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Single-dose therapy of falciparum malaria with mefloquine or pyrimethamine–sulfadoxine*

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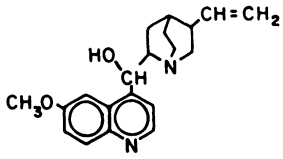
A single oral dose (1.5 g) of mefloquine hydrochloride cured all of 37 patients with falciparum malaria, and a single dose of pyrimethamine (75 mg) plus sulfadoxine (1.5 g) cured 34 of 38 patients. The rates at which parasitaemia and fever abated were similar for the two regimens but mefloquine was associated with a higher incidence of gastrointestinal side effects.

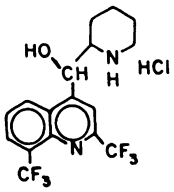
No single drug regimen is completely satisfactory for the management of chloroquine-resistant falciparum malaria in South-East Asia. Currently, when a single-dose drug is required, sulfadoxine–pyrimethamine (Fansidar, Roche Laboratories) is the treatment of choice, providing a complete cure in 80–90% of cases (*1–3*).[a] When a patient can be admitted to hospital this combination, together with a course of intravenous or oral quinine, produces the best therapeutic result currently obtainable with commercially available drugs (*4*).

Mefloquine hydrochloride is an important new antimalarial developed within the US Army's drug development programme. It is an analogue of quinine and of the experimental drug WR 30090 (Fig. 1), which was used successfully to treat chloroquine-resistant falciparum malaria acquired by American servicemen during the war in Viet Nam (*5*), and also indigenous cases in Thailand (*6*). Mefloquine has been used successfully in volunteers infected with chloroquine-sensitive and -resistant strains of *Plasmodium falciparum* (*7*); a dose of 1 g cured 10 of 12 nonimmune patients infected with a drug-resistant strain and a dose of 1.5 g cured all of 8 subjects.

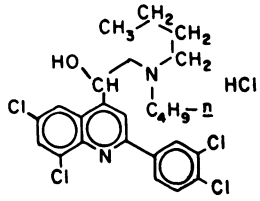
Mefloquine has been found to be active as a suppressant of both falciparum and vivax infections in American volunteers (*8*) and a village population living in a highly endemic area of Thailand.[b] The therapeutic effect of mefloquine was initially studied in Thai patients in 1975; it was found to have a cure rate of 94% when used alone [a] and to provide 100% cure when used following a course of quinine (*9*).



Quinine



Mefloquine hydrochloride



WR 30090

WHO 78607

Fig. 1. Structure of quinoline methanols

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[a] Hall, A. P. et al., unpublished results, 1978.

[b] Pearlman, E. J. et al., unpublished results, 1978.

With the intention of providing further data on the use of mefloquine, a comparison was made of the efficacy and toxicity of single oral doses of sulfadoxine–pyrimethamine and mefloquine in *P. falciparum*-infected patients presumed to be semi-immune to malaria.

PATIENTS AND METHODS

The study was carried out between April and December 1976 at Phrabuddhabat, Saraburi Province, in central Thailand. The area is known to be endemic for chloroquine-resistant falciparum malaria (*10*). Current *in vitro* data confirm the high level of chloroquine resistance of *P. falciparum* in patients reporting for treatment in the area.[c] Patients were selected from those attending the hospital out-patient department and the passive detection centre of the National Malaria Eradication Project regional headquarters in Phrabuddhabat. There is apparently no transmission of malaria in the town of Phrabuddhabat or in the immediate vicinity. Most patients had acquired the disease while working in forest areas some distance from their homes.

Patients were considered eligible for the study if they were males at least 18 years of age with moderate parasitaemia (the possible side effects of the two drugs have not been completely evaluated in pregnant women and young children). Patients were generally not accepted if the asexual parasite count was less than 1000 or more than 100 000 per μl of blood. Patients in coma, with severe jaundice or uncontrollable vomiting, or with evidence of renal, pulmonary, or cardiac complications were not admitted to the study. Subjects had to be willing to sign a consent form after details of the study had been given. The use of a new drug and the need for prolonged follow-up and repeated venipuncture were explained to the subjects before signatures were requested. An information sheet in the Thai language, containing details of the study, was given to each patient.

Patients considered eligible for the study were admitted to the male medical ward of the hospital and their progress was followed by one of the investigators; clinical rounds were conducted at least twice daily. Quantitative parasite counts (*11*) were performed every 8 hours until asexual parasitaemia had disappeared, and at each follow-up visit. A detailed record of symptoms and physical signs was kept by the physician during hospitalization and at follow-up visits.

In addition, clinical laboratory assessment of blood, kidney, and liver function was carried out on admission and at intervals during hospitalization and follow-up. Serum samples were screened for quinine and sulfonamide on admission and at follow-up visits in order to detect any additional treatment with antimalarial drugs.

Patients were kept in the hospital an average of 4 days and then followed up on days 10, 15, 21, 28, 38, 50, and 60 after admission. On discharge, patients were driven home and a record was kept of their home addresses. If a patient failed to keep a follow-up appointment, an attempt was made to see him at home.

Mefloquine was supplied by the Walter Reed Army Institute of Research and the sulfadoxine–pyrimethamine was purchased locally. The drugs were administered by one of the investigators and the patients were checked to make sure that they had swallowed the tablets. Alternate patients were assigned to one of the following single-dose regimens:

1. Fansidar, three tablets (pyrimethamine 75 mg, sulfadoxine 1.5 g).

2. Mefloquine hydrochloride, six tablets (1.5 g).

In addition, antipyretics, analgesics, intravenous fluids, and suppressants of nausea and diarrhoea were used as clinically indicated.

Treatment results were evaluated according to the World Health Organization criteria originally conceived to evaluate chloroquine resistance (*12*): " S " indicates clearance of asexual parasitaemia and maintenance of a negative blood film for 28 days after therapy; " RI " refers to initial clearance of parasitaemia followed by recrudescence within 28 days after treatment; " RII " indicates initial reduction in the level of parasitaemia but failure to clear in 7 days; and " RIII " indicates no reduction in parasitaemia following treatment.

RESULTS

Ninety-one patients were admitted to the study and followed for at least 7 days. Of these, 75 (82%) were followed for at least 28 days and 50 (55%) for 60 days.

There was no significant difference between the two treatment groups with regard to age, initial parasite count, or percentage returning to areas of transmission during the period of follow-up.

[c] Teerakiartkamjorn, C. et al., unpublished results, 1978.

Cure rates

In patients followed for at least 28 days, 100% of the mefloquine group (37/37) were radically cured (S response). Of the sulfadoxine–pyrimethamine group, 89% (34/38) were cured; there were two RI failures and two RII failures (Table 1). The two RI recrudescences were detected on days 21 and 28 of follow-up and may have been due to reinfection, although the patients denied having returned to areas of malaria transmission. After recrudescence, treatment with mefloquine resulted in radical cure in both cases, as did retreatment of the two patients with RII failures.

Four patients were found to have blood films positive for *P. falciparum* after day 28 in the sulfadoxine–pyrimethamine group (two on day 37 and two on day 38 following treatment of the initial infection). Six patients became positive for *P. vivax*—two on day 28 and one on each of days 16, 36, 50, and 60 of follow-up.

In the mefloquine group, none of the patients followed for up to 60 days developed new *P. falciparum* parasitaemias. Three patients were found to have *P. vivax* parasitaemias, one on each of days 50, 57, and 60 after treatment of the initial falciparum infection.

Side effects

The two regimens were alike in their association with symptoms of malaria, e.g., headache and dizziness, but differed in their association with gastrointestinal complaints (Table 2). Nausea, vomiting, and diarrhoea were more common in the mefloquine group than in the sulfadoxine–pyrimethamine group. However, no patient had severe vomiting or diarrhoea, and these symptoms were easily managed with routine medication.

Clinical laboratory results

There was no significant difference between the two groups, either before or during therapy, in respect of routine haematological or biochemical parameters. Those abnormalities that did occur were probably related to the malaria rather than to either therapeutic regimen, and most had disappeared by the end of the follow-up period.

DISCUSSION

Mefloquine has been shown to be a safe and effective single-dose antimalarial in two hospital studies of chloroquine-resistant falciparum malaria.

The mefloquine toxicity encountered in the present study, while not severe, could probably be reduced in future formulations of the drug. Two preparations have been used in field studies in Thailand. Based on data obtained from the administration of the drug to volunteers in the United States of America, the preparation used in the present study appeared to have a faster rate of absorption than that used in

Table 1. Results of treatment

Regimen	Number of patients	Mean asexual parasite count per μl before treatment	Mean fever clearance time (hours)	Mean parasite clearance time (hours)	Therapeutic result				Cure rate (%)
					RI	RII	RIII	S	
sulfadoxine–pyrimethamine	38	25 770	64	67	2	2	0	34	89
mefloquine	37	24 750	58	62	0	0	0	37	100

Table 2. Symptoms encountered during the first 4 days of hospitalization (numbers of patients affected)

Symptom	Regimen			
	Fansidar (48 patients)		mefloquine (49 patients)	
	No.	%	No.	%
headache	45	94	46	94
dizziness	44	92	47	96
nausea	28	58	41	84
vomiting	14	29	25	51
diarrhoea	8	17	13	27

previous studies; it produced higher peak levels approximately 4 hours after administration, and this probably led to the gastrointestinal side effects (Desjardins, R. E., personal communication). The drug could probably be formulated to provide slower absorption in order to reduce and extend peak levels.

Sulfadoxine–pyrimethamine was not associated with demonstrable side effects in this study. We encountered skin rashes in two patients in a previous study (*3*) and these may have been related to the administration of the drug. We have not seen serious side effects in any previous study despite therapeutic use of the drug in several hundred patients and chemosuppressive administration to a thousand or more.

Mefloquine appears to have a prolonged metabolic half-life in man. No patients treated with mefloquine in the present study were reinfected with *P. falciparum* during the follow-up period, in many cases as long as 60 days, despite having returned to areas of intensive malaria transmission. This fact suggests that mefloquine will be useful as a chemosuppressant, and tends to corroborate the very successful suppressive use of mefloquine in a village population living in a highly endemic area.[d]

Sulfadoxine–pyrimethamine remains the most effective commercially available single-dose treatment for chloroquine-resistant falciparum malaria. Our group continues to recommend, however, that in severe or complicated cases of falciparum malaria, and in cases exhibiting high levels of parasitaemia, quinine be used in conjunction with this drug combination. Sulfadoxine–pyrimethamine is preferably given together with the first dose of quinine, which should be continued at a rate of 650 mg orally or intravenously every 8 or 12 hours until symptoms and parasitaemia show evidence of abating. This regimen can be expected to cure nearly all patients (*4*).

[d] Pearlman, E. J. et al., unpublished results, 1978.

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RÉSUMÉ

CHIMIOTHÉRAPIE DU PALUDISME À FALCIPARUM: ADMINISTRATION D'UNE DOSE UNIQUE DE MÉFLOQUINE OU DE PYRIMÉTHAMINE–SULFADOXINE

La méfloquine a été employée en Thaïlande pour traiter des cas d'infection à *Plasmodium falciparum*. Il s'agit d'une préparation pour prise unique et elle a été comparée à la pyriméthamine–sulfadoxine, médicament également administré à raison d'une dose unique. Les malades adultes du sexe masculin qui se sont portés volontaires pour l'expérimentation du produit en milieu hospitalier ont été acceptés pour autant qu'ils présentaient une parasitémie modérée et une infection exempte de complications. Ces malades sont demeurés sous surveillance pendant une période de 60 jours au maximum et, parmi ceux qui ont été suivis au moins pendant 28 jours, les cas traités par la méfloquine — au nombre de 37 — ont été tous guéris, alors que 34 sur les 38 cas traités par la pyriméthamine–sulfadoxine (soit 89%) l'ont été avec un plein succès. L'administration de méfloquine a toutefois provoqué des effets secondaires sous la forme de troubles gastro-intestinaux légers et ceci avec une forte incidence, alors qu'aucun signe patent de toxicité n'a été relevé avec l'emploi de pyriméthamine–sulfadoxine. Le temps nécessaire à l'élimination des parasites et de la fièvre, comparable dans les deux types de traitement, a été du même ordre que celui constaté lorsqu'on recourt à la quinine.

En cas d'atteinte paludique à falciparum grave ou présentant des complications, les auteurs ne peuvent recommander l'emploi de l'un ou l'autre de ces produits comme médication unique. Le schéma de traitement le plus efficace actuellement est une combinaison de quinine et de pyriméthamine–sulfadoxine. Il devrait être possible de mettre au point une formulation de méfloquine permettant de minimiser ou d'éliminer les effets secondaires au niveau gastro-intestinal, ce qui accroîtrait l'intérêt de cette préparation pour le traitement du paludisme au moyen d'une dose unique de médicament. La longueur de sa demi-vie dans l'organisme humain et son activité antipaludique prolongée font de la méfloquine un chimiosuppresseur d'avenir.

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