# Research Recherche

*Bulletin of the World Health Organization*, 61 (2): 299-305 (1983)



# A phase II clinical trial of mefloquine in patients with chloroquine-resistant falciparum malaria in Thailand

T. HARINASUTA,[1] D. BUNNAG,[1] & W. H. WERNSDORFER[2]

*A double-blind, randomized, dose-finding, phase II mefloquine trial was carried out in 147 adult male patients suffering from acute, uncomplicated, falciparum malaria and admitted to the Hospital for Tropical Diseases, Bangkok, between January 1980 and April 1981. Mefloquine was administered as a single oral dose of 500, 750, or 1000 mg (base) in the form of the hydrochloride. The clinical and parasitological responses were satisfactory with all three dosage regimens. The cure rates for the 1000-, 750-, and 500-mg doses were 100%, 92.5%, and 95% respectively, over an observation period of 63 days.*

*The side-effects, which were transient and generally mild, included nausea, vomiting, and diarrhoea. No significant changes were noted in haematological or biochemical parameters in any of the three groups. Sinus bradycardia, which started 4-7 days after drug administration and lasted for a few weeks, was seen in 10 patients. It was symptomless and needed no treatment.*

*Acute brain syndrome was observed in one patient on day 21 after receiving a 1000-mg dose of mefloquine.*

*Mefloquine was well tolerated in one case of acute renal failure, in 10 cases of moderately severe malaria with jaundice, in 13 cases with glucose-6-phosphate dehydrogenase deficiency, and in one case of thalassaemia.*

*Mefloquine showed no effect on either gametocytes of* Plasmodium falciparum *or tissue forms of* P. vivax.

*Mefloquine hydrochloride was found to be an effective drug for the treatment of falciparum malaria and tended to produce a more rapid clinical and parasitological response at the highest tested dose of 1000 mg (base).*

Mefloquine, a 4-quinoline methanol derivative that is chemically related to quinine, has the chemical structure shown in Fig. 1. The compound was developed at the Walter Reed Army Institute of Research, Washington, DC, USA, for the prevention and treatment of chloroquine-resistant falciparum malaria. A number of reports have been published (*1-6*) on its effectiveness in human malaria, including infections caused by multi-drug-resistant strains of the parasite. Doses used for treatment of adults have varied from 400 to 1500 mg (*7*).

In Thailand, most strains of *Plasmodium falciparum* are resistant to antimalarial drugs currently in use; more than 90% of infections with this parasite are resistant to chloroquine. Among the *P. falci-*

[1] Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

[2] Research and Technical Intelligence, Malaria Action Programme, World Health Organization, Geneva, Switzerland. Requests for reprints should be addressed to this author.

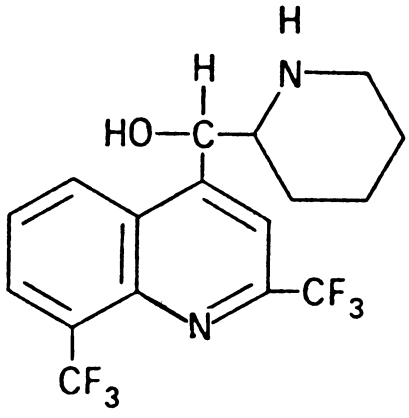


Fig. 1. Chemical structure of mefloquine (α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol).

*parum* infections seen recently at the Hospital for Tropical Diseases, Bangkok, about 90% were resistant to sulfadoxine/pyrimethamine (*8*) and about 25–50% to quinine (*9*, *10*).

The present study was undertaken to determine the optimal dose of mefloquine required for the treatment of falciparum malaria in adults.

## PATIENTS AND METHOD

The study was carried out in adult male patients suffering from acute, uncomplicated falciparum malaria and admitted to the Hospital for Tropical Diseases, Mahidol University, Bangkok, between January 1980 and April 1981. Informed consent was obtained from the patients, who stayed in the hospital throughout the 63-day study period. The hospital is in a non-transmission area. Patients with complications or other diseases were excluded from the study. A total of 150 male adults between the ages of 15 and 65 years entered the trial.

Each patient was given a complete clinical examination, covering history of illness, symptoms and signs, body weight and height, laboratory examination of blood (haemoglobin level, red blood cell count, haematocrit, total and differential white blood cell counts, platelet count, reticulocyte count), and biochemical investigations (estimations of serum glucose, blood urea, serum bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, serum creatinine, serum cholesterol, serum albumin, and proteins). The tests were done before drug administration and during the follow-up period on days 4, 7, 14, 28, and 63. Urinalysis was carried out daily during the first week after treatment and again on days 28 and 63. Electrocardiograms (ECG) were taken on days 0, 1, 4, 7, 28, and 63. Chest X-rays, quantitative tests for glucose-6-phosphate dehydrogenase (G6PD), and tests for haemoglobin type were also carried out on day 0.

Malaria parasite counts of asexual forms and gametocytes were done every 12 hours while the parasitaemia lasted, and then daily throughout the observation period.

The symptoms and signs were recorded once or twice daily during the first week and then at weekly intervals.

### *Drug administration*

The patients were assigned randomly to a drug regimen and received, in a double-blind design, either 500, 750, or 1000 mg of mefloquine (50 patients per dose level), given as tablets each containing 250 mg (base) of the active drug in the form of the hydrochloride. Sachets were supplied according to a random code and contained 2, 3, or 4 tablets of mefloquine and an appropriate number of placebo tablets to give a total of 4 tablets per sachet. The clinician was unaware of the total amount of active drug given to the patient until the end of the trial.

The drug was taken as a single oral dose, with a glass of water, under supervision. If considered necessary, the patients received other drugs such as analgesics (paracetamol), sedatives (diazepam), intravenous fluids, vitamin supplements, etc. No other antimalarial drug was given unless there was a recrudescence or a relapse due to *P. vivax*, for which the patients then received standard treatment.

## RESULTS

Patients were omitted from the analysis if they vomited within a few hours of taking the drug. Only 118 patients completed the 63-day follow-up period, and of these, 40 had received a 500-mg dose of mefloquine, 40 had received 750 mg, and 38 had received 1000 mg. All subjects showed a good initial response and were cleared of fever and parasitaemia.

### *Body weight*

There were no significant differences in the mean body weight of the patients in the three groups, either at the beginning or at the end of the trial. The average body weight at the beginning was 51–52 kg (range, 42–73 kg) and at the end, 54 kg. There was a wide variation in weight gain among individual patients, though the differences between the 3 groups were not significant. The gain in weight by most of the patients could be attributed to control of the infection, good

food, and hygienic conditions during the period of the study.

*Body temperature*

All patients had a raised body temperature on day 0. In the 500-mg group, the mean duration of fever after drug administration was 37.08 h (Table 1), with a rate of pyrexia clearance of 30% in 24 h, 70% in 36 h, and 74% in 48 h. In one patient, the fever lasted 96 h, and in another 105 h after mefloquine treatment.

In the 750-mg group, the average duration of fever after drug administration was 34.75 h. Patients were cleared of pyrexia at a rate of 40% in 24 h, 67.3% in 36 h, and 75% in 48 h. In a few patients, the fever lasted for 72 h, and in 3 cases for 84, 106, and 135 h, respectively, after drug administration.

In the 1000-mg group, the average duration of fever was 29.26 h after drug administration. Patients were cleared of pyrexia at a rate of 40% in 24 h, 70.8% in 36 h, and 81% in 48 h. All patients in this dose group were cleared of fever within 84 h.

*Parasitaemia*

*500-mg dose.* All 50 patients given 500 mg of mefloquine had parasitaemia with asexual forms of *P. falciparum* on day 0, and all were cleared by day 5 (Table 2). Recrudescence was seen in one patient on day 14 and in one on day 32.

The rate of clearance of asexual parasitaemia was 12% in 36 h, 46% in 48 h, and 90% in 84 h (Table 1).

Gametocytes were present in 7 patients on day 0, in 22 on day 4, and persisted in 5 patients until day 28. On day 63, no gametocytes were observed.

There were 11 cases of relapse due to *P. vivax* (Table 3).

*750-mg dose.* All 49 patients maintained in the study had parasitaemia with asexual forms of *P. falciparum* on day 0, and all were cleared by day 5 (Table 2). One patient was again positive on day 14, one on day 20, and one on day 22.

The rate of clearance of asexual parasitaemia was 20% in 36 h, 50% in 48 h, and 86% in 84 h (Table 1).

Gametocytes were present in 5 patients on day 0, in 17 on day 4, and persisted in 3 until day 28. On day 63

Table 1. Time required for clearance of fever and parasitaemia after administration of a single dose of mefloquine

| Dose (mg) | No.of patients | Fever | | | Parasitaemia | | |
|---|---|---|---|---|---|---|---|
| | | Pretreatment level (°C)[a] | Clearance time (h)[a] | Standard error (h) | Pretreatment level (per mm$^3$) | Clearance time (h)[a] | Standard error(h) |
| 500 | 50 | 38.79 ± 0.92 | 37.08 ± 28.18 | 3.31 | 58 844 ± 140 625 | 56.06 ± 19.98 | 2.83 |
| 750 | 49 | 38.69 ± 0.84 | 34.75 ± 25.47 | 3.60 | 42 679 ± 80 721 | 54.32 ± 20.55 | 2.94 |
| 1000 | 48 | 38.38 ± 0.88 | 29.26 ± 21.39 | 3.12 | 39 356 ± 50 265 | 49.67 ± 21.14 | 3.05 |

[a] Mean ± standard deviation.

Table 2. Effect of mefloquine on falciparum parasitaemia

| Day of treatment | 500-mg dose | | 750-mg dose | | 1000-mg dose | |
|---|---|---|---|---|---|---|
| | No. positive | Mean parasitaemia (per mm$^3$) | No. positive | Mean parasitaemia (per mm$^3$) | No. positive | Mean parasitaemia (per mm$^3$) |
| 0 | 50 | 58 844 | 49 | 42 679 | 48 | 39 356 |
| 1 | 45 | 46 599 | 48 | 35 994 | 47 | 35 864 |
| 2 | 29 | 807 | 27 | 225 | 23 | 1 484 |
| 3 | 9 | 119 | 11 | 11 | 6 | 10 |
| 4 | 5 | 9 | 1 | 1.36 | 0 | |
| 5 | 0 | | 0 | | 0 | |
| 6 | 0 | | 0 | | 1[a] | |
| 7 | 0 | | 0 | | 1[a] | |

[a] This patient was negative for *P. falciparum* on days 3, 4, and 5 but positive on day 6 (66 rings/mm$^3$) and day 7 (99 rings/mm$^3$), and negative thereafter.

Table 3. Number of cases of relapse due to *P. vivax* malaria after mefloquine treatment of falciparum malaria

| Days after administration of mefloquine | 500-mg dose (40 patients) | 750-mg dose (40 patients) | 1000-mg dose (38 patients) |
|---|---|---|---|
| 8–14 | 0 | 0 | 0 |
| 15–21 | 0 | 0 | 0 |
| 22–28 | 0 | 0 | 0 |
| 29–35 | 0 | 1 | 1 |
| 36–42 | 3 | 1 | 2 |
| 43–49 | 3 | 5 | 6 |
| 50–56 | 2 | 6 | 6 |
| 57–63 | 3 | 3 | 1 |
| Total | 11 (27.5%) | 16 (40%) | 16 (42%) |

no gametocytes were found.

There were 16 cases of relapse due to *P. vivax* (Table 3).

*1000-mg dose.* Parasitaemia with asexual forms of *P. falciparum* was observed in 48 patients on day 0, and all were cleared by day 4 (Table 2). One patient became positive again on days 6 and 7, but was again negative on subsequent days. This may have resulted from blood invasion from an exoerythrocytic infection that was already under incubation.

The rate of clearance of asexual parasitaemia was 27% in 36 h, 50% in 48 h, and 94% in 84 h (Table 1).

Gametocytes were present in 5 patients on day 0, in 16 on day 4, and in one until day 28. On day 63 no gametocytes were found.

There were 16 cases of relapse due to *P. vivax* (Table 3).

*Comparative response.* Table 4 shows the comparative parasitological response to mefloquine at the three dose levels (*15*). In the 1000-mg group, an S-type response was seen in all 38 patients who completed the study. In the 750-mg dose group, three cases of RI-type recrudescence occurred, on days 14, 20, and 22, respectively. Two cases of RI-type recrudescence were observed in the 500-mg group, on days 14 and 32, respectively.

### *Spleen*

Most of the patients in all 3 groups had a moderately enlarged spleen on day 0 (1–2 units) (*11*). A significant reduction in the number of enlarged spleens occurred in all groups within 4 weeks of drug administration, with no significant difference among the groups.

Table 4. Response of *P. falciparum* to mefloquine, given in a single oral dose of 500, 750, or 1000 mg, over a 63-day follow-up period

| Mefloquine dose (mg) | No. of patients completing 63-day follow-up period | Parasitological response[a] | | | |
|---|---|---|---|---|---|
| | | S | | RI | |
| | | No. | % | No. | % |
| 500 | 40 | 38 | 95.0 | 2 | 5 |
| 750 | 40 | 37 | 92.5 | 3 | 7.5 |
| 1000 | 38 | 38 | 100 | 0 | |

[a] WHO classification. See ref. *15*. No RII or RIII responses were seen at any dose level.

### *Liver*

Most of the patients in all 3 groups (43–46 per group) had a moderately enlarged liver on day 0 (mean enlargement, 2.5 cm below costal margin). In most cases, a reduction in the size of the liver occurred by day 28 after mefloquine administration and the results for the 3 groups were not significantly different.

### *Cardiovascular system*

The blood pressure of all the patients was within normal limits and no change was observed after mefloquine treatment. Sinus bradycardia (pulse rate of 46–50 per minute) was seen in 2 patients in the 500-mg group, 3 in the 750-mg group, and 5 in the 1000-mg group. The bradycardia started between days 4 and 7 and the pulse rate returned to normal within the next few weeks without treatment. There were no clinical symptoms. One subject in the 1000-mg group developed an atrioventricular block which returned to normal in 2 weeks. ECG studies did not reveal any evidence of myocarditis.

### *Haematology*

No significant changes were seen in any of the haematological parameters except for a depressed total white blood cell count in one case, which is described below. A general rise in haemoglobin, haematocrit, and red blood cell count was observed in all patients during the study. The mean haemoglobin level was 6–7 mmol/litre at the beginning of the study and 8.5 mmol/litre at the end. Haematocrit levels increased from an initial mean of 0.33 to 0.42 at the end of the study.

A G6PD deficiency was observed in 13 patients (6 in the 1000-mg group, 4 in the 750-mg group, and 3 in the 500-mg group) and one patient had thalassaemia. All of these patients tolerated mefloquine well, with

no evidence of haemolysis.

One patient receiving 750-mg of mefloquine had a total white blood cell count of $7.2 \times 10^9$/litre on day 0. This decreased to $2.8 \times 10^9$/litre on day 1 and to $2.5 \times 10^9$/litre on day 4, rising again on day 7 to $3.5 \times 10^9$/litre, to return to normal by day 14 ($7.6 \times 10^9$/litre). There was no change in the differential count, except for a rise in the proportion of eosinophils from 4% on day 0 to 22% on day 14.

*Biochemical parameters*

No significant drug-related changes were seen in any of the biochemical parameters.

Before drug administration on day 0, raised serum bilirubin, aspartate aminotransferase, and alanine aminotransferase values were noted in 5 patients in the 1000-mg group, in 4 in the 500-mg group, and in 1 in the 750-mg group, indicating jaundice due to severe malaria. A few patients developed raised aminotransferase levels later during the study, but these were not considered to be drug-related and were probably due to viral hepatitis.

One patient in the 500-mg group did not appear to be very ill when given the drug on day 0, but the laboratory results received after drug administration showed a raised serum creatinine (836 μmol/l) and serum urea (22 mmol/litre) on day 0. This patient responded well to mefloquine and his renal functions became normal by day 7.

In none of the patients did urine examinations show any significant change due to mefloquine.

*Side-effects*

The main side-effects reported were headache, nausea, vomiting, a feeling of weakness, loss of appetite, and diarrhoea (Table 5). Malaria fever by itself is associated with headache, nausea, vomiting, and a feeling of weakness and this has to be taken into consideration in analysing these subjective symptoms. Headache was reported by 94–100% of subjects in all dose groups and was not considered to be drug-related.

Mild to moderate diarrhoea was observed in 12% of the 500-mg group, 10% of the 750-mg group, and 12% of the 1000-mg group. The change concerned more the character of the stools, which were soft and semisolid, rather than their frequency.

None of the symptoms was severe, and there was no statistically significant difference in the incidence of side-effects among the 3 dosage groups.

Itching, maculopapular rash, and urticaria were noted in one patient 2 hours after his receiving a 750-mg dose of mefloquine.

*Side-effects on the central nervous system*

The only significant changes observed in the central nervous system were one case of dizziness and two of "acute brain syndrome", discussed below.

One patient who had received 500 mg of mefloquine developed a hearing difficulty and severe dizziness. Two weeks after drug administration this patient recovered fully without specific treatment; there was no previous history of similar episodes.

*Acute brain syndrome.* One patient in the 1000-mg group (case no. 2052) had convulsions on day 21, followed by loss of consciousness for 10 minutes. He developed psychosis, showing abnormal behaviour and having hallucinations. The psychiatric consultation report indicated acute brain syndrome. The electroencephalogram (EEG) and the cerebrospinal fluid were normal. This patient had complained of depression in the previous week. He made a complete recovery in 10 days; there was no previous history of such behavioural changes and he was not addicted to any drugs.

A 45-year-old male (case no. 2115) received, by mistake, two doses of mefloquine of 1000 mg each at an interval of 52 hours. He was omitted from the study but was kept in the hospital for observation. He complained of ringing in the ears and vertigo 5 hours after

Table 5. Side-effects of mefloquine observed during first four days after administration of a single oral dose

| Side-effect | 500-mg dose (50 patients) | | 750-mg dose (49 patients) | | 1000-mg dose (48 patients) | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Nausea | 15 | 30 | 14 | 28 | 10 | 20 |
| Vomiting | 7 | 14 | 8 | 16 | 9 | 18 |
| Dizziness | 1 | 2 | 0 | | 0 | |
| Acute brain syndrome | 0 | | 0 | | 1 | 2 |
| Diarrhoea (more than 3 stools per day) | 6 | 12 | 5 | 10 | 6 | 12 |
| Itching and rash | 0 | | 1 | 2 | 0 | |

the second dose of mefloquine and, 20 hours later, of a sensation of warmth and something "crawling" on his back. He had vertigo and an unsteady gait. His body temperature was normal and his blood pressure was 110/70 mmHg. He answered questions but the answers were incoherent. He lost consciousness for about six hours and then gradually recovered; his EEG was normal. The psychiatric diagnosis was acute psychosis. There was no previous history of a similar episode and the patient denied taking any drug. Recovery was complete.

## DISCUSSION

This study has shown that mefloquine hydrochloride, in single doses of 500, 750, and 1000 mg (base), is effective in treating acute falciparum malaria in Thailand. More than 50% of the patients studied had contracted the disease near the Thai–Kampuchean border where *P. falciparum* is highly resistant to the antimalarial drugs in current use, including chloroquine, amodiaquine, and sulfadoxine/pyrimethamine (*12*). Therefore, a single dose of 500–1000 mg of mefloquine can be considered to be effective in treating multiresistant falciparum malaria. The clinical and parasitological response is rapid and the cure rate high at 90–100%.

The main side-effects observed during the study were related to the gastrointestinal tract. About 10–30% of patients had nausea, vomiting, and loose stools or diarrhoea. The symptoms were mild and required no specific treatment. The incidence of these side-effects was similar in all 3 groups. Malaria itself produces these symptoms, but they seem to be aggravated to some extent by the drug.

Severe dizziness and tinnitus were reported by one patient. Another patient, who had inadvertently received 2 g of mefloquine, suffered from neuropsychiatric disturbance characterized by dizziness and behavioural changes, from which he recovered completely. Another case exhibited a similar episode on day 21 after drug administration. This was diagnosed as acute brain syndrome. None of these patients had a previous history of any such disorders. When symptoms occur 2–3 weeks after administration of a single dose of a drug, it is difficult to ascribe these side-effects to the drug. However, two further cases of neuropsychiatric disturbance, occurring in the second week after mefloquine administration, have been observed in the course of other clinical investigations. Considering that mefloquine has been found to have a long half-life in volunteers (6–22 days), it is likely that either the active drug or its metabolites are responsible for these side-effects, but this needs further study.

Relapses due to *P. vivax* occurred after day 30 in all 3 groups. This delay is probably related to the long half-life of mefloquine. The relapses indicate that the drug has no effect on the tissue form of *P. vivax*.

Mefloquine apparently had no effect on gametocytes of *P. falciparum*.

The initial efficacy of mefloquine is not surprising, since it is a new drug. Most of its predecessors, such as chloroquine, amodiaquine, proguanil, and sulfadoxine/pyrimethamine, showed similarly impressive cure rates when first tested. After perhaps 5–10 years of widespread use, however, parasite populations emerged that could survive concentrations of the drug that previously killed the parasite. It may be predicted that resistance will also develop to mefloquine. Studies carried out *in vitro* have already demonstrated the emergence of resistance after serial passages in the presence of increasing concentrations of the drug (*13*). A bitter lesson was learnt from chloroquine, and lately sulfadoxine and pyrimethamine, when their indiscriminate use for prophylaxis and casual self-medication was followed by the appearance of resistant strains. Mefloquine must therefore be introduced with strict precautions to prevent a similar course of events (*14*). Combination with other antimalarial drugs may delay resistance. Adequate baseline data on the susceptibility of local strains should be collected from all parts of the endemic area before the introduction of the drug, and regular monitoring should be carried out thereafter.

## CONCLUSION

A single dose of mefloquine was found to be effective in the treatment of falciparum malaria in adult males. The trend towards earlier clearance of fever and parasitaemia and radical cure in all patients so treated favours the choice of 1000 mg (base) as the effective dose, even though in this study the results obtained with 500 and 750 mg were also impressive. The recovery, weight gain, and rise in haemoglobin were satisfactory in all treatment groups.

## ACKNOWLEDGEMENTS

The authors wish to thank Professor Chamlong Harinasuta, Dean of the Faculty of Tropical Medicine, Mahidol University, Bangkok, for his encouragement, Professor U. K. Sheth for his help in preparing the manuscript, and

Mrs N. Valabrègue for reviewing it. The authors appreciate the assistance given by the staff and technicians of the Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok. Thanks are also due to all the patients who participated in the study.

The study was supported by the Chemotherapy of Malaria component of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

## RÉSUMÉ

### ESSAI CLINIQUE (PHASE II) DE LA MÉFLOQUINE EN THAÏLANDE CHEZ DES MALADES PORTEURS D'UN PALUDISME À FALCIPARUM CHLOROQUINO-RÉSISTANT

Un essai de phase II relatif à la méfloquine, effectué en double aveugle et de manière aléatoire dans le but de déterminer la posologie optimale, a été effectué chez 147 adultes du sexe masculin atteints d'un paludisme aigu à falciparum sans complications et admis à l'hôpital des maladies tropicales de Bangkok, entre janvier 1980 et janvier 1981. La méfloquine a été administrée par voie orale en dose unique de 500, 750 ou 1000 mg (base) sous forme de chlorhydrate. Les trois posologies ont suscité des réponses satisfaisantes sur le plan clinique et parasitologique. Le pourcentage de guérisons obtenu avec les doses de 1000, 750 et 500 mg a été respectivement de 100%, 92,5% et de 95% sur une période d'observation de 63 jours.

Les effects secondaires, qui ont été passagers et en général bénins, comprenaient des nausées, des vomissements et de la diarrhée. Aucune modification sensible des paramètres hématologiques ou biochimiques n'a été notée dans aucun des trois groupes. Chez 10 malades, on a observé une bradysinusie qui a commencé 4 à 7 jours après l'administration du médicament et a duré quelques semaines. Elle est restée asymptomatique et n'a pas nécessité de traitement.

Un syndrome cérébral aigu a été observé chez un malade 21 jours après l'administration d'une dose de 1000 mg de méfloquine.

Le médicament a été bien toléré par un malade présentant une insuffisance rénale aiguë, 10 malades atteints d'un paludisme modérément grave avec ictère, 13 sujets porteurs d'un déficit en glucose-6-phosphate-déhydrogénase et un thalassémique.

La méfloquine n'a eu aucun effet sur les gamétocytes de *Plasmodium falciparum* ni sur les formes tissulaires de *P. vivax*.

Le chlorhydrate de méfloquine s'est révélé efficace pour le traitement du paludisme à falciparum; il a tendance à produire une réponse clinique et parasitologique plus rapide à la dose la plus forte de l'essai, soit 1000 mg (base).

## REFERENCES

1. ROZMAN, R. S. & CANFIELD, C. J. *Advances in pharmacology and chemotherapy*, **16**: 1-43 (1979).
2. RIECKMANN, K. H. ET AL. *Bulletin of the World Health Organization*, **51**: 375 (1974).
3. TRENHOLME, G. M. ET AL. *Science*, **190**: 792 (1975).
4. CLYDE, D. F. ET AL. *Antimicrobial agents and chemotherapy*, **9**: 384 (1976).
5. HALL, A. P. *British medical journal*, **1**: 323 (1976).
6. HALL, A. P. ET AL. *British medical journal*, **1**: 1626 (1977).
7. DOBERSTYN, E. B. ET AL. *Bulletin of the World Health Organization*, **57**: 257-279 (1979).
8. HARINASUTA, T. ET AL. *South-east Asian journal of tropical medicine and public health*, **13**: 1-34 (1982).
9. BUNNAG, D. ET AL. In: *Tenth International Congresses on Tropical Medicine and Malaria, Manila, Philippines, 1980.*
10. CONGSUPHAJAISIDDHI, T. ET AL. *Annals of tropical paediatrics*, **1**: 21 (1981).
11. HACKETT, L. W. *Journal of the National Malaria Society*, **3**: 121 (1944).
12. UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. *Drug-resistant malaria*, Geneva, World Health Organization, 1982.
13. PETERS, W. ET AL. *Annals of tropical medicine and parasitology*, **71**: 419-427 (1977).
14. UNDP/WORLD BANK/WHO UPDATE. *Bulletin of the World Health Organization*, **61**: 169-178 (1983).
15. BRUCE-CHWATT, L. J., ed. *Chemotherapy of malaria*, 2nd ed., Geneva, World Health Organization, 1981 (Monograph Series, No. 27).