A phase-III clinical trial of mefloquine in children with chloroquine-resistant falciparum malaria in Thailand*

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Mefloquine is a highly effective drug for the treatment of falciparum malaria among adults, but studies of its effects on children are lacking. An open, noncomparative trial of mefloquine was therefore carried out among 84 children aged 5–12 years who were patients at the Hospital for Tropical Diseases, Mahidol University, Bangkok, Thailand. The drug was administered as a single dose of 18–29 mg base per kg body weight. Eighty-two of the 84 children completed a 42-day period of post-treatment observation. The drug was well tolerated also by 11 children with glucose-6-phosphate dehydrogenase deficiency, and all the children in the study cleared their parasitaemia initially (average clearance time, 65 hours). Furthermore, the clinical-chemical parameters measured exhibited no drug-related changes during the study. The radical cure rate of nearly 98% and high tolerance indicate that mefloquine can be used effectively and safely for the treatment of children aged 5–12 years who are suffering from uncomplicated falciparum malaria.

MATERIALS AND METHODS

An open, noncomparative trial was carried out among 84 children of either sex, aged 5–12 years, with acute, uncomplicated falciparum malaria, who had been admitted to the Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, during the period January 1982 to July 1984. Informed consent of the children’s parents was obtained before they were included in the trial. The children remained in hospital as inpatients during the entire study period of 42 days. Those with severe or complicated malaria or severe accompanying diseases or those for whom oral therapy was not possible were not admitted to the study.

On the day of admission to the trial (D₀), the children were thoroughly examined clinically and their history of illness, symptoms and signs, body weight and height were noted. Subsequently, they were examined on a daily basis from day 0 to day 7 (D₀–D₇) and then periodically on days 10, 14, 21, 28, 35, and 42 of the study. While the parasitaemia lasted, counts of malarial parasite asexual forms and gametocytes were made every 12 hours and subsequently on a daily basis throughout the study. Haematological investigations (haemoglobin level, red blood cell count, erythrocyte volume fraction
(haematocrit), as well as total and differential white blood cell counts) were carried out prior to drug administration and on D₁. Assays of blood urea, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, serum albumin, serum bilirubin, serum cholesterol, as well as of serum glucose and proteins were performed before administration of mefloquine and repeated on D₇ and D₁₂. Urine was analysed on D₀, D₁, D₃, D₇, and D₁₂, and electrocardiograms (ECGs) were recorded daily from D₀ to D₁₀ and then periodically on D₁₄, D₂₁, D₂₅, D₃₅, and D₄₂. The following investigations were also carried out on each child on D₂: chest X-ray, qualitative determination of glucose-6-phosphate dehydrogenase, and tests for haemoglobin type.

Drug administration

Tablets of mefloquine, each containing 250 mg base, were administered orally, in crushed form, as a single dose (Table 1); also shown in the Table are the subweight groupings of the 56 children who received two tablets of mefloquine.

If required by their clinical conditions, some patients also received other drugs, such as analgesics (e.g., paracetamol), vitamins, or anthelmintics. Recrudescences or relapses caused by *P. vivax* were treated using standard methods.

RESULTS

A total of 84 patients were admitted to the study. Two patients withdrew, leaving 82 who completed the 42 days' trial. The mean age of participants was 8.9 years (range: 5–12 years), and their mean body weight on D₀ was 25 kg (range: 15–41 kg).

<table>
<thead>
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<th>No of children</th>
<th>Body weight range (kg)</th>
<th>No. of tablets</th>
<th>Dose per kg body weight (mg/kg)</th>
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<tbody>
<tr>
<td>3</td>
<td>15–16</td>
<td>1.5</td>
<td>24</td>
</tr>
<tr>
<td>56</td>
<td>17–25</td>
<td>2</td>
<td>20–29</td>
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<tr>
<td>20</td>
<td>26–35</td>
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</tr>
<tr>
<td>3</td>
<td>39–41</td>
<td>3</td>
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Children who received 2 tablets

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<th></th>
<th>Body weight range (kg)</th>
<th>No. of tablets</th>
<th>Dose per kg body weight (mg/kg)</th>
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<tr>
<td>7</td>
<td>21</td>
<td>2</td>
<td>24</td>
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<tr>
<td>21</td>
<td>22–25</td>
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</table>

Clinical findings

In all cases, the systolic and diastolic blood pressures of the children were normal. The majority of patients had pulse rates consistent with their age and body temperature. ECG studies revealed sinus arrhythmia in 56 patients. The arrhythmia occurred in 7 patients on D₀, in 14 on D₁, in 31 on D₃, in 40 on D₁, in 41 on D₆, in 36 on D₇, in 42 on D₁₀, in 25 on D₁₄, and in 19 on D₂₈. The cardiac rhythms of all patients reverted to normal by the end of the study period without any specific treatment. The majority of patients had enlarged livers and spleens on D₀, but these decreased appreciably in all cases by D₄₂.

Laboratory investigations

The haemoglobin level, erythrocyte volume fraction, and red blood cell count of the majority of patients were within normal limits, and the values of these parameters improved during the study period. A deficiency of glucose-6-phosphate dehydrogenase was observed in 11 patients, but no drug-induced adverse effects, such as haemolysis, were observed in any of them. The total and differential white blood cell counts of the children were normal, although many exhibited high eosinophil counts that were probably related to concurrent helminthic infections. The levels of serum bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and creatinine of the children were normal, and no drug-related changes were observed during the study. Furthermore, there were no abnormal changes in the results of urine analysis before and after drug administration. Examination of stools on D₀ revealed that 80% of patients had helminthic infection caused by hookworm, *Ascaris lumbricoides*, *Trichuris trichuria*, or *Strongyloides stercoralis*.

Body temperature

Sixty patients had an elevated body temperature (measured orally) on D₀ (mean: 37.8 ± 1.1 °C). The mean duration of fever after drug administration was 48.5 ± 36.6 hours, with pyrexia clearing in 52% of sufferers in 24 hours, 67% in 48 hours, and 88% in 72 hours. In one patient fever lasted 105 hours, and in another persisted for 85 hours after treatment.

Parasitological response

All 82 patients had asexual parasitaemia on D₀ (mean parasitic count: 26 345 per mm³) and all were cleared by D₆. The mean parasite clearance time was 64.8 ± 17.9 hours, and the rate of clearance was 21% of patients in 48 hours, 80% in 72 hours, and 95% in 96 hours.
Two cases of R1 recrudescence occurred on D14 and D21, respectively. The patients involved weighed 20 kg and 21 kg, respectively, and received 2 tablets of mefloquine (24 mg base per kg body weight). Gametocytes occurred in 51% of patients on D9, in 72% on D14, in 45% on D17, in 28% on D24, and in 4.5% on D42. Also, P. vivax was detected in 12 patients between D23 and D45 (one case each on D23, D25, D27, D32, and D45 and two cases each on D34, D40, and D42).

Side-effects

Side-effects of the drug treatment were categorized as minimal, mild, or moderate. Vomiting occurred in three patients (3.6%), diarrhoea in five (6.0%), and mild abdominal pain in two (2.4%).

Discussion

The results of the study indicate that administration of mefloquine in a dose of 17-29 mg base per kg body weight was effective in treating falciparum malaria among children aged 5-12 years (cure rate, 97.5%).

The two patients who exhibited R1 responses received a daily dose of two tablets of mefloquine (24 mg base per kg body weight). These patients weighed 20 kg and 21 kg, respectively; nevertheless, S-type responses were observed in five other patients in this weight range, who also received the same dose of the drug. S-type responses were also observed in 21 patients who received a dose of 19 mg mefloquine per kg body weight. The R1 response reported therefore appears not to be related to the dose of mefloquine per kg body weight. However, the levels of the drug in the blood of the two patients with R1 responses were not determined, and it is therefore difficult to correlate such responses with the administered dose.

Based on the results reported here, radical cure of falciparum infection in children aged 5-6 years and weighing less than 15 kg should be achieved with a dose of 1.5 tablets of mefloquine, with 2 tablets in children of 6-11 years weighing up to 25 kg, and with 2.5 tablets in children of up to 12 years of age. The incidence of side-effects using these regimens was low, and consisted of vomiting and mild to moderate diarrhoea in 4-6% of the patients. The drug was well tolerated. Symptomless and reversible sinus arrhythmia occurred in 68% of the children, beginning on D0-D4, with a peak incidence on D3, but gradually reverted to normal by about D20.

In summary, it can therefore be concluded that mefloquine administered in a single dose of 1.5-2.5 crushed tablets (250 mg base each) is an effective and well-tolerated drug for the treatment of falciparum malaria among children aged 5-12 years.

Acknowledgements

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Résumé

ÉSSAI CLINIQUE DE PHASE III DE LA MÉFLOQUINE CHEZ DES ENFANTS ATTEINTS DE PALUDISME A FALCIPARUM CHLOROQUINORÉSISTANT EN THAILANDE

L'activité antipaludique de la méfloquine, un quinolyl-4 carbinal apparenté par sa structure à la quinine, a été largement étudiée chez les adultes atteints de paludisme à falciparum. Ce médicament s'est montré très efficace administré en dose unique de 15-20 mg de base par kg de poids corporel. Toutefois, aucune étude n'avait été entreprise à l'échelle suffisante chez des sujets plus jeunes.

Par conséquent, un essai ouvert, non comparatif, a été effectué à l'Hôpital des Maladies tropicales de l'Université Mahidol à Bangkok, chez 84 enfants de deux sexes, âgés de 5 à 12 ans (âge moyen 9 ans). Tous ces enfants étaient atteints de paludisme à falciparum déclaré, non compliqué.

La numération parasitaire moyenne avant traitement était de 26 345 parasites par mm³ de sang. Les malades ont été soumis à un examen clinique complet avant le traitement puis à intervalles réguliers pendant une période de suivi d'au moins 42 jours, des examens parasitologiques, hématologiques et biochimiques ont été effectués ainsi qu'un électrocardiogramme.

La méfloquine a été administrée en une dose unique de 18-29 mg de base par kg de poids corporel. Sur les 84 enfants étudiés, 82 ont été suivis jusqu'au bout de la période d'observation, soit 42 jours après le traitement. Dans un premier temps, la parasitémie a disparu chez tous les
malades, au bout d’un temps moyen de 65 heures. Puis on a observé des recrudescences chez deux malades (les jours 14 et 21) et des rechutes manifestes à *Plasmodium vivax* dans 12 cas entre les jours 23 et 45. La fièvre tombait en moyenne dans les 49 heures suivant le traitement.

La méfloquine a été bien tolérée, même chez les 11 enfants présentant un déficit en glucose-6 phosphate déshydrogénase. Dans la plupart des cas, les paramètres hémato-logiques se sont améliorés au cours de la période étudiée, et les paramètres cliniques et biochimiques n’ont présenté aucune modification liée au traitement. Au début de l’étude, la plupart des enfants présentaient une hépatomégalie et une splénomégalie, qui avaient considérablement régressé au bout de 42 jours. L’électrocardiogramme a montré une arythmie sinusale chez 7 enfants au début de l’étude ; ce nombre est passé à 56 après administration de la méfloquine, avec un maximum de cas le jour 10. À la fin de l’étude, l’électrocardiogramme de tous les enfants était revenu spontanément à la normale.

Le taux de guérison obtenu, de près de 98%, ainsi que la bonne tolérance du médicament, indique que la méfloquine est à la fois efficace et sans danger pour le traitement des enfants âgés de 6 à 12 ans atteints de paludisme à *falciparum* non compliqué.

REFERENCES