In vivo and in vitro responses to quinine and quinidine of Plasmodium falciparum*

A. Sabchareon, T. Chongsruphaisiddhi, V. Sinhasivanon, P. Chanthavanich, & P. Attanath

A total of 66 Thai children with uncomplicated falciparum malaria were treated orally with regimens of either quinine or quinidine. Radical cures were observed in 85% (28 of 33) of the children who received quinine and in 88% (29 out of 33) of those who received quinidine. Treatment failures in both groups were RI responses.

The mean trough level of quinine (10 μmol/l) was about 2.5-times less than that of quinidine (25 μmol/l). The electrocardiograms of the two treatment groups differed significantly in that there was an acute prolongation of the QT interval in 56% of those who received quinidine compared with 21.0% of those given quinine. In vitro assays of the pretreatment drug susceptibilities of the isolates of Plasmodium falciparum indicated that the mean minimum inhibitory concentration (MIC) for quinidine (1.44 μmol/l) was about half that for quinine (3.02 μmol/l). Although both drugs are equally effective, quinine is recommended for treatment of multidrug-resistant malaria in paediatric patients, primarily because of the cardiac effects produced by quinidine.

Since about 1981 there has been a significant decline in the effectiveness of quinine for the treatment of chloroquine-resistant falciparum malaria in Thailand (1). In vitro studies (1–3) have revealed that this is related to a corresponding decrease in the innate susceptibility of Plasmodium falciparum strains to quinine. Although the combination quinine–tetracycline has remained highly effective for treatment of falciparum malaria in adults (4, 5), extended administration of tetracyclines to young children is generally contraindicated (6). Treatment of multiresistant falciparum infections in paediatric patients has become a significant problem. We have recently reported, however, that a single dose of mefloquine (17–29 mg base per kg body weight) is highly effective in treating falciparum malaria among children aged 5–12 years (cure rate, 97.5%) (7). In order to prevent the emergence of mefloquine-resistant parasites, use of the drug has been restricted for the treatment of patients with microscopically diagnosed falciparum malaria and is available only in malaria clinics and a few hospitals in Thailand (S. Pinichpongsa, personal communications, 1986 and 1987).

Use of regimens of quinine that extend over at least 7 or 8 days are both safe and effective for paediatric patients (1). Recently, quinidine has been recommended as an alternative treatment for falciparum malaria in adults (8, 9); however, its efficacy in paediatric patients has not been evaluated. The present study was therefore undertaken to compare the efficacy of quinine and quinidine in treating children with multidrug-resistant falciparum malaria, and to evaluate possible mechanisms of treatment failures by monitoring serum drug levels during treatment and by assaying the in vitro drug susceptibility of P. falciparum strains to quinine and quinidine.

MATERIALS AND METHODS

Patients

A prospective, randomized trial involving 72 children with uncomplicated falciparum malaria was conducted from July 1984 to January 1985. Parents of all the children gave informed consent for partici-
Table 1. Mean body temperature, erythrocyte volume fraction, and parasite count in 66 Thai children in the study with falciparum malaria

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of children</th>
<th>Male</th>
<th>Female</th>
<th>Mean temperature (°C)</th>
<th>Mean EVF</th>
<th>Geometric mean parasite count (per μl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinine</td>
<td>33</td>
<td>19</td>
<td>14</td>
<td>39.0</td>
<td>0.26</td>
<td>14 200</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(38.0–40.6)</td>
<td>(0.12–0.36)</td>
<td>(800–97 400)</td>
</tr>
<tr>
<td>Quinidine</td>
<td>33</td>
<td>18</td>
<td>15</td>
<td>39.1</td>
<td>0.26</td>
<td>14 800</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(37.5–45.0)</td>
<td>(0.13–0.38)</td>
<td>(700–84 300)</td>
</tr>
</tbody>
</table>

* Measured orally.

* EVF = erythrocyte volume fraction

* Figures in parentheses are the range.

pation in the study. The patients were all Thai and were mainly from the south-eastern region of the country, near the Thai-Kampuchean border. The children’s ages ranged from 2 to 12 years (mean, 6.7 years). Diagnosis of *P. falciparum* infection was based on clinical signs and symptoms and confirmed by microscopic examination of Giemsa-stained thick and thin blood films. The children exhibited asexual parasitaemia levels of 700–97 400 parasites per μl (Table 1), and urine samples from all the patients were negative for 4-aminoquinolines in the Dill-Glazko test (10) and for sulphonamides in the lignin test (11). All the children were admitted to the Hospital for Tropical Diseases, Bangkok, for treatment and observation for 28 days, and of the 72 originally included in the study, 66 (92%) completed the full 28-day follow-up period.

**Laboratory studies**

Samples of blood were taken from each child and the haemoglobin concentration, erythrocyte volume fraction, differential leucocyte count, as well as the bilirubin, albumin, globulin, alkaline phosphatase, transaminase, cholesterol, urea nitrogen, and creatinine levels determined. Urine was tested for albumin, sugar, and bilirubin levels, as well as for the presence of sediments. All laboratory tests were conducted on the day after the child had been admitted to the hospital and then weekly for 4 weeks after initiation of drug administration. No significant or unusual laboratory finding was noted for the children during the study. Asexual parasites were counted every 12 hours during parasitaemia and then daily for the remainder of the study.

**Drug regimens**

An extended 8-day course of quinine, which has been recommended for the treatment of quinine-resistant falciparum malaria in paediatric patients (1), was administered to 33 of the children. Quinine sulphate* was given as 10 mg base per kg body weight every 8 hours for 4 days and the dose increased to 15 mg base per kg every 8 hours for the next 4 days. Quinidine sulphate* was administered as 10 mg base per kg every 8 hours for 7 days to a second group of 33 children. Since this study was the first evaluation of the efficacy of quinidine for the treatment of falciparum malaria in children, the same dosage schedule as quinine was not used in order to avoid any possible cardiotoxic effects.

Patients were randomly assigned to quinine or quinidine regimens, and medications were given orally as crushed pills. Electrocardiograms (ECGs) were recorded daily, on day 2 and day 1, as well as 2 hours after the morning dose from day 0 to day 7 of the study. One child had abnormal prolongation of the corrected QT interval (QTc) before drug administration, and the ECG records of this patient were excluded from the study. The results of the treatments were categorized as S (clearance within 7 days, without subsequent recrudescence) or RI (clearance of asexual parasitaemia, followed by recrudescence) according to the grades of resistance defined by WHO (12). There were no RII (marked reduction of asexual parasitaemia but no clearance) or RIII (no marked reduction of asexual parasitaemia) responses to either the quinine or quinidine regimens.

**Blood drug levels**

Plasma quinine or quinidine levels were determined prior to administration of the first dose of the drug, 4 hours following its administration, and then daily before the morning dose throughout the course of the treatment. The level in plasma of quinine or

*Thai Government Pharmaceutical Organisation.

*Labatec, Pharma S.A., Geneva, Switzerland.
quinidine was determined using the method reported by Cramer & Isaksson (13). Pre-administration drug plasma levels represented the trough values and those 4 hours after administration the peak plasma level on day 0.

**In vitro assays**

Prior to treatment, the in vitro susceptibility of isolates of *P. falciparum* to quinine, quinidine, chloroquine, and mefloquine was determined using the standardized procedure recommended by WHO (12, 14). The minimum inhibitory concentration (MIC) was defined as the lowest concentration that completely inhibited schizont formation.

**RESULTS**

**In vivo responses**

There were no apparent differences in the response of the *P. falciparum* infections to either the 8-day course of quinine or the 7-day course of quinidine, and both drugs appeared equally effective as antimalarials. The mean fever clearance times (47.6 hours for quinine and 51.6 hours for quinidine) and the parasite clearance times (98.8 hours for quinine and 94.5 hours for quinidine) for both regimens were comparable. Recrudescences occurred between day 21 and day 27 in five (15%) of the patients treated with quinine and between day 17 and day 21 in four (12%) of those who received quinidine. All treatment failures were RI responses. The clinical side-effects included transient and generally mild nausea. Tinnitus and dizziness were reported by older children on both quinine and quinidine regimens.

**Electrocardiogram effects**

Electrocardiogram effects occurred among patients in both the quinine and quinidine groups (Table 2). Some of those treated with quinine exhibited a significant acute prolongation of the QTc (8 patients) and a significant prolongation of the PR intervals (16 patients) compared with pre-treatment baseline values. Acute prolongation of the QTc (19 patients) and PR intervals (27 patients) was also noted among children treated with quinidine. The prolonged QTc interval was significant ($P<0.01$, $\chi^2$ test) in more patients of the quinidine group (55.9%) than in those of the quinine group (21%). Moreover, the frequency of prolonged QTc intervals among patients treated with quinidine was 3.5-times greater than among those who received quinine. The frequencies of prolonged PR intervals in the two treatment groups were similar. During the afebrile periods from day 3 to day 8 of the study, sinus arrhythmias were noted among 10 patients in the quinine group and among seven in the quinidine group.

**Plasma quinine and quinidine levels**

The levels of quinidine in plasma were generally about 2.5-times lower than those of quinine, although
Table 3. Minimum in vitro inhibitory concentrations for quinine, quinidine, chloroquine, or mefloquine for Plasmodium falciparum isolates from children in the study

<table>
<thead>
<tr>
<th>Minimum inhibitory concentration (µmol/l)</th>
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<tbody>
<tr>
<td>Quinine (n = 64)</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Standard deviation</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Median</td>
</tr>
</tbody>
</table>

Equivalent doses of the two drugs were administered during the first 4 days of therapy (Fig. 1). There were no apparent differences in the plasma levels of the two drugs for treatment successes and failures.

In vitro responses

The in vitro susceptibility of 64 of the 66 isolates of P. falciparum to quinine, quinidine, or chloroquine as well as that of 44 to mefloquine are shown in Table 3. Based on these results, the parasites were resistant to chloroquine and generally susceptible to mefloquine. The mean value of the MIC for chloroquine was 3.10 µmol/l, while that for mefloquine was 0.124 µmol/l. All of the MICs for chloroquine were greater than the level that has been defined as indicating resistance to the drug (0.16 µmol/l), while for mefloquine four (9.1%) of the MICs were 0.64 µmol/l.

The MICs for quinine (mean, 3.02 µmol/l) were significantly greater (P < 0.05, Student’s t-test) (Table 3). There were no apparent differences between the in vitro patterns of drug sensitivity to quinine or quinidine for patients who were eventually treatment failures compared with those who were treated successfully. Also, for either group there were no differences between the isolates collected before treatment and following treatment failure.

DISCUSSION

Over the past 5–6 years, the efficacy of quinine for the treatment of falciparum malaria in Thailand has diminished significantly. The following two alternative approaches have been recently evaluated: extending the therapy with quinine to 8 days with an increased dose on days 4–7; and substituting quinidine for quinine (1, 8).

Although there were no significant differences in the antimalarial efficacies of either quinine (28 out of 33 (84.8%) cures) or quinidine (29 out of 33 (87.9%) cures) for paediatric patients who followed comparable dosage schedules, the following two interactive factors may have contributed to the small number of treatment failures with these drugs: achieving and maintaining an adequate drug plasma level; and the innate drug susceptibilities of the parasites. Both these factors were similar for quinine and quinidine. Plasma levels of quinine (25 µmol/l) were significantly higher than those of quinidine (10 µmol/l), and the in vitro susceptibility of the parasites to quinine (MIC, 3.02 µmol/l) was significantly lower than that to quinidine (MIC, 1.44 µmol/l). Variations in either of these factors or their interaction in an individual patient could be significant for the successful outcome of treatment of infection caused by multidrug-resistant strains of P. falciparum, which have only recently developed resistance to quinine.

We have reported in a recent study that the ratio of the concentration of quinidine in red blood cells to that in plasma was 1.15, whereas the concentration of quinine was significantly lower in red blood cells than in plasma (15). In addition to the low MIC values for quinidine, the relatively high concentration of the drug in red blood cells may be a major factor in explaining its high efficacy.

The significant prolongation of QTc and PR intervals we have reported indicates that these effects are quinine- and quinidine-related. The sinus arrhythmias previously observed before administration of antimalarials in 3 out of 120 (2.5%) children with symptomatic falciparum malaria (16), but in 17 out of 72 (23.6%) children during the therapy with quinine or quinidine (afebrile periods) in the present study suggest that the arrhythmias we observed were drug-related.

Although Chongsuphajasiddhi et al. (7) reported that there was no abnormal prolongation of QTc and PR intervals for patients treated with mefloquine, the frequency of mefloquine-related reversible sinus arrhythmias that they reported (68%) is three times greater than the level we observed for patients treated with quinine or quinidine.

In conclusion, it can be stated that for treatment of multidrug-resistant falciparum malaria in paediatric patients, an 8-day course of quinine provides high cure rates and is associated with minimal serious side-effects; nevertheless, in many areas where quinine is not readily available, a 7-day course of quinidine can be used as an alternative therapy provided the patients are closely monitored for possible cardiovascular effects.
ACKNOWLEDGEMENTS

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RÉSUMÉ

RÉPONSE IN VIVO ET IN VITRO DE PLASMODIUM FALCIPARUM À LA QUININE ET À LA QUINIDINE

Une étude a été entreprise pour comparer le résultat du traitement du paludisme à falciparum par la quinine et la quinidine chez des enfants thaïlandais et pour évaluer l’influence éventuelle de la concentration sérique du médicament et de la chimiosensibilité du parasite sur les échecs thérapeutiques. Cette étude, qui s’est déroulée de juillet 1984 à janvier 1985, a porté sur 72 enfants atteints de paludisme à falciparum non compliqué chez lesquels le nombre de parasites asexués par microlitre de sang variait entre 700 et 97 400. Tous les enfants ont été admis à l’Hôpital des Maladies tropicales de Bangkok pendant la durée du traitement. Soixante-six d’entre eux ont été suivis pendant toute la période d’observation de 28 jours.

Les enfants ont été répartis au hasard en deux groupes de 33 sujets qui ont été traités, l’un avec la quinine, l’autre avec la quinidine. Le premier groupe a reçu du sulfate de quinine par voie orale à raison de 10 mg de base par kg de poids corporel toutes les 8 heures pendant 4 jours, dose qui a été portée à 15 mg pendant les 4 jours suivants. Le deuxième groupe a reçu du sulfate de quinidine par voie orale à raison de 10 mg de base par kg de poids corporel toutes les 8 heures pendant 7 jours.

Un électrocardiogramme (ECG) a été réalisé une fois par jour, l’avant-veille et la veille de l’administration du médicament, puis deux heures après la première dose de la journée du jour 0 au jour 7. Chez un des enfants, on a noté un allongement significatif des intervalles QT corrigés (QTc) avant l’instauration du traitement et les ECG de cet enfant ont été exclus.

Les concentrations plasmatiques de quinine et de quinidine ont été mesurées avant l’administration de la première dose de médicament, 4 heures après celle-ci, et ensuite quotidiennement, avant la première dose de la journée, pendant toute la durée du traitement.

Sur les 66 isolés de Plasmodium falciparum recueillis avant le traitement, 64 ont été soumis à des essais de sensibilité à la quinine, à la quinidine et à la chloroquine, tandis que 44 étaient également soumis à un essai de sensibilité à la méfloquine. Tous ces essais ont été effectués selon la méthode recommandée par l’OMS.

L’étude a montré que la quinine et la quinidine avaient une efficacité équivalente et que le temps nécessaire à la disparition de la fièvre et de la parasitémie était comparable pour les deux médicaments. Le taux de guérison a été de 85% avec la quinine et de 88% avec la quinidine. Dans tous les cas où il y a eu échec du traitement, on a observé une réponse RI. Parmi les effets secondaires, on a noté des nausées légères et transitoires, des bourdonnements d’oreille et des vertiges.

Un allongement important de l’intervalle QT corrigé (QTc) a été noté chez un pourcentage significativement plus élevé (P<0,001) d’enfants traités à la quinidine (56%) que d’enfants traités à la quinine (21%). Par contre, il n’y a pas eu de différence significative entre les deux groupes en ce qui concerne l’allongement des intervalles PR. Pendant les périodes afébriles, du jour 3 au jour 8, on a noté des arythmies sinusales chez 10 des enfants traités avec la quinine et chez 7 de ceux qui avaient reçu de la quinidine.

Les minimums de concentration sérique ont été environ 2,5 fois plus faibles pour la quinidine que pour la quinine, mais on n’a pas observé de différence dans le profil de concentrations sériques entre les patients guéris et ceux chez lesquels le traitement a échoué. En ce qui concerne la réponse in vitro, la concentration minimale inhibitrice (CMI) a été environ deux fois plus faible pour la quinidine que pour la quinine (P<0,05). La pharmacosensibilité des parasites isolés chez les patients traités soit avec la quinine, soit avec la quinidine, n’a pas présenté de différence significative. De même, il n’y a pas eu de différence de CMI entre les isolés de P. falciparum recueillis dans chaque groupe avant traitement et après échec du traitement. Dans tous les cas, la CMI de chloroquine dépassait de 0,16 μmol/l la concentration à partir de laquelle on considère qu’il y a chloroquinorésistance. La plupart des isolés se sont montrés sensibles à la méfloquine, mais pour 4 d’entre eux (9%) la CMI de cette substance a été de 0,64 μmol/l.

En conclusion, on peut dire qu’un traitement de huit jours à base de quinine donne des taux élevés de guérison avec un minimum d’effets secondaires importants; toutefois, dans les régions où il est difficile de se procurer ce médicament, on peut le remplacer par la quinidine à condition de suivre attentivement les patients pour détecter tout effet cardiovasculaire éventuel.
REFERENCES


