

Management of Multiple Drug-resistant Malaria in Viet Nam

T T Hien,*_{MD}, N V VinhChau,**_{MD}, N N Vinh,***_{MD}, N T Hung,[†]_{MD}, M Q Phung,**_{MD},
L M Toan,**_{MD}, P P Mai,**_{MD}, N T Dung,**_{MD}, D T HoaiTam,[‡]_{MD}, K Arnold,[§]_{MD}

Abstract

Malaria is still the most common infectious cause of mortality and morbidity in Viet Nam as it is in many developing countries in the tropics. The presence of resistance to available antimalarials and compliance in the target population are factors that influence the choice of drugs and regimens.

In order to develop an ideal treatment for malaria, we conducted several clinical trials in patients with the disease in different settings. The results of these trials suggest that a combination of single dose artemisinin (or its derivatives) and mefloquine is the most effective, safe and practical treatment for acute non-complicated malaria due to multidrug-resistant Plasmodium falciparum. Concerning severe and complicated malaria, parenteral or rectal multi-doses of artemisinin or analogues are recommended due to their rapid parasite clearance time and other possible anti-cytoadherence effects. With its rapid parasite clearance, very early treatment of uncomplicated cases with artemisinin (and derivatives), especially at a health post level may help to prevent the development of complications, consequently reducing the number of severe cases and the malaria mortality rate.

Ann Acad Med Singapore 1997; 26:659-63

Key words: Artemether, Artemisinin, Artemisinin suppositories, Artesunate, Malaria, Mefloquine

Introduction

Malaria is the world's most important parasitic infection, affecting up to 500 million people a year and killing at least 2 million.¹ Although the malaria situation in Viet Nam has improved compared to the 1980s and the early 1990s, hundreds of thousands of people still suffer from this debilitating infection each year. There were over 500 000 cases of malaria with 198 deaths in 1996 in Viet Nam. In addition, resistance to the available antimalarial drugs is increasing, especially chloroquine, sulfadoxine-pyrimethamine and quinine.²

In the last ten years, the most important change in the management of malaria has been the introduction of artemisinin and other derivatives of the Chinese herb "qinghaosu" as first-line treatment particularly for severe and complicated malaria. Artemisinin has been evaluated extensively in the treatment of multiple-drug resistant falciparum malaria in China, Myanmar and Thailand. The early laboratory and clinical studies in

China provided the basis for clinical trials at the Centre for Tropical Diseases. Since 1987 both open and double-blind randomised comparative studies have been performed looking at the efficacy of these first generation endoperoxides. The artemisinin used was initially manufactured in China but more recently in Viet Nam from locally grown *Artemisia annua* plants. Two essential questions have been addressed: which is the best regimen(s) and whether artemisinin and related drugs can reduce the mortality in severe malaria.

Materials and Methods

In the studies of acute uncomplicated malaria, patients were included if they (or their accompanying relative) gave informed consent, had asexual forms of *P. falciparum* in the peripheral blood smear and quantitative parasite count of between 5000/μL and 500 000/μL, had fever and/or symptoms or signs of acute uncomplicated malaria (e.g., head or body aches, chills,

* Vice Director and Head, Malaria Research Unit, Centre for Tropical Diseases

** Physician, Centre for Tropical Diseases

§ Consultant, Centre for Tropical Diseases

*** Head

Infectious Diseases Ward A, Centre for Tropical Diseases

† Head

Infectious Diseases Ward C, Centre for Tropical Diseases

‡ Lecturer

Department of Infectious Diseases

Medical School of Ho Chi Minh City, Viet Nam

Address for Reprints: Dr Tran Tinh Hien, 190 Ben Ham Tu Q5 Ho Chi Minh City Viet Nam.

rigors, sweating and palpable spleen). Patients were excluded if they had severe malaria (defined below), had significant concomitant disease (cardiac, hepatic, renal, tuberculosis, and drug addiction), had mixed *P. falciparum*-*P. vivax* infections, a history of allergy to the drug under study or had received the study drug within the previous 72 hours or they were in the first trimester of pregnancy.

In studies of severe and complicated malaria, patients with the above-mentioned symptoms and signs of acute malaria were included if they had one or more of the following: Glasgow Coma Score of less than 11 (cerebral malaria); jaundice (serum bilirubin $>2.5\text{ mg\%}$ [$50\text{ }\mu\text{mol/L}$]) with a parasite count of more than $100\,000/\mu\text{L}$; renal failure (oliguria and/or anuria with urine output less than 400 ml per 24 hours, serum creatinine $>3\text{ mg\%}$ [$250\text{ }\mu\text{mol/L}$]); hypoglycaemia (blood glucose $<40\text{ mg\%}$ [$2.2\text{ }\mu\text{mol/L}$]); hyperparasitaemia ($>10\%$ red blood cells infected or parasite count $>500\,000/\mu\text{L}$); and shock (systolic blood pressure $<80\text{ mmHg}$ with cool extremities). Patients who fulfilled the entry criteria of the study were allocated at random to a treatment schedule using a computer-generated block randomisation number contained in a sealed envelope.

The efficacy and the safety of the drug was assessed by clinical response [fever clearance time (FCT): the time between the start of treatment until the first of 3 successive temperature readings of less than 37.5°C taken at 6 hourly intervals, disappearance of the symptoms and signs and the absence of important side-effects due to the drug, time to regain full consciousness in comatose cases; fatality rate for severe malaria] and parasite response [parasite clearance time' (PCT): 50%, 90%, and 100% of initial parasite count in the peripheral blood smear; PCT 100% is the time between the start of treatment until the first of 3 successive negative counts taken at 6 hourly intervals].

All the data were registered on standard forms and entered into a computer database. Statistical analysis of the data (Student's t-test, ANOVA test or Chi square (χ^2) test for normally-distributed data, the Mann-Whitney U test and other non-parametric tests for non-normally distributed data) was performed using Epi-Info (version 5.01a, World Health Organisation, Centers for Disease Control), SPSS and STATISTICA Software.

Results and Discussion

Uncomplicated *Falciparum* Malaria

The first two comparative studies of artemisinin suppositories and oral quinine in uncomplicated falciparum malaria in adults and children were performed in 1989 and 1990. The results of these studies confirmed that the parasite clearance effect of artemisinin suppositories (15 mg/kg at $T=0$ and $+4$ hours, 10 mg/kg twice a day on days 2 and 3) was more rapid than that of the oral

quinine. Unfortunately, recrudescence rates following artemisinin treatment were quite high, 50% versus 23.3% of quinine-treated adults ($P < 0.05$), and 23.3% versus 16.3% respectively in children.^{3,4}

Various dosage regimens of artemisinin and its derivatives have been suggested. Early studies in China suggested that an optimum total treatment dose was 3 g (about 50 mg/kg) given orally over 3 to 5 days and that the initial dose should not be less than 10 mg/kg .⁵ The difficulty in finding a reliable assay to determine the plasma concentrations of artemisinin and its derivatives has limited the availability of pharmacokinetic data. In addition, interpretation of the plasma concentration-time profile is complicated because the drugs (except artemisinin) are rapidly hydrolysed to the principal active metabolite, dihydroartemisinin, which binds tightly to erythrocyte membranes. Thus, the therapeutic regimens currently recommended for these drugs are largely empirical⁶⁻⁸ or based on pharmacodynamic measures, particularly measures of parasite clearance which have proved more useful in drug evaluation and the planning of dose regimens.

A dose-ranging comparative study was performed from 1993 to 1994 to elucidate the optimal dose of oral artemisinin and its derivatives for uncomplicated falciparum malaria (unpublished data). Ninety-four patients were recruited into this study and received one of six treatment schedules as follows:

- (i) artemether (an oil-soluble ether derivative) 160 mg,
- (ii) artemisinin 500 mg,
- (iii) artemisinin 1000 mg,
- (iv) artesunate (a water-soluble hemisuccinate derivative) 100 mg,
- (v) artesunate 200 mg and
- (vi) dihydroartemisinin (an active metabolite) 60 mg as a single oral dose.

There was no significant difference in fever clearance time (FCT) and parasite clearance time 100% (PCT100) between the 6 groups (Fig. 1). The parasite clearance effect of a single oral dose of 500 mg of artemisinin or 100 mg of artesunate was the same as the higher doses. Artemisinin and its derivatives used in our studies have been well tolerated. No serious adverse reactions were reported.

One of the primary criteria for a good antimalarial drug, besides efficacy and safety, should be acceptability to the target population. Before the era of qinghaosu, patients often did not complete the full course of treatment if it was for a duration of more than 3 days. Experience from different regions has shown that a regimen of quinine every 8 hours for 3 days plus tetracycline every 8 hours for 7 days produced an almost 100% cure rate in hospitalised patients (personal data) but less than 70% cure in malaria patients treated at a commu-

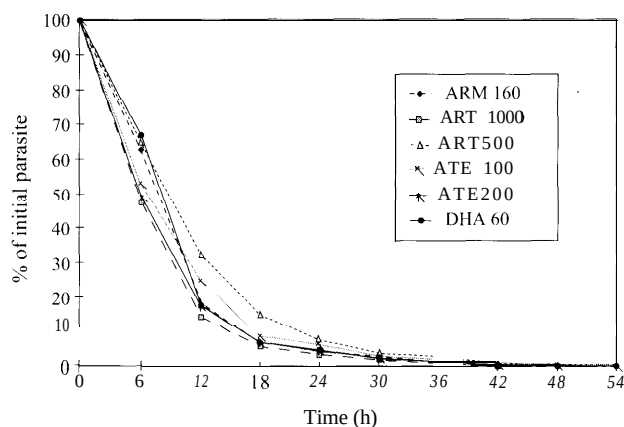


Fig 1. Parasite clearance expressed as a percentage of initial parasite counts for different doses of artemisinin and derivatives. ARM 160: Artemether 160 mg. ART 1000: Artemisinin 1000 mg. ART 500: Artemisinin 500 mg. ATE 100: Artesunate 100 mg. ATE 200: Artesunate 200 mg. DHA 60: Dihydroartemisinin 60 mg.

nity health station with over 50% of patients discontinuing their treatment when they felt better (unpublished data). In order to determine a practical regimen suitable for patients in developing areas with very limited financial resources, we have performed four prospective comparative trials of a combination of single-dose artemisinin and single-dose mefloquine for treating patients with uncomplicated falciparum malaria. Two studies have been conducted in hospital in-patients and 2 in a rural out-patient clinic. A total of 405 adults and 139 children were recruited. The randomised comparative treatment schedules were:

- (i) artemisinin (15 mg/kg) as a single dose plus mefloquine (15 mg/kg),
- (ii) artemisinin (15 mg/kg) as a single dose plus sulfadoxine-pyrimethamine (SP),
- (iii) artemisinin (15 mg/kg) alone for 5 days,
- (iv) quinine (30 mg/kg/day for 7 days) plus SP and
- (v) mefloquine-sulfadoxine-pyrimethamine (MSP).

Adults received oral artemisinin and children artemisinin suppositories. In the artemisinin-mefloquine group, the recrudescence rate during a 28-day follow-up period was 15% in the adult in-patients, and zero in the adult and children out-patients. This compares with rates of 33.3% in the artemisinin 5-day treatment group and 47.3% and 46.1% in the artemisinin plus SP in in-patients and out-patients, respectively ($P < 0.05$). The results showed that artemisinin as a single dose (oral in adults and suppository in children) in combination with mefloquine was effective in rapidly lowering parasitaemia and in preventing recrudescence.

The rectal administration of artemisinin in patients with disease-related nausea and/or vomiting would obviously provide a useful therapeutic advance, particularly in areas where parenteral administration is difficult. Although there are no data on bioavailability of

the suppositories or stability on storage, they have retained full clinical efficacy after storage at room temperature in Viet Nam for a year in our study. Unfortunately, our previous studies have confirmed the reports of other investigators that the main disadvantage of artemisinin (or its derivatives) is the unacceptably high recrudescence rates following short course monotherapy (less than 7 days). Compliance is likely to be poor with more prolonged treatment courses, especially in the community. It may be better to combine a rapidly acting drug, artemisinin, with another drug that has a long elimination half-life, such as mefloquine. This regimen would combine the efficacy and high compliance of short-course treatment with effective prevention of recrudescence.

Severe and Complicated Falciparum Malaria

The most important question is whether artemisinin and its derivatives can reduce the mortality of severe and complicated falciparum malaria. A four-year double-blind controlled trial involving 560 Vietnamese adults with severe falciparum malaria treated with artemether or intramuscular quinine has been performed in our centre. Although PCT 100% was shorter in the artemether group [72 (54 to 102) versus 90 (66 to 108) hours, $P < 0.001$]; FCT was slower [127 (26 to 60) versus 90 (50 to 144) hours, $P < 0.001$], and time to full recovery of consciousness and to leave hospital were all slower than with quinine ($P < 0.005$). There was no significant difference in the case fatality rate between the two groups (13% in the artemether group and 17% in the quinine group). Hypoglycaemia was associated with quinine treatment (RR 2.7, 95% confidence interval: 1.7 to 4.4, $P < 0.001$). There were no other serious side effects in either group."

The concept that artemisinin suppositories could be used to manage severe malaria is an exciting one. Three clinical studies have been carried out to investigate the hypothesis.¹¹⁻¹³ The initial dose of artemisinin suppositories was 1200 mg (20 mg/kg in children) followed by a maintenance dose of 400 mg (10 mg/kg in children) 12 or 24 hourly for 72 hours. The same dosage would be re-administered if the suppositories were expelled within two hours of insertion. In the initial study (1992), we found the efficacy of artemisinin suppositories to be comparable with either intravenous artesunate or intravenous quinine in the treatment of cerebral malaria." However, there were fewer cases in the artemisinin group because of shortage of supply of the drug from the manufacturer. A third study was conducted in 175 severe patients randomly assigned to receive one of the following treatments: intramuscular artemether (4 mg/kg followed by 2 mg/kg daily), IM artesunate or intravenous artesunate (2 mg/kg followed by 1 mg/kg daily) or artemisinin suppositories (20 mg/kg followed by 10

mg/kg at +4 hours then daily). All cases received 750 mg mefloquine as a single dose after regaining consciousness or at day 4 for the prevention of recrudescence. This trial was carried out between March 1992 and September 1994 in Tan Phu regional hospital. The overall case fatality rate in this study was 13.7% (24/175) (10.2% in those receiving artesunate IM, 11.1% in those receiving artemether IM, 16.6% in those receiving artesunate IV and 17.6% in those receiving artemisinin suppositories). There was no significant difference in efficacy between the 4 treatments (Chi square = 1.66, $P = 0.64$).¹³

Why is it that the new and powerful antimalarial drug artemisinin (and its derivatives) does not reduce the case fatality rates in hospitalised patients? These patients are severely ill, they may have been treated unsuccessfully elsewhere with different drugs and they may have developed complications before they or their families decided to go to the central hospital. At this late stage, the antimalarial treatment seems to be no longer the most important measure. The failure of treatment in patients who die may be due to pathological processes which are irreversible by the time these patients are seen in the hospitals.

The number of deaths from severe malaria in Viet Nam, however, continues to fall from 4646 cases in 1991 to 198 in 1996. It is likely that artemisinin and its derivatives have contributed to the decline in malaria mortality rate, not by being more effective in treating the lethal form of the disease, but by reducing the number of severe cases. By rapidly clearing the parasitaemia in addition to a possible anti-cytoadherence effect,¹⁴ artemisinin and its derivatives may help to prevent the development of complications when these drugs are given early to malaria patients, particularly at peripheral level of health care system. Another possible advantage of qinghaosu, demonstrated in Thailand, is a reduction of the transmission potential of falciparum malaria with artemisinin treatment. The deployment of these compounds may prevent the spread of multi-drug resistant diseases.¹⁵ These factors may explain the improvement of malaria situation in China and Viet Nam. It is of importance and interest that in spite of widespread, prolonged use of artemisinin and derivatives in China and Viet Nam there has been no reported clinical or *in vitro* resistance. Mefloquine resistance is possibly significant in Thailand but not yet in Viet Nam. In fact the combination of artemisinin with mefloquine may delay the development of resistance to either drug. Even if mefloquine resistance is a problem, as in Thailand, the combination with artemisinin or derivatives has been reported as still effective.¹⁶

Conclusion

In conclusion, the combination of artemisinin (or derivatives) in either oral or suppository formulation

TABLE I: RECOMMENDATION FOR DRUG AND DOSAGE IN THE TREATMENT OF MULTIPLE-DRUG RESISTANT MALARIA

	Uncomplicated Malaria		Severe Malaria	
	Dosage/ route	Schedule for administration	Dosage/ route	Schedule for administration
Artemisinin	15-20 mg/kg oral or suppository	single dose* or for 7 days	20 mg/kg suppository	at 0, +24, +48, +72 hours*
Artesunate	2-3 mg/kg then 1 mg/kg orally	loading dose daily for 7 days*	2-3 mg/kg then 1 mg/kg IV or IM	loading dose daily*
Artemether	3 mg/kg then 2 mg/kg orally	loading dose daily for 7 days*	3 mg/kg then 2 mg/kg IM	loading dose daily*

* Single dose of artemisinin (or derivatives) with 500-750 mg of mefloquine or complete 7-day course to prevent recrudescence

(500 mg to 1000 mg of artemisinin or equivalent) and mefloquine (15 to 25 mg/kg) seems to be the most effective, safe and practical regimen for the treatment of falciparum malaria at various levels of the health care system (household, community health station or hospital), especially in developing countries (Table I). The rectal administration of artemisinin to patients with non-complicated or complicated falciparum malaria would obviously constitute a useful therapeutic advance, particularly in areas where parenteral administration is difficult. Although artemisinin and its derivatives are the most rapidly effective antimalarial drugs, they did not reduce the fatality rate in referral hospitals. With the rapid parasite clearance however, very early treatment of uncomplicated cases with artemisinin (and its derivatives) especially at a health post level may help to prevent the development of complications, consequently reducing the number of severe cases and the malaria mortality rate.

REFERENCES

1. WHO Report. Fighting diseases, fostering development. Geneva: World Health Organization, 20 May 1996.
2. Hien T T, Arnold K. Clinical experience with drug combinations for the treatment of malaria in Vietnam (Abstract No. TuSS I-5). Proceedings of 13th International Congress for Tropical Medicine and Malaria; 1992 Nov 29-Dec 4; Jomtien, Pattaya, Thailand. Thailand: Faculty of Tropical Medicine, Mahidol University, 1992.
3. Arnold K, Hien T T, Chinh N T, Phu N H, Mai I'. A randomised comparative study of artemisinin suppositories and oral quinine in acute falciparum malaria. *Trans R Soc Trop Med Hyg* 1990; 84:499-502.
4. Hien T T, Tam D T H, Cuc N T K, Arnold K. Comparative effectiveness of artemisinin suppositories and oral quinine in children with acute falciparum malaria. *Trans R Soc Trop Med Hyg* 1991; 85:210-1.
5. Qinghaosu: Antimalarial Co-ordinating Research Group. Antimalarial studies on Qinghaosu. *Chin Med J* 1979; 92:811-6.
6. Hien T T, White N J. Qinghaosu. *Lancet* 1993; 341:603-8.
7. White N J. Artemisinin: current status. *Trans R Soc Trop Med Hyg* 1994; 88:3-4.

8. Barradell L B, Fitton A. Artesunate: A review of its pharmacology and therapeutic efficacy in the treatment of malaria. *Drug* 1995; 50:714-41.
 9. Hien T T, Arnold K, Hung NT, Loc I' P, Dung NT, Cuong B M, et al. Single dose artemisinin-mefloquine treatment for acute uncomplicated falciparum malaria. *Trans R Soc Trop Med Hyg* 1994; 88:688-91.
 10. Hien T T, Day N P J, Phu N H, Mai N T H, Chau T T H, Loc P P, et al. A controlled trial of artemether or quinine in Vietnamese adult with severe falciparum malaria. *N Engl J Med* 1996; 355:76-83.
 11. Hien T T, Arnold K, Vinh H, Cuong B M, Phu N H, Chau T T H, et al. Comparison of artemisinin suppositories with intravenous artesunate and intravenous quinine in the treatment of cerebral malaria. *Trans R Soc Trop Med Hyg* 1992; 86:582-3.
 12. ThanhPhuong C X, Bethell D B, Phuong P T, Tuyet Mai T T, Nhu Thuy T T, Thamh Ha N t, et al. Comparison of artemisinin suppositories, artesunate and intravenous quinine for the treatment of severe childhood malaria. *Trans R Soc Trop Med Hyg* 1997; 91:335-42.
 13. Vinh H, Huong N N, BichHa T T, Cuong B M, Phu N H, Chau T T H, et al. Severe and complicated malaria treated with artemisinin or artesunate or artemether in Vietnam. *Trans R Soc Trop Med Hyg* 1997; 91:465-7.
 14. Udomsangpetch R, Pipitaporn B, Krisna S, Angus B, Pukrittayakamee S, Bates I, et al. Antimalarial drugs reduce cytoadherence and rosetting of *P.falciparum*. *J Infect Dis* 1996; 173:691-8.
 15. Price R N, Nosten F, Luxemburger C, Kuile F O, Paiphun L, White N J, et al. Effects of artemisinin derivatives on malaria transmissibility. *Lancet* 1996; 347: 1654-8.
 16. White NJ. The treatment of malaria. *N Engl J Med* 1996; 335:800-6.
-