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Single-dose treatment of falciparum malaria with mefloquine: field studies with different doses in semi-immune adults and children in Burma

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Different doses of mefloquine (20 and 30 mg/kg of body weight in children, and 750 and 1000 mg in adults) were tested in controlled clinical trials in 89 children and 60 adults who were semi-immune carriers of Plasmodium falciparum. *There was no significant difference in the efficacy of the two doses, either in the children or in the adults. An RI-type resistance was found in 1 adult, when recrudescence occurred on day 7, and in 4 children, who showed recrudescence on day 14. In all 5 patients, spontaneous disappearance of parasites was observed at further parasitological checks, thus indicating that mefloquine has a prolonged action. One patient who vomited after taking the drug was successfully retreated with mefloquine on day 14.*

Nausea, giddiness, and vomiting are the three symptoms most frequently attributed to mefloquine. The incidence of nausea and giddiness was similar in both dosage groups, but the adults in the higher dosage group had a significantly higher frequency of vomiting than those in the low-dose group.

In view of the rapid and reliable action of a single dose, mefloquine seems to be the drug of choice for treatment of cases of falciparum malaria that are resistant to 4-aminoquinolines and to sulfonamide-pyrimethamine combinations. A dose of 20 mg per kg of body weight for children and 750 mg for adults is sufficient for treatment of semi-immune persons.

Like many other countries, Burma is confronted with several problems in its fight against malaria. Resistance of *Plasmodium falciparum* to 4-aminoquinolines is widespread and resistance has also been reported to pyrimethamine, proguanil, and other antimalarials (*1*). An RI type of response is encountered frequently with a single dose of a combination of sulfadoxine and pyrimethamine, while RIII resistance was recently observed in three children who received a single dose of sulfalene-pyrimethamine.[a]

Emergence of resistance has considerably altered the standard schemes of treatment and prophylaxis of malaria in several countries and the situation will continue to deteriorate as long as operational, socioeconomic, and technical difficulties hamper efforts to interrupt the transmission of the disease.

In view of the increasing resistance of *P. falciparum* to several drugs, the development of mefloquine, a new antimalarial, is of the utmost importance.

The objective of the present trial was to evaluate the efficacy and tolerance of different doses of mefloquine, in field conditions, in children and adults suffering from falciparum malaria.

Mefloquine is a quinoline-methanol derivative, and is chemically related to quinine. Single oral doses of 1-1.5 g have been successful in treating falciparum malaria. Side-effects such as nausea, vomiting, diarrhoea, and giddiness were reported in a few patients. In Thailand, a single oral dose of 1.5 g of mefloquine cured all 37 patients with falciparum malaria but was often associated with gastrointestinal disturbances (*2*).

MATERIALS AND METHODS

Study area and population

The trial was carried out between 15 January and 31 March 1981 in patients attending the outpatient de-

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[a] TIN, FRANCO & NYUNT HLAING *Comparative drug trial of a sulfadoxine-pyrimethamine combination and sulfalene-pyrimethamine combination against* Plasmodium falciparum *infections in semi-immune populations of Burma*. WHO unpublished document, WHO/MAL/81.932, 1981.

partment of the township hospital at Thandaung, Karen State, Burma. This is situated about 300 km north of Rangoon, in a hilly forested area with many streams, where malaria transmission is perennial. The peak transmission months are June–July, at the start of the monsoon season, and October–November, just after the rains have ended. *Anopheles minimus* and *A. balabacensis* are the vectors.

Methods

Altogether, 1830 people of all age groups and both sexes who were suffering from fever or had a recent history of fever were examined for the presence of malaria parasites. A Giemsa-stained thick blood smear was prepared for each subject, and the gametocytes and trophozoites were counted against 400 leukocytes (assuming a count of 8000 leukocytes/mm^3). A total of 381 people were found to be positive for malaria parasites; of these, 60 adults over 13 years of age with a body weight of 35 kg or more and with parasitaemia of more than 400 trophozoites/mm^3, and 89 children aged 5–12 years and weighing 10–30 kg were included in the trial. The interval between taking the blood sample and administering the mefloquine was less than 2 hours. None of the patients had any other detectable disease.

For the adults, a randomized, double-blind, comparative trial of two different doses of mefloquine was carried out in two groups of 30 subjects. Members of one group received 750 mg of mefloquine base (3 × 250 mg tablets of mefloquine plus one placebo tablet) and the other group received 1000 mg of mefloquine base (4 × 250 mg tablets of mefloquine).

The children were divided into two groups and a randomized, open-label, comparative trial of two different doses of mefloquine was carried out. Members of one group received 20 mg of mefloquine per kg of body weight and the other group received 30 mg per kg of body weight.

Follow-up blood smears were taken daily up to day 7 and then weekly for another 3 weeks. (The day of screening and administration of mefloquine was taken as day 0.) A smear was declared negative only when 200 microscopic fields had been examined and found to be negative.

The patients were asked to attend at the hospital for regular follow-up, but those who failed to do so were visited at their homes by a member of the team. Only four patients were admitted as inpatients for a few days.

Since the trial was conducted in the field, in a rural environment without modern facilities, only the laboratory tests essential for the diagnosis and follow-up of falciparum malaria, i.e., the determination of parasitaemia, were carried out. The body weight and axillary temperature of each patient were recorded at the beginning of the study.

RESULTS

Adults

As can be seen from Table 1, clearance of asexual blood forms of *P. falciparum* was obtained within 7 days of administration of mefloquine in all 30 patients of group 1 (750 mg) and in 29 of the 30 patients of group 2 (1000 mg). The mean parasite count before treatment with mefloquine was 8696 asexual parasites per mm^3 (range 400–106 000).

The mean parasite clearance time for the two treatment groups was 1.7 ± 1.1 days for group 1 and 1.8 ± 1.3 days for group 2. There was no significant difference between the two groups in the number of subjects whose parasitaemia was cleared within 1–2 days or in 3 or more days (Fisher's exact test, $P > 0.05$).

One patient in group 2 was found to be negative for asexual blood forms on days 1–6, but showed recrudescence on day 7. Further checks on days 14, 21, and 28 were again negative for asexual forms and

Table 1. Clearance of asexual blood forms of *P. falciparum* in 60 adults after administration of a single dose of mefloquine

Treatment group	No. of patients cleared of asexual parasitaemia							No. of patients with recrudescence			No. of patients not cleared within 7 days
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 14	Day 21	Day 28	
Group 1 (750 mg)	18	8	2	1	0	1	0	0	0	0	0
Group 2 (1000 mg)	17	8	1	1	1	1	0	0	0	0	1

gametocytes of *P. falciparum* without further treatment. No recrudescence was observed in the remaining 59 cases during the follow-up period of 28 days.

Side-effects of mild to moderate intensity were observed in 26 (86.6%) of the patients of group 1 and in 27 (90.0%) of the patients of group 2 (Table 2).

Fisher's exact test (2-tailed) was used to compare the incidence of nausea and vomiting in the two groups. The difference in the frequency of nausea was not significant; however, a statistically significant difference was found for the incidence of vomiting, which was markedly more frequent in the higher-dose group ($P < 0.01$).

Table 2. Incidence of side-effects in 60 adults treated with a single dose of mefloquine

Side-effect	No. of patients affected		Total
	750-mg dose	1000-mg dose	
Nausea	10	14	24
Vomiting	3	15	18
Giddiness	25	25	50
Epistaxis		1	1
Diarrhoea		2	2

Children

Clearance of asexual blood forms of *P. falciparum* was obtained within 7 days of treatment with mefloquine in 45 of the 47 patients in group 1 (20 mg/kg of body weight) and in 41 of the 42 patients in group 2 (30 mg/kg) (Table 3). The mean parasite count before treatment was 7949 asexual parasites per mm^3 (range 160–128 000).

The mean parasite clearance time for the two groups was 2.7 ± 1.7 days for group 1 and 2.7 ± 1.8 days for group 2. One child in group 1 and 3 in group 2 showed recrudescence of asexual parasitaemia on day 14. However, all 4 patients were found to be negative on days 21 and 28 without further treatment.

Two children in group 1 were not cleared of asexual blood forms within 7 days but were found to be negative for asexual forms and gametocytes of *P. falciparum* on days 14, 21, and 28.

In one patient, who had received 625 mg of mefloquine (corresponding to 29.8 mg/kg of body weight), trophozoites were still present on day 14. He was treated with a further 625 mg of mefloquine on that day, and on day 15 no parasites were detected. The patient remained negative throughout the following 4 weeks. The lack of response after the first dose of mefloquine may have been due to vomiting.

Side-effects (mainly nausea, vomiting, and giddiness) were observed in 29 (61.7%) of the patients in group 1 and in 24 (57.1%) of the patients in group 2 (Table 4). In all cases the intensity of the side-effects was considered mild.

Table 4. Incidence of side-effects in 80 children treated with a single dose of mefloquine

Side-effect	No. of patients affected		Total
	20 mg/kg of body weight	30 mg/kg of body weight	
Nausea	5	5	10
Vomiting	10	9	19
Giddiness	19	20	39
Pain in epigastrium	1		1
Epistaxis		1	1
Diarrhoea		1	1

Table 3. Clearance of asexual blood forms of *P. falciparum* in 89 children after administration of a single dose of mefloquine

Treatment group	No. of patients cleared of asexual parasitaemia							No. of patients with recrudescence			No. of patients not cleared within 7 days
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 14	Day 21	Day 28	
Group 1 (20 mg/kg of body weight)	11	18	3	7	0	4	2	1	0	0	2
Group 2 (30 mg/kg of body weight)	12	13	3	6	3	2	2	3	0	0	1

There was no statistically significant difference between the two groups in the time needed for clearance of parasitaemia or the type and incidence of side-effects.

DISCUSSION

Mefloquine was found to be equally effective for treatment of falciparum malaria in semi-immune subjects, whether given in a dose of 750 mg or 1000 mg for adults, and 20 or 30 mg per kg of body weight for children. The parasite clearance rate was 98.3% in adults and 96.6% in children on or before day 7.

The recrudescence rates were 1.7% for adults and 4.5% for children, all at RI level. Of the 4 children showing recrudescence, 1 received 20 mg while the other 3 received 30 mg of mefloquine per kg of body weight. Hence, it seemed that recrudescence was not influenced by the dose given. The 5 patients with recrudescence of parasitaemia did not need any further treatment as the parasites were not detected in further checks. This is probably a result of the long-acting nature of mefloquine. One patient, who vomited after having taken the drug, had a parasitaemia that persisted for 14 days, and was retreated successfully with mefloquine. During the 4-week observation period, no recrudescence was observed after day 14; hence mefloquine has a suppressive effect for at least that period.

Mefloquine did not seem to have any stimulating effect on the production of gametocytes but it also did not have any gametocytocidal effect.

In the children, the incidence of side-effects (mainly nausea, giddiness and, to a lesser extent, vomiting) was almost identical in both dosage groups. However, in the adults, a statistically significant difference was found in the incidence of vomiting in the two dosage groups. This side-effect was markedly more frequent in the group given the higher dose.

In view of the rapid and reliable action of a single dose, mefloquine seems to be the drug of choice for treatment of falciparum malaria that is resistant to 4-aminoquinolines and to sulfonamide-pyrimethamine combinations. From the results of the present trial, a single dose of 20 mg/kg of body weight for children, and 750 mg for adults, seems to be sufficient for treatment of semi-immune persons.

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RÉSUMÉ

TRAITEMENT DU PALUDISME À FALCIPARUM PAR UNE DOSE UNIQUE DE MÉFLOQUINE : RÉSULTATS D'ÉTUDES PRATIQUES DE DIVERSES POSOLOGIES CHEZ DES ADULTES ET DES ENFANTS SEMI-IMMUNS EN BIRMANIE

Différentes posologies de méfloquine (20 et 30 mg/kg de poids corporel chez les enfants, ainsi que 750 mg et 1000 mg chez les adultes) ont été éprouvées dans des essais cliniques contrôlés, effectués sur 89 enfants et 60 adultes, tous porteurs semi-immuns de *Plasmodium falciparum*.

Il n'a pas été observé de différences statistiquement significatives entre l'efficacité des deux doses, ni chez les enfants ni chez les adultes.

Une résistance de type RI a été constatée chez un adulte qui a présenté une recrudescence au septième jour et chez quatre enfants (4,5%) qui ont eu une recrudescence le quatorzième jour. Chez ces cinq malades, une disparition spontanée des parasites a été observée lors de contrôles parasitologiques ultérieurs, ce qui indique que la méfloquine a une action prolongée. Un malade, qui avait vomi après l'absorption du médicament, a été traité à nouveau avec succès par la méfloquine au quatorzième jour.

Nausées, vertiges et vomissements sont les trois symptômes les plus fréquemment attribuables à la méfloquine. Alors que la fréquence des deux premiers symptômes était presque la même dans les groupes recevant les deux posologies, les vomissements étaient nettement plus fréquents chez les adultes ayant reçu la dose supérieure (1000 mg).

Compte tenu de l'action rapide et fiable d'une dose unique, la méfloquine semble le médicament de choix pour le traitement des cas de paludisme à falciparum résistants aux amino-4 quinoléines et aux associations de sulfamide-pyriméthamine.

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