3 group (67.2%) and the DHA-PQP group (67.9%). On day 1, 32.3% of the patients treated with MAS3 still had fever compared with only 22.8% of the group treated with DHA-PQP ($P = 0.025$). On day 2, the proportion of patients treated with MAS3 left with fever was 7.0%, compared with 2.3% among the patients treated with DHA-PQP ($P = 0.02$).

Patients in the DHA-PQP group cleared their parasites more quickly on day 1 of treatment with 62% of all patients cleared of parasites compared with 49% of the MAS3 arm ($P = 0.005$). By day 2, more than 94% of the patients in both groups had cleared their parasites.

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	No. of cases by day after treatment initiation									Total
	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56	Day 63	
DHA–PQP	–	1	1 (–)	1 (–)	1	6	14	2 (1)	13	39 (36)
MAS3	–	–	–	–	3	6	10	12 (11)†	16 (14)	47 (44)

†One case was diagnosed with *P. vivax* and *P. malariae*.

Analysis presented for the ITT analysis and values in () for the PP analysis.

Table 3 Appearance of *Plasmodium vivax* and *Plasmodium malariae* in the 63-day follow-up period of the trial

	Dihydroartemisinin–piperazine	Mefloquine–artesunate	Relative risk (95% CI)	P†
Dizziness	9/67 (13.4%)	26/72 (36.1%)	2.69 (1.36–5.31)	0.002
Vomiting	14/142 (9.9%)	29/153 (19%)	1.92 (1.06–3.49)	0.03
Nausea	15/90 (16.7%)	29/105 (27.6%)	1.66 (0.95–2.89)	0.07
Anorexia	15/96 (15.6%)	26/101 (25.7%)	1.65 (0.93–2.92)	0.08
Sleeping disorders	16/138 (11.6%)	36/156 (23.1%)	1.80 (1.04–3.13)	0.03
Palpitations	9/127 (7.1%)	23/153 (15%)	2.12 (1.02–4.42)	0.04
Blurred vision	10/153 (6.5%)	21/170 (12.4%)	1.89 (0.92–3.89)	0.08

†chi squared test.

Table 4 Adverse events that appeared in the first 3 days after the start of the treatment

Anaemia

Patients in both treatment groups showed similar haematological recovery during the 63-day follow-up period. For the MAS3 group, the mean (SD) Hct rose from 35.7% (6.7) at day 0 to 40.2% (3.8) at day 63; in the DHA–PQP group, this increase went from 35.6% (6.8) on day 0 to 40.0% (3.7) on day 63.

Safety and adverse events

No serious adverse events were reported during this study, but many patients reported lesser adverse events (the majority of which were difficult to differentiate from symptoms of malaria). Table 4 presents the proportion of patients reporting symptoms on the first 3 days after the start of the treatment. A significantly higher proportion of patients from the MAS3 group reported vomiting ($P = 0.03$), dizziness ($P = 0.002$), palpitations ($P = 0.04$) and sleep disorders ($P = 0.03$) than in the DHA–PQP group.

If we consider all symptoms reported since day 0, we see that for every symptom the proportions of patients who report episodes, in both treatment groups is highest at day 0 and invariably reduces over the following 3 days. Patients treated with DHA–PQP reported significantly fewer adverse events on day 1 ($P = 0.0006$) and day 2 ($P = 0.01$). By day 3, all symptoms were reported equally

Table 5 Mean number of adverse events reported by patients treated with DHA–PQP and MAS3

	MAS3	DHA–PQP	P†
Day 0	6.20	5.85	Ns*
Day 1	5.12	3.86	0.0006
Day 2	2.74	1.91	0.01
Day 3	1.21	1.09	Ns*

†chi-squared test.

*Ns = Not significant, $P > 0.05$.

between both groups (Table 5). The most marked differences for all patients were seen for dizziness where on day 1 of the treatment 61% of the MAS3 group reported this symptom compared with 41.9% in the DHA–PQP group, while on day 0 these proportions had been 65.5% and 64.4%, respectively. Similarly, for vomiting, among DHA–PQP patients, 24.6% vomited on day 0 and 12.5% on day 1, compared with 28.2% and 21.4%, respectively, for MAS3 and 49.8% of DHA–PQP patients reported anorexia on day 0 and 34.5% on day 1 compared with 53.8% and 47.8%, respectively, for MAS3.

Discussion

This study showed that both DHA–PQP and artesunate–mefloquine were highly efficacious treatments for

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uncomplicated multidrug-resistant falciparum malaria Cambodia. DHA–PQP caused a significantly faster fever and parasite clearance on the first day of treatment. These results confirm the results of other published trials from Asia (Denis *et al.* 2002; Ashley *et al.* 2004, 2005; Karunajeewa *et al.* 2004; Tran *et al.* 2004; Smithuis *et al.* 2006).

A 3-day regimen of artesunate and mefloquine is currently the national protocol for the treatment of falciparum malaria in Cambodia. Since the introduction of this regimen in 2001, it has proved highly efficacious in routine efficacy surveillance organized by the Ministry of Health but the frequent occurrence of adverse events associated with mefloquine poses a threat to adherence. A fixed combination is under development (<http://www.dndi.org>) but is not yet available. The need to prescribe the drugs separately also makes non-adherence more likely and increases the risk of the emergence of drug resistance. In terms of adverse events, patients who were treated with DHA–PQP reported significantly less episodes of vomiting, dizziness, sleeping disorders and palpitations in the first 3 days after the start of the treatment. These are all well-known side effects of mefloquine treatment. Patients treated with DHA–PQP also reported a significantly lower number of adverse events on day 1 and day 2. The symptoms that were recorded are similar to those of acute malaria which makes it possible that the superior tolerability of DHA–PQP is partially explained by the more rapid fever and parasite clearance. In any case, this is a favourable effect for patients in terms of overall response to treatment. Active screening for adverse events using a symptom questionnaire might have led to some over-reporting, but we would expect this to be similar in both groups. We believe that this appreciably better tolerability, combined with the fact that it is a fixed combination, will be an important factor in encouraging good adherence among all patients, although the earlier relief of symptoms with DHA–PQP might carry the risk of some patients taking an incomplete treatment course. Emphasis on enhancing patient treatment literacy and empowerment is thus necessary to avoid this potential problem. PQP is also not available as monotherapy which is another advantage of deploying this combination. The cost of DHA–PQP, at around 1.2 USD for an adult treatment which is cheaper than MAS3 (currently around 3 USD for the same treatment), is likely to make this treatment attractive to National malaria control programs. The advantages described make this combination highly appropriate for routine use in programme settings. It could be deployed fairly easily as part of a decentralized outreach strategy that attempts to bring the treatment of *P. falciparum* malaria closer to remote communities.

This trial was conducted using four doses of DHA–PQP at 0, 8, 24 and 48 h. This is still a slightly complicated regimen. Research in Thailand in 2005 (Ashley *et al.* 2005) reported similarly high efficacy of a once daily regimen with three doses at 0, 24 and 48 h.

In conclusion, DHA–PQP is a highly efficacious and better-tolerated fixed dose combination antimalarial which would be a good alternative to artesunate–mefloquine for the treatment of uncomplicated falciparum malaria in Cambodia.

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References

- Ashley EA, Krudsood S, Phaiphun L *et al.* (2004) Randomized, controlled dose-optimization studies of dihydroartemisinin–piperaquine for the treatment of uncomplicated multidrug-resistant falciparum malaria in Thailand. *The Journal of Infectious Diseases* **190**, 1773–1782.
- Ashley EA, McGready R, Hutagalung R *et al.* (2005) A randomized, controlled study of a simple, once-daily regimen of dihydroartemisinin–piperaquine for the treatment of uncomplicated, multidrug-resistant falciparum malaria. *Clinical Infectious Diseases* **41**, 425–432.
- Brockman A, Paul REL, Anderson T *et al.* (1999) Application of genetic markers to the identification of recrudescing *Plasmodium falciparum* infections on the northwestern border of Thailand. *The American Journal of Tropical Medicine and Hygiene* **60**, 14–21.
- Chatterjee P (2005) Cambodia's fight against malaria. *The Lancet* **366**, 191–192.
- Denis MB, Davis TM, Hewitt S *et al.* (2002) Efficacy and safety of dihydroartemisinin–piperaquine (Artekin) in Cambodian children and adults with uncomplicated falciparum malaria. *Clinical Infectious Diseases* **35**, 1469–1476.
- Ezedinachi EN, Ekanem OJ, Chukwuani CM *et al.* (1999) Efficacy and tolerability of a low-dose mefloquine–sulfadoxine–pyrimethamine combination compared with chloroquine in the treatment of acute malaria infection in a population with multiple drug-resistant *Plasmodium falciparum*. *The American Journal of Tropical Medicine and Hygiene* **61**, 114–119.
- Karunajeewa H, Lim C, Hung TY *et al.* (2004) Safety evaluation of fixed combination piperaquine plus dihydroartemisinin

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- (Artekin) in Cambodian children and adults with malaria. *British Journal of Clinical Pharmacology* 57, 93–99.
- Krudsood S, Looareesuwan S, Silachamroon U *et al.* (2002) Artesunate and mefloquine given simultaneously for three days via a prepacked blister is equally effective and tolerated as a standard sequential treatment of uncomplicated acute *Plasmodium falciparum* malaria: randomized, double-blind study in Thailand. *The American Journal of Tropical Medicine and Hygiene* 67, 465–472.
- Kuile FO, Nosten F, Luxemburger C *et al.* (1995) Mefloquine treatment of acute falciparum malaria: a prospective study of non-serious adverse effects in 3673 patients. *Bulletin of the World Health Organization* 73, 631–642.
- Newcombe RG (1998) Interval estimation for the difference between independent proportions: comparison of eleven methods. *Statistics in Medicine* 17, 873–890. Available at: http://www.cardiff.ac.uk/medicine/epidemiology_statistics/ci-proportion.xls, accessed in July 2006.
- Nosten F, van Vugt M, Price R *et al.* (2000) Effects of artesunate–mefloquine combination on incidence of *Plasmodium falciparum* malaria and mefloquine resistance in western Thailand: a prospective study. *Lancet* 356, 297–302.
- Piaggio G, Elbourne DR, Altman DG *et al.* (2006) Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA* 295, 1152–1160.
- Price RN, Uhlemann AC, Brockman A *et al.* (2004) Mefloquine resistance in *Plasmodium falciparum* and increased *pfmdr1* gene copy number. *Lancet* 364, 438–447.
- Smithuis F, Kyaw MK, Phe O *et al.* (2006) Efficacy and effectiveness of dihydroartemisinin–piperaquine versus artesunate–mefloquine in falciparum malaria: an open-label randomised comparison. *Lancet* 2006 367, 2075–2085.
- Tran TH, Dolecek C, Phan PM *et al.* (2004) Dihydroartemisinin–piperaquine against multidrug-resistant *Plasmodium falciparum* malaria in Vietnam: randomised clinical trial. *Lancet* 363, 18–22.
- WHO (2003) *Position of WHO's Roll Back Malaria Department on malaria treatment policy*. Available at: http://www.who.int/malaria/docs/who_apr_position.pdf. Accessed in June 2005.
- WHO (2006) *Guidelines for the Treatment of Malaria*. (WHO/HTM/MAL/2006.1108) WHO. Available at: <http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf>, accessed in June 2006.
- Yeung S, Pongtavornpinyo W, Hastings IM, Mills AJ & White NJ (2004) Antimalarial drug resistance, artemisinin-based combination therapy, and the contribution of modeling to elucidating policy choices. *The American Journal of Tropical Medicine and Hygiene* 71 (Suppl. 2), 179–186.

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Une étude randomisée ouverte pour évaluer l'efficacité et la tolérance du dihydroartémisinine–pipéraqouine dans le traitement de la malaria falciparum non compliquée au Cambodge

OBJECTIFS Comparer l'efficacité et la tolérance du dihydroartémisinine–pipéraqouine (DHA–PQP) à celles d'un régime à base de méfloquine de trois jours (MAS3) pour le traitement de la malaria falciparum non compliquée au Cambodge.

METHODE Etude Randomisée ouverte de non infériorité sur 64 jours.

RESULTATS 464 patients ont été inclus dans l'étude. Les taux guérison au jour 63 ajustés par les résultats du génotypage par la réaction en chaîne de la polymérase étaient de 97,5% (IC95%: 93,8–99,3) pour le DHA–PQP et de 97,5% (IC95%: 93,8–99,3) pour le MAS3, $P = 1$. Il n'y avait aucun effet adverse sérieux, mais de façon significative, des épisodes de vomissement ($P = 0,03$), des vertiges ($P = 0,002$), des palpitations ($P = 0,04$), et des troubles de sommeil ($P = 0,03$) ont été rapportés dans le groupe du traitement au MAS3, ce qui était consistant avec les profils d'effets secondaires du méfloquine.

CONCLUSION le DHA–PQP était aussi efficace que le MAS3, mais bien mieux toléré, le rendant ainsi plus approprié pour l'usage en routine dans le cadre d'un programme. Cette combinaison à dose fixe de grande efficacité, sûre et plus accessible pourrait devenir le traitement de choix pour la malaria à *Plasmodium falciparum* au Cambodge.

mots clés efficacité, tolérance, dihydroartémisinine–pipéraqouine, malaria falciparum

B. Janssens *et al.* **DHA–PQP vs. MAS3 against malaria in Cambodia**

Estudio abierto y aleatorizado para evaluar la eficacia y la tolerabilidad de la dihidroartemisinina-piperaquina para el tratamiento de la malaria no complicada por falciparum en Cambodia

OBJETIVOS Comparar la eficacia y la tolerabilidad de la dihidroartemisinina-piperaquina (DHA–PQP) con la de un régimen de 3 días de mefloquina (MAS3), para el tratamiento de la malaria no complicada por falciparum en Cambodia

MÉTODO Estudio aleatorizado, abierto, de no-inferioridad, durante 64 días.

RESULTADOS Se incluyeron 464 pacientes en el estudio. Las tasas de curación en el día 63, ajustadas por genotipaje mediante PCR, fueron del 97.5% (95% IC: 93.8–99.3) para DHA–PQP y del 97.5% (95%IC: 93.8–99.3) para MAS3, $P = 1$. No se observaron eventos adversos serios, pero si se reportó un número significativo de episodios de vómitos ($P = 0.03$), mareos ($P = 0.002$), palpitaciones ($P = 0.04$), y desórdenes del sueño ($P = 0.03$) entre el grupo de tratamiento con MAS3, algo consistente con el perfil de efectos secundarios de la mefloquina.

CONCLUSIONES La DHA–PQP fue tan eficaz como la MAS3, además de ser mejor tolerada, siendo más apropiada para el uso dentro del marco de un programa de rutina. Esta combinación de dosis fija, altamente eficaz, segura y más asequible, podría convertirse en el tratamiento de elección para malaria por *Plasmodium falciparum* en Cambodia.

palabras clave eficacia, tolerabilidad, dihidroartemisinina-piperaquina, malaria por falciparum