COMPARATIVE CLINICAL TRIAL OF TWO-FIXED COMBINATIONS DIHYDROARTEMISININ-NAPTHOQUINE-TRIMETHOPRIM (DNP®) AND ARTEMETHER-LUMEFANTRINE (COARTEM®/ RIAMET®) IN THE TREATMENT OF ACUTE UNCOMPLICATED FALCIPARUM MALARIA IN THAILAND

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Abstract. An open randomized comparison of two-fixed dose artemisinin derivative-containing combination regimens was conducted in adults with acute uncomplicated multidrug resistant falciparum malaria in Thailand. DNP®, a combination of dihydroartemisinin with napthoquine and trimethoprim developed recently in China, has been evaluated in China, Vietnam, Cambodia and Thailand. This study was performed to compare the safety, tolerability and efficacy of DNP® and artemether-lumefantrine/ Coartem®. One hundred and thirty eligible uncomplicated falciparum malaria patients were enrolled into the study. Patients were randomly assigned in a 2:1 ratio into group A, which received DNP® one tablet twice a day for one day; and group B, which received Coartem®/ Riamet® four tablets twice a day for 3 days. The cure rates at 28-day were 99% and 97% in group A and group B, respectively. No serious adverse events occurred. We concluded that both DNP® and Coartem®/ Riamet® were safe, well tolerated and highly efficacious in the treatment of acute uncomplicated falciparum malaria in Thailand.

INTRODUCTION

Malaria has always been a major killer in the tropics. It remains one of the largest global health care problems of the 21st century. Multidrug resistance and compliance with treatment are still major obstacles to be confronted. Efficacious and easily administered drugs are urgently needed. With problems of multidrug resistant falciparum malaria in Thailand (Bunnag and Harinasuta, 1987; Looareesuwan *et al*, 1992a; Nosten *et al*, 1996), the rationale of combining drugs with independent modes of action and different resistance mechanisms is to improve therapeutic efficacy and to prevent or delay the emergence or development of resistance (Peters, 1990; White, 1998). Recent guidelines in treating malaria strongly recommend the use of combinations of artemisinin derivatives with other antimalarial agents (WHO, 2001).

Recently, clinical trials of a combination of artesunate with mefloquine has proved this to be a very effective and well-tolerated regimen (Looareesuwan *et al*, 1992b; 1994; 1996a; Nosten *et al*, 1994; Price *et al*, 1995; 1997), therefore this regimen has been chosen for the treatment of multidrug resistant falciparum malaria in Thailand. However, some patients cannot tolerate the adverse effects of mefloquine.

Coartem®/ Riamet®, an oral fixed-dose combination tablet, consisting of 20 mg of artemether (half-life circa 1 hour) and 120 mg of lumefantrine (half-life 3 days), was developed in China and has been registered for use in many countries (von Seidlein, *et al*, 1997; Hatz *et al*, 1998; van Vugt *et al*, 1998; 1999; Looareesuwan *et al*, 1999; van Agtmael *et al*, 1999; Bakshi *et al*, 2000; Lefevre *et al*, 2001). The currently recommended treat-

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ment is a six-dose regimen given over three days (Looareesuwan *et al*, 1999; van Agtmael *et al*, 1999; Lefevre *et al*, 2001).

Dihydroartemisinin, an active metabolite of all artemisinin derivatives, has also been evaluated in Thailand for the treatment of falciparum malaria since 1994 (Klayman, 1985; Looareesuwan *et al*, 1996b; Wilairatana *et al*, 1998). *In vitro*, it is 2-3 times more active than the derivatives and can reduce parasitemia by 90% within 24 hours after administration. Clinical trials in Thailand revealed 80-90% cure rates depending on the dosage and duration of treatment (Looareesuwan *et al*, 1996b; Wilairatana *et al*, 1998).

DNP® (compound napthoquine), which consists of 160 mg of dihydroartemisinin, 400 mg of naphthoquine and 200 mg of trimethoprim, was also developed in China, and has been used in clinical trials in China, Vietnam, Cambodia and Thailand in over 1,000 patients (Wilairatana *et al*, 2002). The results of these studies have shown good efficacy (Professor GQ Li, personal communication). This drug was donated free of charge by Professor GQ Li, Republic of China. The advantages of this fixed combination drug are the short duration of treatment and ease of administration (one tablet is given 12 hours apart for 1 day). The aim of this study was to determine the safety, tolerability and efficacy of DNP® and Coartem®/ Riamet®.

MATERIALS AND METHODS

All patients who fulfilled the inclusion criteria [acute uncomplicated falciparum malaria, either sex (if female, a pregnancy test had to be negative before enrollment into the study), positive asexual forms of *P. falciparum* in blood smear, weight more than 40 kg and age more than 14 years, able to take oral medication, agree to stay in the hospital for at least 28 days, informed consent provided by patients or guardians must be obtained] were included in the trial. They were admitted to the Bangkok Hospital for Tropical Diseases and remained there for 28 days to exclude reinfection and to assess the safety, tolerability and efficacy of DNP® and Coartem®/ Riamet®. We excluded severe malaria, according to the WHO criteria (2000), severe vomiting not allowing oral medication, pregnancy or lactation, significant concomitant systemic diseases or disease requiring therapy, and ingestion of other antimalarials in the past 14 days, or presence of urine sulphonamides or 4-aminoquinolones upon admission. This study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

Clinical evaluation, including vital signs and full physical examination including neurological examination, were evaluated every day for the first 7 days, and weekly thereafter. Body temperature, pulse and respiratory rates were recorded every 4 hours and blood pressure was measured every 12 hours throughout the study. Laboratory measurements, including hematological and biochemistry examination, were performed at baseline, and on days 7, 14, 21 and 28. Parasitological examinations, consisting of thick and thin blood films, were also evaluated every 12 hours until the film was negative, then daily for 28 days. Blood films were considered negative if no parasites were seen in 200 oil-immersion microscopic fields. The malaria parasite count per μl was obtained by calculation against 1,000 red blood cells or 200 white blood cells in thin and thick blood film, respectively.

Each patient was randomly assigned in a ratio 2:1 into groups A:B as follows: group A received DNP® (compound naphthoquine) one tablet orally twice a day for one day (total dose = 2 tablets); group B received Coartem®/ Riamet® 4 tablets orally twice a day for 3 days (total dose = 24 tablets).

The parameters of the response to treatment were the 28-day cure rate, parasite clearance time and fever clearance time. The cure rate at day 28 (cured patients/ evaluable patients x 100%) was defined as the absence of parasite recrudescence during 28 days of in-patient follow-up. Parasite clearance time (PCT) was defined as the time from the start of treatment until the first negative blood film and blood films remaining negative for the next 24 hours. Fever clearance time (FCT) was taken as the period from the start of treatment until the oral temperature decreased to 37.5ºC and remained below this temperature for the next 48 hours. Side-effects were defined as signs and symptoms that occurred or became more severe after drug administration. If there were RI, RII or RIII failure (World Health Organization, 1973), standard antimalarial regimens of the hospital would be given. All patients were to be treated symptomatically, as indicated according to the standard practice of the hospital.

We performed statistical analysis using the

Epi Info Version 6.04 (USD, Inc, Stone Mountain, GA, USA) software package. The means of various parameters for the 2 groups were compared by Student *t*-test, while using the chi-square test or Fisher's exact test where appropriate for comparing categorical variables. Two-tailed tests were used throughout and a p-value < 0.05 was considered statistically significant.

RESULTS

A total of 130 eligible patients (89 in group A and 41 in group B) admitted to the Bangkok Hospital for Tropical Diseases were enrolled into the study. These two groups were comparable before treatment in all demographic, clinical and laboratory characteristics except for the high incidence of liver enlargement in group A, which did not interfere with the objective of the study (Table 1). The baseline clinical signs and symptoms of both groups were also similar and reflected the underlying malaria infection.

After treatment, 16 patients (12%) withdrew from the study [9 (10%) and 7 (17%) in group A

Table 1
Clinical and laboratory characteristics of study groups before treatment.

	Group A[a] (n = 89)	Group B[b] (n = 41)	p-value
Male: Female	57 : 32	30 : 11	0.31
Age			
Mean (SD)	25.4 (12.1)	28.3 (13.5)	0.21
Min-Max	14 - 62	14 - 73	
Height			
Mean (SD)	155.5 (12.7)	159.6 (7.5)	0.10
Min-Max	130 - 185	147 - 172	
Weight			
Mean (SD)	50.5 (9.6)	50.5 (8.0)	0.98
Min-Max	40.0 - 87.4	40.0 - 75.5	
Fever			
Duration (days)	5.6 (5.1)	3.9 (4.7)	0.07
Highest temperature	37.9 (0.9)	37.7 (0.9)	0.19
No. of patients with			
Hepatomegaly (%)	16 (18)	16 (39)	< 0.01
Splenomegaly (%)	13 (15)	4 (10)	0.45
First malaria attack	45 (51)	15 (37)	0.17
Initial parasite count			
Geometric mean			0.38
Min-max	14 - 203,720	80 - 172,380	
Laboratory data [Mean (SD)]			
Packed cell volume (%)	34.1 (7.1)	36.4 (6.8)	0.09
WBC count (per μl)	5.6 (4.9)	5.7 (1.8)	0.83
BUN (mg/dl)	14.2 (5.9)	13.5 (6.8)	0.59
Cr (mg/dl)	0.88 (0.18)	0.91 (0.20)	0.53
TB (mg/dl)	1.3 (1.2)	1.7 (1.4)	0.12
DB (mg/dl)	0.36 (0.58)	0.57 (0.53)	0.06
SGOT (U/l)	41.2 (52.6)	44.6 (40.4)	0.72
SGPT (U/l)	31.0 (25.9)	41.0 (39.8)	0.39
Albumin (g/dl)	3.9 (0.4)	3.7 (0.4)	0.11
AP (U/l)	107.5 (58.8)	120.1 (48.3)	0.25

WBC = white blood cell.
[a]DNP® (compound naphthoquine) one tablet orally twice a day for one day (total dose = 2 tablets).
[b]Coartem®/ Riamet® 4 tablets orally twice a day for 3 days (total dose = 24 tablets).

Table 2
Therapeutic responses.

	Group A[a] (n = 89)	Group B[b] (n = 41)	p-value
No. of patients with 28-days' follow-up	80	34	0.26
No. (%) cured at 28 days	79	33	0.53
Recrudescence on day	28	21	
Fever clearance time			
Mean (SD)	32.8 (27.7)	41.2 (37.3)	0.35
Min-Max	4 - 156	4 - 144	
Parasite clearance time			
Mean (SD)	43.9 (17.4)	48.1 (15.1)	0.18
Min-Max	9 - 124	22 - 104	
No. of patients with *P. vivax*	1	0	

[1]DNP® (compound naphthoquine) one tablet orally twice a day for one day (total dose = 2 tablets).
[2]Coartem®/ Riamet® 4 tablets orally twice a day for 3 days (total dose = 24 tablets).

and group B, respectively] for reasons unrelated to their treatments. All had negative blood films and were well upon discharge from hospital. Thus, 114 out of 130 patients (88%) remained in the hospital for a full 28 days' follow-up. Only patients who were followed for 28 days were included in calculations of drug efficacy.

Table 2 shows the parasitological and clinical responses to the treatments. The cure rate at 28-day revealed high efficacy in both groups (99% and 97% in groups A and B, respectively). Two cases (one in each group) had RI responses. These two cases and another patient treated with DNP® who had positive asexual forms of *Plasmodium vivax* in blood smears were successfully treated with the standard antimalarial regimens of the hospital. Similar to the cure rate, both fever and parasite clearance times showed no significant differences. Parasitemia in most of the patients was not detected in their blood smears within 72 hours. Fig 1 shows the percent reduction in parasitemia after treatment.

No deterioration in clinical or biochemical responses, or deaths, occurred after treatment in either group. In addition, there were no serious adverse events and neurological or neuropsychiatric manifestations during treatment and during the 28-day period. Some minor symptoms, such as nausea, headache, dizziness occurred in 4, 5 and 7 cases in group A and in 2, 2 and 4 cases in group B, respectively. However, these signs and symptoms could not be differentiated from malaria signs and symptoms since they disappeared simultaneously with fever within 1-4 days after treatment.

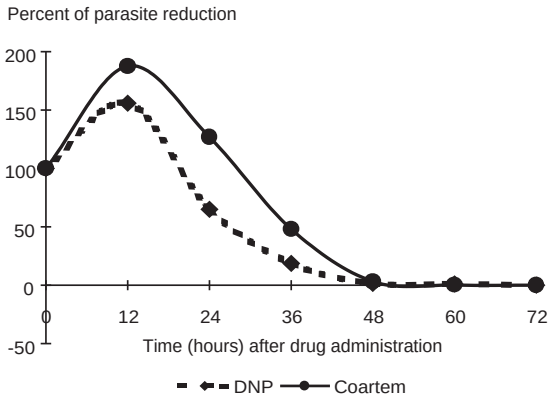

Fig 1–Mean parasitemia as compared to parasitemia at the onset of treatment.

DISCUSSION

Artemisinin derivatives are potent, rapidly-acting antimalarials that can reduced parasitemia by more than 90% within 24 hours in uncomplicated malaria cases. However, the rate of recrudescence within 28 days when used alone can be as high as 10-100%, depending upon dosage, duration of treatment and severity of disease (Arnold *et al*, 1990; Bunnag *et al*, 1991; Hien *et al*, 1991; Li *et al*, 1994). Artemisinin derivatives are often

combined with other long-acting antimalarials, (in group A combined with naphthoquine, dihydroartemisinin and trimethoprim and in group B combined with lumefantrine), to improve efficacy and patient compliance. The rationale underlying the use of combinations is the same as that underlying the standard multidrug treatments for tuberculosis, patients with HIV and most cases of cancer. The advantages of adding artemisinin derivatives to the combination are as follows: the rapid killing of parasites by the artemisinin derivatives accelerates the therapeutic response, prevents dangerous early treatment failure in cases of high-grade resistance, reduces the parasite biomass and provides gametocytocidal activity (Looareesuwan *et al*, 1999). The benefits of adding an appropriate and suitable long-acting drug is to prevent recrudescence by killing residual parasites, to reduce the chance of a resistant mutant surviving, and in addition the long-acting antimalarial might protect the artemisinin derivatives from the emergence of resistance in low-transmission areas. Combined administration of artemisinin derivatives and longer-acting antimalarials, such as pyronaridine and mefloquine, have been being evaluated in uncomplicated malaria in many countries. At present, Roll Back Malaria, under the World Health Organization, recommends the use of artemisinin-based combinations. In Thailand, the combinations (*eg* quinine-tetracycline, artesunate-mefloquine and artemether-lumefantrine) have been registered for use and recommended for the treatment of multidrug resistant falciparum malaria. However, minor adverse effects are relatively common with quinine-tetracycline and artesunate-mefloquine. Currently, there is no fixed combination of artesunate and mefloquine available in the market. DNP® and Coartem®/ Riamet® have the advantage of being fixed combinations. Moreover, DNP® has a short duration of treatment and possibly lower cost than the other drugs.

In this study, all patients responded satisfactorily to the two treatment regimens with similarly high levels of efficaciousness (99% and 97% cure rates at 28 days, respectively). The combinations of the individual drugs and the role of synergy between naphthoquine, dihydroartemisinin and trimethoprim remain to be determined. Interestingly, with the shorter duration (1-day treatment with 2 doses) of DNP®, when compare with the 3-day treatment with 6 doses of Coartem®/ Riamet®, might give better patient compliance to complete the treatment course.

In conclusion, this study indicated that DNP® is as effective and well-tolerated as Coartem®/ Riamet®, and may be an alternative treatment to the standard combination treatment of uncomplicated multidrug resistant falciparum malaria, such as in Thailand. However, additional studies in special groups (in children, pregnant women and field trials) are needed in order to get more information about DNP® in general practice.

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