Tropical Medicine and International Health doi:10.1111/j.1365-3156.2006.01724.x

VOLUME 11 NO 11 PP 1653–1660 NOVEMBER 2006

An open label randomized comparison of mefloquine–artesunate as separate tablets *vs.* a new co-formulated combination for the treatment of uncomplicated multidrug-resistant falciparum malaria in Thailand

Elizabeth A. Ashley[1,2,3], Khin Maung Lwin[1,2], Rose McGready[1,2,3], Win Htay Simon[1], Lucy Phaiphun[1], Stephane Proux[1,2], Nantawan Wangseang[1], Walter Taylor[4], Kasia Stepniewska[2,3], Wimon Nawamaneerat[1], Kyaw Lay Thwai[1], Marion Barends[1,2], Wattana Leowattana[2], Piero Olliaro[3,4], Pratap Singhasivanon[2], Nicholas J. White[2,3] and François Nosten[1,2,3]

1 *Shoklo Malaria Research Unit, Tak, Thailand*
2 *Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand*
3 *Centre for Tropical Medicine and Vaccinology, Churchill Hospital, Oxford, UK*
4 *UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, World Health Organization, Geneva, Switzerland*

Summary

BACKGROUND Delivering drugs in a fixed combination is essential to the success of the strategy of artemisinin-based combination therapy. This prevents one drug being taken without the protection of the other, reducing the chance of emergence and spread of drug resistant strains of *Plasmodium falciparum*. A lower tablet burden should also facilitate adherence to treatment. A new fixed combination of mefloquine plus artesunate has been developed. This was compared with the conventional regimen of separate tablets for the treatment of uncomplicated multidrug-resistant falciparum malaria.

METHODS On the north-western border of Thailand 500 adults and children with uncomplicated falciparum malaria were randomized to receive either the new fixed combination or separate tablets. They were followed up weekly for 63 days.

RESULTS The day 63 polymerase chain reaction-adjusted cure rates were 91.9% (95% CI 88.2–95.6) in the fixed combination group and 89.2% (85.0–93.4) in the loose tablets group ($P = 0.3$). There was a lower incidence of early vomiting in the group receiving the fixed combination.

CONCLUSION This new fixed combination of mefloquine and artesunate was efficacious, well tolerated and convenient to administer.

keywords artemisinin, fixed combination, malaria, mefloquine

Background

Artemisinin-based combination therapy is now the recommended treatment for uncomplicated falciparum malaria (WHO 2006). The success of this policy change in practice will depend on the population coverage achieved, high levels of adherence to treatment, low cost of the drugs and preferably regulation so that the drugs in a combination treatment are not available separately as this will threaten the useful lifespan of the combination. The best way to prevent one drug being taken without the partner drug is to deploy the treatment as a fixed combination and to take loose drugs off the market. There are currently only two artemisinin-based fixed combinations available, artemether–lumefantrine and dihydroartemisinin–piperaquine; and only the former has international registration. More fixed combinations are needed urgently. Recently the Drugs for Neglected Diseases Initiative (DNDi, http://www.dndi.org) has supported the development of two new fixed combinations: artesunate plus amodiaquine and artesunate plus mefloquine.

For the past 12 years, artesunate in combination with mefloquine has been the first-line treatment for uncomplicated falciparum malaria in Thailand. The greatest use of

the drugs has been along the north-western border of Thailand, an area of multiple drug resistance. Deployment of the combination has led to a reduction in incidence of falciparum malaria and has been associated with a halt of mefloquine resistance (Nosten *et al.* 2000). The total dose of mefloquine given is 25 mg base/kg body weight and it is usually divided into doses of 15 and 10 mg/kg on the second and third days of treatment. Delaying mefloquine improves tolerability and absorption, but such a regimen cannot be converted to a fixed drug combination. In previous studies in this area the mefloquine dose was split into three daily doses of 8 mg/kg combined with 4 mg/kg/day of artesunate. Efficacy was approximately 95% (Ashley *et al.* 2004, 2005). South-east Asia is not the only part of the world to rely on mefloquine and artesunate combination therapy. Parts of the Amazon region, e.g. Peru and Bolivia, have adopted the combination as first-line treatment for falciparum malaria in recent years to tackle the problem of worsening sulfadoxine–pyrimethamine resistance.

The aim of this study was to assess the efficacy and safety of mefloquine plus artesunate given either as a fixed combination or as loose tablets for the treatment of uncomplicated falciparum malaria in a randomized open label controlled trial.

Patients and methods

Patients, weighing more than 5 kg, aged 6 months to 65 years, with symptomatic falciparum or mixed (falciparum + vivax) malarial infections were recruited from six clinics along the Thai–Myanmar border, an area of unstable, low and seasonal malaria transmission (Luxemburger *et al.* 1996). Three clinics were in Mae La, a camp for 40 000 displaced persons mainly of the Karen ethnic group, and three clinics were in Thai villages where migrant workers from Myanmar come for medical treatment.

Exclusion criteria were pregnancy or lactation, ≥4% red blood cells parasitized, signs or symptoms of severe malaria, treatment with mefloquine in the previous 60 days or other contraindications to mefloquine treatment. Written, informed consent to participate was obtained in either Karen or Burmese language with a witness present. The study was approved by three ethics committees: the Faculty of Tropical Medicine Ethical Committee, Mahidol University, Thailand; the Oxford Tropical Research Ethics Committee; and the World Health Organization Secretariat Committee on Research Involving Human Subjects.

The duration of symptoms before presentation, any drugs taken and results of a physical examination were recorded on a standard case record form. Patients had capillary blood sampling for malaria smear, haematocrit (Hawksley® Micro Haematocrit centrifuge) and polymerase chain reaction (PCR) genotyping. Thick and thin blood films were stained with Giemsa and counts expressed as the number of parasites per 1000 red blood cells or, for lower parasitaemias, per 500 white blood cells. Blood samples were taken for complete blood count and standard biochemical tests (creatinine, aspartate and alanine aminotransferases and total bilirubin). Patients younger than 15 years had blood sampling for mefloquine and artesunate levels to compare population pharmacokinetic profiles between the two treatment groups. This will be reported separately.

Antimalarial drug treatments

The first treatment, MASF, consisted of fixed artesunate and mefloquine (Far-Manguinhos, Brazil). Tablets came in two strengths: artesunate 25 mg + mefloquine hydrochloride 55 mg *paediatric* tablets or artesunate 100 mg + mefloquine hydrochloride 220 mg *adult* tablets. The treatment was given once a day for 3 days. Patients weighing 5–8 kg received one paediatric tablet per day, those weighing 9–17 kg received two paediatric tablets, those weighing 18–29 kg received one adult tablet and those weighing 30 kg and over received two adult tablets.

The second drug regimen, MASL, consisted of loose artesunate (Arsumax®, 50 mg tablets, Sanofi-Synthélabo, France) and mefloquine (Lariam®, 250 mg tablets, Roche). All patients received approximately 4 mg/kg/day artesunate for 3 days and 25 mg/kg mefloquine split as 15 and 10 mg/kg/day on the second and third days of treatment respectively. This is the standard regimen in this area.

Each dose was taken under supervision and repeated in full if vomiting occurred within 30 min of administration, or halved if the patient vomited 30 min to 1 h after dosing. For very young children unable to swallow tablets a suspension was made by placing the combination tablet in a spoon of water for about 30 s or crushing the loose tablets and mixing with water. All drugs were stored under field conditions and samples reanalysed at the end of the study to check for stability.

Randomization

Patients were randomized in blocks of 20 by a statistician using a computer-generated randomization (STATA, ver. 8) not disclosed to investigators at the study site. The treatment allocation was concealed in numbered sealed envelopes prepared under the supervision of DNDi and Far-Manguinhos and sent to the site. The envelopes were

opened and the allocation revealed only after enrolment in the study.

Monitoring for adverse events

Adverse events were defined as signs and symptoms that occurred or became more severe after treatment started. We actively screened for such symptoms at each visit. Serious adverse events were defined as death, a life-threatening reaction, an event requiring hospitalization or resulting in disability or any important medical event that might require intervention to prevent one of these outcomes. Abnormal haematology or biochemistry laboratory results were classified using National Cancer Institute Common Toxicity Criteria (NCI 1999).

Follow-up

Tympanic temperature (Braun Thermoscan^{TM} LF40) and blood smear were checked daily until fever and parasite clearance. Thereafter patients attended the clinic weekly for clinical examination, symptom inquiry, malaria smear and haematocrit tests. Biochemistry and haematology tests were repeated on day 28.

Management of reappearance of *Plasmodium falciparum* during the follow-up period

Patients with recurrence of malaria parasitaemia were treated with a 7-day regimen of artesunate (2 mg/kg/day) which was combined with doxycycline (4 mg/kg once daily) in patients > 8 years old. PCR genotyping for allelic variation in three loci (merozoite surface proteins 1 and 2 and glutamate-rich protein) was used to distinguish recrudescence from reinfection (Brockman *et al.* 1999). One hundred enrolment samples were selected randomly and genotyped to be used to establish the population allele frequency and for classifying second infections. Paired samples with multiple bands at two or more gene loci were assigned either to the recrudescent or to the new infection groups depending on the probability of the allelic combination of each of the three gene loci at each time-point.

Laboratory quality control

Quality control of malaria blood smear readings was performed internally with 50% of enrolment slides, 10% follow-up slides and all slides reported as showing reappearance of malaria during follow-up subjected to a second blind reading. Discrepancies were resolved by a third reading.

Study endpoints and statistical analysis

The sample size was sufficient to detect a difference in cure rates of 97% and 90% with 95% confidence and 80% power allowing a 10% drop-out rate. The main efficacy endpoints were the day 63 PCR-adjusted cure rates of each treatment calculated using Kaplan–Meier survival analysis with log rank test for significance. Patients presenting up to 1 week late for the final appointment were included in the day 63 analysis. Where possible, indeterminate PCR results were assigned either to the recrudescent or to the new infection groups, depending on the probability of either at each time-point. Those that could not be reallocated because there were no other decisive PCR results on that day were censored on the day of the last negative malaria smear. Patients with vivax malaria during follow-up were censored from the cure rate analysis on the day of *P. vivax* appearance. Secondary efficacy endpoints were times to fever and parasite clearance. Rates of appearance of vivax malaria during follow-up were also calculated using Kaplan–Meier survival analysis. Safety and tolerability endpoints were the incidence of anaemia and other adverse events. Non-normally distributed continuous variables were compared using Mann–Whitney *U* or Kruskal–Wallis tests, as appropriate. Differences in proportions were compared using the chi-squared test. Data were double entered into a database constructed in Microsoft Access 2003. Statistical programs used were SPSS 11.0 for Windows (SPSS Inc. Chicago, IL, ISA), STATA (Ver. 8, StataCorp LP, TX, USA) and EPIINFO^{TM} (Ver. 1.0, 2000, CDC, Atlanta, GA, USA).

Results

The first patient was enrolled on 16 November 2004 and follow-up was completed for all patients on 29 June 2005 (Figure 1). One patient fainted after randomization and was withdrawn from the study without receiving any study drug. One patient randomized to loose tablets received the fixed combination in error. The intention-to-treat analysis was modified, analysing this patient in the MASF group. Baseline characteristics of the patients are shown in Table 1. The median (range) number of visits to the clinics was 12 (1–15) in the MASF group and 11 (1–14) in the MASL group. The doses of mefloquine and artesunate received in both groups were very similar. The mean (SD) total dose of mefloquine given was 25 (4.9) mg/kg in the MASF group and 25.2 (3.4) mg/kg in the MASL group, and artesunate 12.5 (2.4) mg/kg in the MASF group compared with 12.0 (1.2) mg/kg in the MASL group.

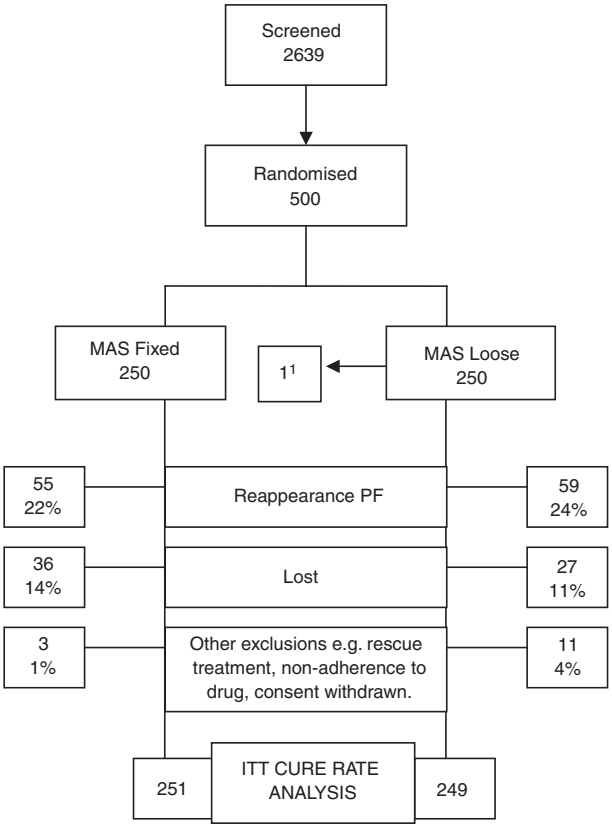

Figure 1 Patient flow diagram. [1]One patient randomized to receive loose drugs received the fixed combination.

Laboratory quality control

Eight hundred and fifty slides were rechecked. The pooled sensitivity of the laboratories at all sites for diagnosing malaria-positive slides, using the rechecked result as the reference was 96.4%, specificity 97.8%, positive predictive value 98.3%. The kappa coefficient to evaluate the agreement between the crosschecked positive results ($n = 449$) was 0.87 (95% CI 0.82–0.92).

Half of the enrolment slides were rechecked, of which four were reported as vivax malaria only and two were reported as being over the inclusion limit for parasitaemia. All these patients were kept in the intention-to-treat analysis. All positive slides during follow-up were rechecked. *Plasmodium vivax* could only be found on one slide which had been reported as falciparum malaria recurrence and as this patient was treated for recrudescence, he was censored from the cure rate analysis on that day.

Efficacy endpoints

The day 63 PCR-adjusted cure rates were 91.9% (95% CI 88.2–95.6) in the fixed combination group and 89.2% (85.0–93.4) in the loose tablets group ($P = 0.3$). The Kaplan–Meier survival plot is shown in Figure 2. There were 114 reappearances of falciparum malaria. Of these 69 were classified as new infections, 34 in the MASF group and 35 in the MASL group with a median (range) time to appearance of 51 (14–70) days and 38 (21–63) days

Table 1 Baseline characteristics of the patients

	MASF	MASL
All patients (*n*)	251	249
Males, *N* (%)	174 (69.3)	180 (72.3)
Age (years)	20 (10 m-65)	21 (1–60)
Weight (kg)	47 (7.5–69)	47 (7–75)
Fever duration before admission (days)	2 (0–29)	2 (0–10)
Geometric mean parasitaemia (per μl)	8612	7130
Range	29–288 403	83–190 546
Mixed infection (PF + PV) on admission, *N* (%)	22 (9%)	24 (10%)
Haematocrit %, mean (SD)	37.4 (5.6)	38.4 (5.8)
No. children <15 years	77	69
Males, *N* (%)	41 (53.2)	41 (59.4)
Age (years)	8 (10 months to 14)	10 (1–14)
Weight (kg)	22 (7.5–48)	23 (7–46)
Geometric mean parasitaemia (per μl)	15 230	13 329
Range	69–288 403	148–173 780
Haematocrit %, mean (SD)	34.8 (5.0)	34.8 (5.7)

Results are median (range) unless otherwise stated.

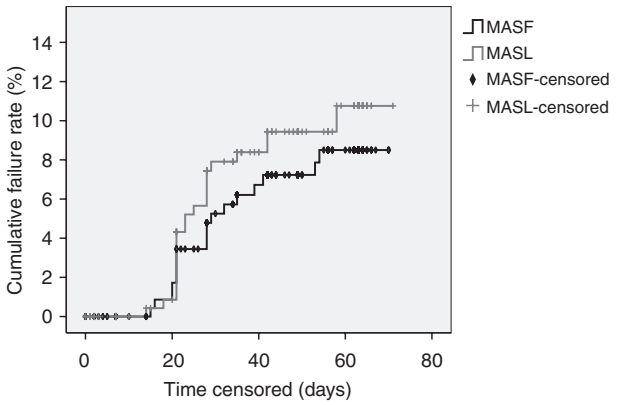

Figure 2 Kaplan–Meier One minus Survival Plot to show cumulative failure rates.

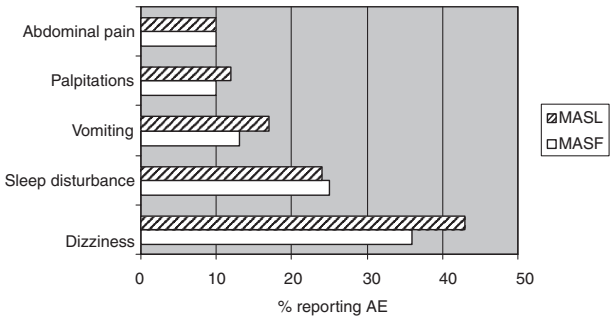

Figure 3 Adverse events absent at baseline but reported at least once before day 7. Vomiting excludes patients who vomited their drug. The numbers of symptomatic patients have been expressed as a percentage of those patients who did not report the symptom at enrolment.

Table 2 Fever and parasite clearance

Treatment	MASF	MASL
Fever clearance: no. of patients febrile (temperature >37.5 °C)		
Day 0	135 (54)	146 (59)
Day 1	41 (16)	49 (20)
Day 2	12 (5)	12 (5)
Parasite clearance: no. of patients blood smear positive		
Day 0	251	249
Day 1	211 (84)	195 (78)
Day 2	98 (39)	71 (29)
Day 3	21 (8)	14 (6)

Values are presented as *N* (%).

respectively ($P = 0.3$). There were 33 recrudescent infections, 13 in the MASF group and 20 in the MASL group with a median (range) time to appearance of 28 (15–54) days and 24 (14–58) days respectively. Twelve PCR results were indeterminate but it was possible to reassign 11 of these as either novel ($n = 3$) or recrudescent ($n = 8$) infections based on the known probability of failure on the day of parasite reappearance by treatment group in order to adjust the cure rate.

The times to fever clearance were similar for both groups (Table 2). Two days following treatment 29% of the patients in the MASL group were still blood smear positive compared with 39% in the MASF group ($P = 0.02$), however there was no significant difference by the following day.

Safety endpoints

Two patients in the MASL group who vomited their first dose of mefloquine repeatedly were given rescue therapy, and withdrawn from the study. Eight patients in the MASF group vomited on the first day but the dose was repeated successfully. There was a statistically significant difference in the incidence of vomiting occurring within 1 h of receiving treatment on the second day, with eight patients (3%) in the MASL group vomiting and none in the group treated with the fixed combination ($P = 0.004$).

There were 12 serious adverse events during the 9 weeks of follow-up; all required hospitalization. Only one was judged to be related to the study drug; a child with repeated vomiting after mefloquine administration in the MASL group required admission for intravenous hydration. The reasons for admission in the other patients were measles, bacterial sepsis, renal colic, pyelonephritis, diarrhoea, vomiting ($n = 2$), dehydration, relapse of pre-existing nephrotic syndrome, palpitations, and pyrexia of unknown origin.

The most common non-serious adverse events are shown in Figure 3 and were similar between both groups. These were recorded from those patients in whom the symptom was absent on admission but developed during follow-up. Transient urticaria was reported in three patients, two in the MASF group on days 7 and 13 respectively and one in the MASL group on day 21. All were judged to be unrelated to treatment.

Paired haematology results of day 0 and day 28 were available for 197 patients in the MASF group and 187 patients in the MASL group. There was one haematological adverse event – a patient in the MASL group had persisting asymptomatic thrombocytopenia which changed from moderate severity on admission (62 000/mm^3) to severe on day 35 (37 000/mm^3). Weekly haematocrit profiles were similar between groups (Figure 4).

Paired biochemistry results were available for 191 patients in the fixed combination group and 192 in the

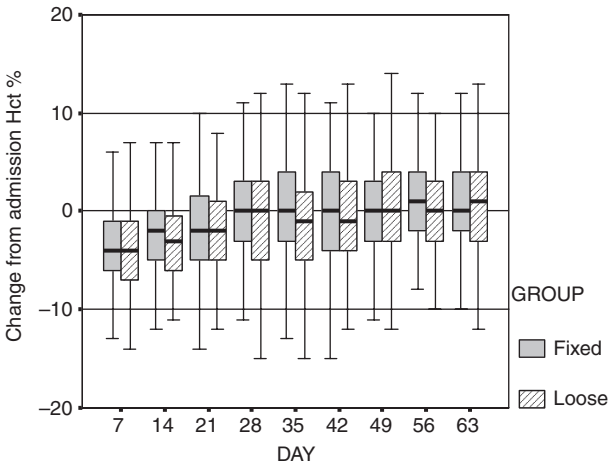

Figure 4 Change from admission haematocrit during the study. The box represents the interquartile range. The median is represented by the line across the box. The whiskers represent highest and lowest values, excluding outliers.

loose tablets group. The commonest abnormality found was the development of isolated or increasing mild to moderate rise in total bilirubin by day 28 noted in 27 of 191 patients (14%) in the MASF group and 18 of 192 patients (9%) in the MASL group ($P = 0.2$). Two patients in the fixed combination group and three in the loose tablet group had a mild asymptomatic increase in aminotransferase levels by day 28 (maximum level of aspartate transaminase 154 U/l, alanine transaminase 138, normal ranges 5–40).

Vivax malaria

Twenty-two patients (9%) in the MASF group and 24 patients (10%) in the MASL group had mixed falciparum and vivax infections on admission. Of these 11 in MASF and seven in MASL had a second vivax infection during follow-up at a median (range) time of 50 (35–70) and 42 (28–56) days respectively. There was a difference in the overall incidence of vivax infections during follow-up. The rate in the MASF group was 34% (95% CI 27–41) compared with 20% (15–27) in the MASL group ($P = 0.008$). The median time to appearance was 49 days in both groups.

Plasmodium falciparum gametocyte carriage

On admission 27 (11%) patients had patent gametocytaemia in the MASF group compared with 24 (10%) in MASL group. Gametocytes appeared during the first week in 11 patients in MASF with a median (range) duration of carriage of 1 (1–6) days and in 10 patients in the MASL group with a median (range) duration of carriage of 2 (1–8) days.

Drug analysis after 8 months storage in tropical ambient temperatures

Samples of the fixed combination and the separate drugs were analysed (Far-Manguinhos) and all drug contents were within 5% of expected values.

Discussion

This study showed good efficacy for the new fixed combination tablet of mefloquine and artesunate which matched that of the same drugs given separately. The weight-adjusted dosing categories worked very well in this population with the majority of patients receiving close to the desired dose. The fixed combination was simple to administer and was better tolerated with a lower incidence of vomiting within 1 h of treatment, probably because of the lower daily dose of mefloquine. This is an advantage because early vomiting after mefloquine has been shown previously to be a determinant of treatment failure (ter Kuile *et al.* 1995). The combination appeared safe with a similar toxicity profile to the drugs given separately. There was no evidence of clinically significant biochemical or haematological toxicity.

The incidence of patent gametocytaemia was very low in both groups, typical of treatment with artemisinin-based combinations. In patients with mixed falciparum and vivax infections at baseline the median time to reappearance of a second vivax infection was 6–7 weeks, a common finding after treatment with a drug with a long terminal elimination half-life such as mefloquine, when the first vivax relapse is suppressed (White 2003). A surprising finding was the higher incidence of vivax infections during follow-up in the fixed combination group; this is unexplained and may have occurred by chance.

The overall cure rates in this study were lower than in previous studies at this site with artesunate–mefloquine. Further *in vitro* and *in vivo* investigations will be necessary to determine whether this reflects genuine decreased sensitivity to mefloquine or chance fluctuations. This fixed combination was easy to administer with a simple age or weight-based dosing regimen, a convenient small tablet size for children, and a significantly reduced daily pill burden (Figure 5). The projected cost of the formulation will be lower than current market prices for the separate tablets. Pharmacokinetic data are awaited to determine whether the similar efficacy observed in this study was associated with similar plasma concentration profiles for the two drugs. The combination of mefloquine and artesunate has

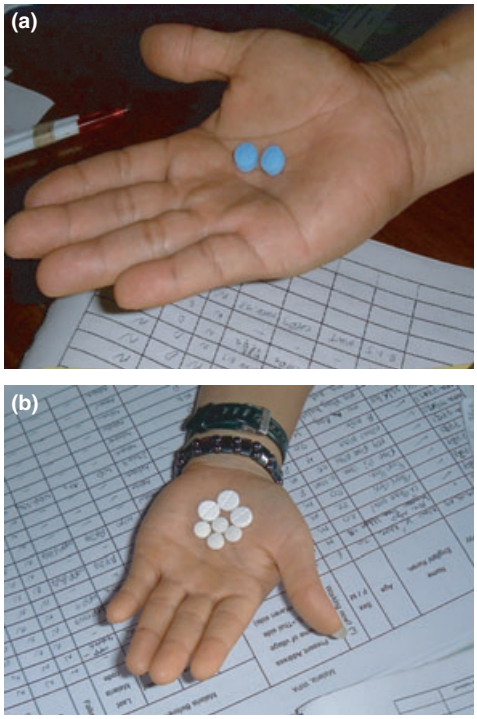

Figure 5 An adult dose of the fixed combination (a) or loose drugs (b).

been highly successful in South-east Asia and the Amazon Region. It should be used in other endemic areas and the fixed formulation will facilitate its deployment.

Acknowledgements

We would like to thank all the patients and staff of the Shoklo Malaria Research Unit who took part in the study. We are grateful to all the partners of the Fixed Dose Artesunate Combination Therapy (FACT) project, especially Dr Jean-René Kiechel the project manager and the team at DNDi, Julie Simpson for protocol development, Solange Wardell and the team at Far-Manguinhos in charge of the Pharmaceutical development and supplies, and Quintiles for study monitoring. The FACT development programme is sponsored by DNDi and has received financial support from the European Union International Cooperation programme (INCO/DEV), Médecins Sans Frontières, and WHO/TDR. The Shoklo Malaria Research Unit is part of the Wellcome Trust-Mahidol University, Oxford Tropical Medicine Research Programme sponsored by The Wellcome Trust of Great Britain.

References

Ashley EA, Krudsood S, Phaiphun L *et al.* (2004) Dose optimization randomized controlled studies of dihydroartemisinin-piperaquine for the treatment of uncomplicated multi-drug resistant falciparum malaria in Thailand. *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 RE, Anderson TJ *et al.* (1999) Application of genetic markers to the identification of recrudescent *Plasmodium falciparum* infections on the northwestern border of Thailand. *American Journal of Tropical Medicine and Hygiene* **60**, 14–21.

ter Kuile FO, Luxemburger C, Nosten F, Thwai KL, Chongsuphajaisiddhi T & White NJ (1995) Predictors of mefloquine treatment failure: a prospective study of 1590 patients with uncomplicated falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **89**, 660–664.

Luxemburger C, Thwai KL, White NJ *et al.* (1996) The epidemiology of malaria in a Karen population on the western border of Thailand. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **90**, 105–111.

NCI (1999) *Common Toxicity Criteria*, Ver. 2.0. National Cancer Institute, Bethesda, MD.

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.

White N (2003) Malaria. In: *Manson's Tropical Diseases*, 21st edn (ed. GCA Zumla) W.B. Saunders, Edinburgh, pp. 1205–1296.

WHO (2006) *Guidelines for the Treatment of Malaria*. World Health Organization, Geneva.

Corresponding Author François Nosten, Shoklo Malaria Research Unit, PO Box 46, Mae Sot, TAK 63110, Thailand. Tel.: +66 55 545021; Fax: +66 55 545020; E-mail: smru@tropmedres.ac

Méfloquine-artésunate en comprimés séparés ou en combinaison pour le traitement de la malaria falciparum multirésistante en Thaïlande: Essai randomisé ouvert

DONNÉES DE BASE L'administration de médicaments en combinaison fixée est essentielle pour le succès des stratégies de traitement à base d'artémisine en combinaison. Cela évite qu'un des médicaments ne soit pris en l'absence de la protection de l'autre, réduisant ainsi les chances d'émergence et de propagation de souches multirésistantes de *Plasmodium falciparum*. La réduction du nombre de comprimés devrait également favoriser la compliance au traitement. Une nouvelle combinaison à dose fixée de méfloquine et d'artésunate a été développée. Elle a été comparée au régime conventionnel utilisant des comprimés séparés pour le traitement de la malaria falciparum multirésistante non compliquée.
MÉTHODES 500 adultes avec une malaria falciparum non compliquée dans la région à la frontière nord-ouest de la Thaïlande ont été randomisés pour recevoir soit la nouvelle combinaison à dose fixée, soit les comprimés séparés. Ils ont ensuite été suivis hebdomadairement pendant 63 jours.
RÉSULTATS Les taux de guérison au jour 63, ajustés par les résultats PCR, étaient de 91.9% (IC95%: 88.2–95.6) pour le groupe recevant la combinaison fixée et 89.2% (IC95%: 85.0–93.4) pour le groupe recevant les comprimés séparés ($P = 0.3$). Les cas de vomissements observés au début du traitement étaient moins élevés dans le groupe recevant la combinaison fixée.
CONCLUSION La nouvelle combinaison à base de méfloquine et d'artésunate était efficace, bien tolérée et facile à administrer.

mots clés artémisinine, combinaison fixée, malaria, méfloquine

Mefloquina-artesunato como comprimidos separados vs. una nueva formulación combinada para el tratamiento de malaria por falciparum no complicada y multiresistente en Tailandia: comparación abierta y aleatorizada

ANTECEDENTES Dar medicamentos en una combinación fija es esencial para el éxito de la estrategia de una terapia de combinación basada en la artemisinina. Esto previene que un medicamento se tome sin la protección de otro, reduciendo la probabilidad del surgimiento y la propagación de cepas resistentes de *Plasmodium falciparum*. Una menor carga de comprimidos también debería facilitar el cumplimiento del tratamiento. Se ha desarrollado una nueva combinación fija de mefloquina más artesunato. Esta se ha comparado con el régimen convencional en comprimidos separados para el tratamiento de malaria por falciparum no complicada y multiresistente.
MÉTODOS En la frontera noroeste de Tailandia, se aleatorizaron 500 adultos y niños con malaria por falciparum no complicada para recibir la nueva combinación fija o los comprimidos por separado. El seguimiento se realizó semanalmente durante 63 días.
RESULTADOS La tasa de curación en el día 63, ajustada por PCR, fue de 91.9% [95%IC 88.2–95.6] en el grupo con combinación fija y de 89.2% [85.0–93.4] en el grupo con dos comprimidos ($P = 0.3$). Se observó una menor incidencia en vómitos tempranos en el grupo que recibió la combinación fija.
CONCLUSIÓN La nueva combinación fija de mefloquina más artesunato fue eficaz, bien tolerada y conveniente a la hora de administrarla.

palabras clave artemisinina, combinación fija, malaria, mefloquina