Susceptibility of *Plasmodium falciparum* to different doses of quinine *in vivo* and to quinine and quinidine *in vitro* in relation to chloroquine in Liberia

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Chloroquine-resistant *Plasmodium falciparum* has been spreading rapidly after its emergence in 1988 in Yekepa. The *in vivo* and *in vitro* susceptibilities to quinine and quinidine, compared to chloroquine, were studied by investigating the number of treatment days required for radical cure and estimating the quinine concentrations concomitantly.

The minimal inhibitory concentrations (MIC) for schizont maturation in all successful *in vitro* tests were $5.12 \times 10^{-6}$ mol/l for quinine and $1.28 \times 10^{-6}$ mol/l for quinidine, indicating that all 50 isolates were sensitive to the two drugs. The IC₅₀ and IC₉₀ values were 0.22 and $0.78 \times 10^{-6}$ mol/l for quinine and 0.07 and $0.26 \times 10^{-6}$ mol/l for quinidine, respectively. In *in vitro* inhibition of parasites by $1.6 \times 10^{-6}$ mol/l of chloroquine was obtained in 31 out of 47 isolates, 16 (34%) being resistant. The IC₅₀, IC₉₀ and geometrical mean MIC for quinine were all about two times higher for the chloroquine-resistant than for the chloroquine-sensitive isolates ($P = 0.006$).

P. falciparum infected children ($n = 64$) were randomly allocated to four groups and treated with quinine (10 mg/kg body weight twice daily) for 1 day (3 doses), 2, 4 and 7 days, respectively. All cleared their parasitaemias by day 4 but 5 out of 15 of those treated with only three doses showed a recurrence of parasitaemia between days 7 and 14; these were considered to be recrudescences. In the other groups, recurrent parasitaemias only occurred between days 17 and 28 and were considered to be reinfections. The mean blood concentrations of quinine in 10 patients on the fourth day of treatment were 17.0, 12.2 and $8.4 \times 10^{-6}$ mol/l at, respectively, 2, 6 and 12 hours after the last dose. These concentrations are above the *in vitro* MIC values.

Quinine remains a highly effective antimalarial drug in Liberia even after the appearance of chloroquine-resistant *P. falciparum* strains; the 3-day course appears to be an efficacious regimen in this semi-immune population.

**Introduction**

Resistance of *Plasmodium falciparum* to chloroquine is now widespread in sub-Saharan Africa (1). Quinine, the main drug for severe and complicated malaria cases, is now an important alternative for patients with even less severe symptoms; however, two disadvantages that affect compliance are the

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Chloroquine-resistant *P. falciparum* first emerged in Yekepa, Liberia, in 1988 and is spreading rapidly. We therefore studied the susceptibility to quinine and quinidine in this area with a standardized *in vitro* methodology and performed an *in vivo* dose-finding investigation on the number of treatment days with quinine required for a radical cure and the drug concentrations thus obtained.

**Material and methods**

**Study area and population**

Yekepa town with about 15,000 inhabitants is situated in the north-east of Liberia and surrounded by villages. James Dolo’s Farm (JDF), one of these villages, is about 10 km from Yekepa. Malaria is hypoenzemic to mesoendemic in Yekepa town and holoendemic in JDF (16).

In December 1988, at the end of the rainy season, blood films were taken from 78 children in JDF (age 1 to 12) and from 100 schoolchildren in Yekepa (area T). All asymptomatic children with pure *P. falciparum* infections with a parasite density between 1000 and 100,000 asexual parasites per μl and with no history of drug intake for the previous two weeks were included in the study. Fully informed consent was obtained from the parents and/or their parents before inclusion in the study.

**In vivo tests**

Sixty-four children from JDF who fulfilled the inclusion criteria for the study were, after age stratification, randomly divided in four groups. Group I received 10 mg quinine per kg body weight three times every 12 hours for 24 hours; groups II, III and IV received the same dose of quinine twice daily for 2, 4, and 7 days, respectively. Quinine was given as tablets of 100 mg and 250 mg quinine hydrochloride, divided into halves and quarters when required. The drug was administered under close supervision. Every day the children were asked about any symptoms possibly related to malaria or the drug taken.

Thick blood films were made daily from days 0 to 5 and then on days 7, 10, 14, 17, 21, 24 and 28. The films stained with Giemsa were considered as negative if no asexual parasite was found after 10 minutes of examination under light microscopy; parasite counts were determined by counting the parasites against 1000 leukocytes, assuming an average leukocyte count of 8000 per μl of blood.

**In vitro tests**

Isolates from 33 children in JDF and 25 schoolchildren in Yekepa were included in a study on the *in vitro* susceptibility of *P. falciparum* to quinine and chloroquine. Isolates from 24 children in JDF were also tested for their susceptibility to quinidine.

A modified Rieckmann’s *in vitro* microtest (17) was used to determine the sensitivity of *P. falciparum* isolates to chloroquine and quinine. A standard procedure* was followed using RPMI culture medium and microtitration plates provided by WHO. Drug concentrations were expressed as amounts of chloroquine per volume of blood and amounts of quinine or quinidine per volume of blood–medium mixture, in accord with previous practices described in the literature. Isolates showing schizont maturation at $1.6 \times 10^{-6}\text{mol/l}$ chloroquine or at $5.12 \times 10^{-6}\text{mol/l}$ quinine/quinidine were considered resistant to the respective drug (18).* A probit analysis of the log dose–response was performed to estimate the effective drug concentrations for 50% (EC$_{50}$), 90% (EC$_{90}$) and 99% (EC$_{99}$) inhibition of schizont maturation.  

**Drug concentrations**

Samples of fingerprick whole blood (100 μl) were taken from twelve children while still on treatment on the fourth day, at 2, 6 and 12 hours after intake of the repeated standard dose of 10 mg quinine per kg body weight. The blood was transferred into plastic Eppendorf tubes and kept frozen at −20 °C before determination of quinine concentrations by HPLC.

**Results**

**In vivo tests**

All 64 children from JDF in the *in vivo* study had pure *P. falciparum* infections with a geometrical mean of 4895 parasites per μl (range, 1000 to 68 000 parasites per μl). Five of them were excluded from the study because they did not take their stipulated course of quinine or attend the follow-up according to schedule. They were not excluded because of lack of efficacy or side-effects from the treatment. The remaining 59 children had cleared their parasitaemia by day 4 (Tables 1 and 2). Between days 7 and 14, five in group 1, however, showed a recurrence (considered as recrudescence of parasitaemia) whereas recurrent parasitaemia (considered as rein-

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fever) occurred in the other three groups between days 17 and 28 (Table 2).

No serious adverse drug reactions were reported, except that 4 of the 15 children over 4 years of age who took quinine for four or seven days, when questioned specifically on the third day, reported transient symptoms: two reported nausea, one had stomach ache, and two had tinnitus.

**In vitro tests**

For quinine, the *in vitro* microtest was attempted on 58 isolates with interpretable results from 50 (86%) tests for quinine (30 from JDF and 20 from Yekepa) and 47 tests (81%) for chloroquine. For quinidine, 23 of 24 (96%) isolates from JDF gave interpretable results.

Schizont maturation was inhibited in all 50 tests by $5.12 \times 10^{-6}$ mol/l quinine (Table 3). This indicated full sensitivity (MIC of $\leq 25.6 \times 10^{-6}$ mol/l) in all isolates. The geometrical mean MIC was $0.80 \times 10^{-6}$ mol/l (range $0.16$ to $5.12 \times 10^{-6}$ mol/l). The two isolates with highest MICs ($2.56$ and $5.12 \times 10^{-6}$ mol/l) were successfully treated with four and seven days of quinine, respectively. When all isolates were added, the calculated mean IC$_{50}$ and IC$_{90}$ were $0.22$ and $0.78 \times 10^{-6}$ mol/l, respectively. The individual IC$_{50}$ values varied between a lowest value of less than $0.1 \times 10^{-6}$ mol/l and a highest value of $1.8 \times 10^{-6}$ mol/l; 15/50 isolates (30%) had IC$_{50}$ values $>0.3 \times 10^{-6}$ mol/l. Quinidine inhibited all isolates at $1.28 \times 10^{-6}$ mol/l (Table 3) with a mean MIC of $0.31 \times 10^{-6}$ mol/l (range, $0.16$ to $1.28 \times 10^{-6}$ mol/l) and with calculated mean IC$_{50}$ and IC$_{90}$ of $0.07$ and $0.26 \times 10^{-6}$ mol/l, respectively.

Chloroquine inhibited 31/47 isolates at a concentration of $1.6 \times 10^{-6}$ mol/l indicating that 16 (34%) isolates were resistant. One out of the 16 resistant isolates showed schizont maturation even at the highest concentration tested, $12.8 \times 10^{-6}$ mol/l. In Table 4 and Fig. 1 the results of quinine *in vitro* tests are presented separately for chloroquine-sensitive and resistant isolates. The IC$_{50}$, IC$_{90}$ and geometric mean MIC for quinine were all about two times higher for the chloroquine-resistant than for the chloroquine-sensitive isolates. This relationship between chloroquine resistance and decreased susceptibility to quinine was highly significant for the IC$_{50}$ and IC$_{90}$ values ($P = 0.006$) according to the Mann-Whitney non-parametric test.

**Drug concentrations**

The whole blood quinine concentrations of 10 patients are shown in Table 5. The mean 2-hour ("peak") concentration, $17.0 \times 10^{-6}$ mol/l, was well above the mean MIC, about $1.0 \times 10^{-6}$ mol/l, or the highest MIC, $5.12 \times 10^{-6}$ mol/l, found for one isolate. Even the trough concentrations at 12 hours, ranging from $4.9$ to $11.8 \times 10^{-6}$ mol/l, were at or above the concentrations required to inhibit parasite growth *in vitro*. Two children with symptoms related

### Table 1: *P. falciparum* clearance in 59 children after treatment with quinine (10 mg/kg body weight orally twice daily) for 1, 2, 4 or 7 days in JDF village, 1988

<table>
<thead>
<tr>
<th>No. of days of treatment</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of children</td>
<td>15</td>
<td>14</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>5.3</td>
<td>5.4</td>
<td>5.4</td>
<td>5.0</td>
</tr>
<tr>
<td>(1-11)*</td>
<td>(2-10)</td>
<td>(1-10)</td>
<td>(1-10)</td>
<td>(1-10)</td>
</tr>
<tr>
<td>Mean parasite density on day 0</td>
<td>4510</td>
<td>5890</td>
<td>4530</td>
<td>5240</td>
</tr>
<tr>
<td>Mean time for parasite clearance (days)</td>
<td>2.2</td>
<td>2.4</td>
<td>2.3</td>
<td>2.2</td>
</tr>
</tbody>
</table>

* Figures in parentheses are the age range in years.

### Table 2: Cumulative incidence of parasitaemia in 59 children after treatment with quinine (10 mg/kg body weight orally twice daily) for 1, 2, 4 or 7 days in JDF village, 1988

<table>
<thead>
<tr>
<th>No. of days of treatment</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of children</td>
<td>15</td>
<td>14</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>No. of children with parasites on:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Day 7</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Day 10</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Day 14</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Day 17</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Day 21</td>
<td>10</td>
<td>7</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Day 24</td>
<td>11</td>
<td>10</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Day 28</td>
<td>12</td>
<td>11</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>

### Table 3: Inhibition of schizont development in *in vitro* tests of *P. falciparum* susceptibility to quinine (n = 50) and to quinidine (n = 23) in Yekepa area, 1988

<table>
<thead>
<tr>
<th>Drug concentration ($\times 10^{-6}$ mol/l)</th>
<th>No. of tests inhibited by quinine</th>
<th>No. of tests inhibited by quinidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.08</td>
<td>0 (0)*</td>
<td>0 (0)</td>
</tr>
<tr>
<td>0.16</td>
<td>1 (2)</td>
<td>9 (39)</td>
</tr>
<tr>
<td>0.32</td>
<td>10 (20)</td>
<td>17 (74)</td>
</tr>
<tr>
<td>0.64</td>
<td>29 (38)</td>
<td>21 (91)</td>
</tr>
<tr>
<td>1.28</td>
<td>45 (90)</td>
<td>23 (100)</td>
</tr>
<tr>
<td>2.56</td>
<td>49 (98)</td>
<td>23 (100)</td>
</tr>
<tr>
<td>5.12</td>
<td>50 (100)</td>
<td>23 (100)</td>
</tr>
</tbody>
</table>

* Figures in parentheses are percentages.
Discussion
In vivo results
The in vivo results suggest that even two days of quinine treatment may be satisfactory, whereas three doses during 24 hours may only be partly curative with a high rate of RI responses although all parasitaemias were reduced to subpatent levels by day 4 (Table 2). The parasitaemias from day 17 onwards in the groups treated for two, four and seven days were considered as reinfections, as the rates of recurrences in the groups treated for two and four days were similar to the rate in the group treated for seven days, except for a minor shift of about three days corresponding to clearance of the drug about three days later in the group treated for seven days. Furthermore, the rate of reinfection was similar to that previously observed after radical cure with chloroquine (19), which also corresponds to the inoculation rate observed in this village (20).

As the study was performed in children, many of them significantly semi-immune, the results have to be treated with caution as regards individuals with low immunity and should not be interpreted as a recommendation for non-immunes. In two previous studies with quinine in Zaire (21) and Quinimax (quinine-quinidine-chinonine) in Madagascar (22), three days of treatment gave 100% clearance of parasitaemia after 60 and 52 hours, respectively, similar to the parasitic clearance of 2.2 to 2.4 days in our study. However, follow-up was for only seven days and failures would have been missed as RI responses around day 14 represented the major part of therapeutic failures in previous studies with quinine treatment in Thailand (23) and Cambodia (24).

There are a few sentinel reports of in vivo quinine failures in Africa (1) among patients not taking the complete seven-day standard treatment, indicating that seven days may be required for a 100% cure rate, or that odd marginally resistant strains may be present in Africa, or that some individuals may achieve abnormally low quinine values in the blood. It may be noted, however, that they all had high residual levels of chloroquine from either previous prophylaxis or treatment and that antagonism between quinine and chloroquine has been reported in vitro (25). In the most recent report of quinine failure (14) two patients from

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Table 4: Minimal inhibitory concentrations (MIC), IC_{50} and IC_{90} of quinine in relation to susceptibility to chloroquine (CQ) of 47 isolates in children from Yekepa area, 1988

| Isolates                  | Chloroquine MIC* (×10^{-6} mol/l) | Quinine MIC* (×10^{-6} mol/l) | Quinine
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th>(×10^{-6} mol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CQ sensitive (n = 31)</td>
<td>0.6 ± 0.3 (0.4–0.8)*</td>
<td>0.64 ± 0.04 (0.16–5.12)</td>
<td>IC_{50} 0.18</td>
</tr>
<tr>
<td>CQ resistant (n = 16)</td>
<td>10.4 ± 0.4 (1.6–25.6)</td>
<td>1.23 ± 0.03 (0.64–2.56)</td>
<td>IC_{90} 1.13</td>
</tr>
</tbody>
</table>

* Figures are means ± standard deviations.

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Table 5: Concentrations of quinine in whole blood in 10 Liberian children on third day of treatment (10 mg/kg body weight twice daily) 2, 6 and 12 hours after the last dose

<table>
<thead>
<tr>
<th>Hours after intake of last dose</th>
<th>No. of children</th>
<th>Quinine concentrations* (×10^{-6} mol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>10</td>
<td>17.0 ± 5.6 (9.9–26.8)*</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>12.2 ± 3.7 (7.3–17.2)</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>8.4 ± 2.2 (4.9–11.8)</td>
</tr>
</tbody>
</table>

* Figures are means ± standard deviations.

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Fig. 1. In vitro susceptibility to quinine (concentrations in blood) of chloroquine-sensitive (1) and chloroquine-resistant (2) P. falciparum isolates from Yekepa area, Liberia, in 1988.
Ghana and Nigeria were unsuccessfully treated for seven days in the United Kingdom but no information was given on possible previous chloroquine prophylaxis, or quinine concentrations during therapy, or the in vitro susceptibility of the parasites.

In vitro results

All isolates were considered as highly sensitive to quinine and even the isolate with the highest MIC (5.12 × 10⁻⁶ mol/l) was successfully treated with quinine (7-day treatment). This supports the WHO criteria for the standardized 24-hour test, with a cut-off MIC of >5.12 × 10⁻⁶ mol/l for resistance. The mean MIC was 0.75 × 10⁻⁶ mol/l compared to 0.37 × 10⁻⁶ mol/l in 1983 (2). Similarly the EC₅₀, EC₉₀ and EC₉₉ were about twice those recorded in 1983. Although the previous study was based on only seven isolates, this may suggest a partial decrease in sensitivity between 1983 and 1988. This is supported by the fact that the isolates with chloroquine-resistant parasites, not present in 1983, were less sensitive to quinine than the sensitive isolates (Table 4, Fig. 1).

A correlation between decreased sensitivities to chloroquine and quinine has previously been suggested (6–8) and chloroquine resistance has been considered a prerequisite for the development of quinine resistance in south-east Asia.

Comparisons of in vitro results with those from other studies is difficult because of differences in the in vitro methodology (1). The expressions of inhibition, e.g., MIC or IC₅₀, and drug concentrations, e.g., blood or blood-medium, also vary. When compared with studies using the same methodology, equivalent results were found in Zaire (7, 21) and Nigeria (3), whereas significantly more resistance was found in Cambodia where many individual MICs were over 5.12 × 10⁻⁶ mol/l (24) together with a 60% failure rate in vivo, and in Thailand where the mean MIC was 3.0 × 10⁻⁶ mol/l (23) with a 15% failure rate in vivo. Previous results from Thailand in 1984 (26) showed an IC₅₀ of 0.24 × 10⁻⁶ mol/l, similar to the IC₅₀ from Liberia in 1988.

In francophone countries, the hypoxanthine method for evaluating 48-hour growth (27) has mostly been used and the susceptibilities are usually expressed as IC₅₀ values. An individual IC₅₀ value for quinine of 0.3 × 10⁻⁶ mol/l has been considered as indicative of resistance (4–6). Thus, although the mean IC₅₀ values have been similar to that obtained in our study, the individual results in Cameroon (6), Senegal (4) and Guinea (5) have been interpreted as indicating the existence of several resistant strains. In our study, 15 individual isolates (30%) also had IC₅₀ values above 0.3 × 10⁻⁶ mol/l and yet were successfully treated with even shorter courses of quinine than the standardized seven days. This indicates that a higher IC₅₀ value than 0.3 × 10⁻⁶ mol/l is a more accurate cut-off for resistance, at least when evaluated according to the standardized 24-hour test.

Drug concentrations

The concentrations of quinine showed up to threefold individual variation which is in accord with previous studies (28, 29). The quinine concentrations were measured in whole blood as compared to plasma in previous studies. Considering that the ratio of red cell to plasma concentrations in one previous study varied between 0.49 and 0.26 (30), the values obtained in our study are as expected from data in previous studies both on patients and volunteers (29).

All peak concentrations during the third day of treatment were well above MIC values in the in vitro test and even the trough concentrations were above the MICs. From previous pharmacokinetic studies it may be assumed that the concentrations during the first day of treatment were also above these MIC levels (31). This supports the efficacy of the treatment, although effective drug concentrations in vivo in whole blood or plasma may not necessarily correspond exactly to effective drug concentrations in vitro in the blood-medicine mixture because of the different conditions such as plasma binding, etc.

That two of the older children with side-effects had high peak concentrations confirms previous studies where plasma concentrations above 5 mg/l (= 12.5 × 10⁻⁶ mol/l) were associated with cinchonism (32, 33) and were reported more often in older than younger children (23). To avoid transient side-effects such as cinchonism, a lower dosage of quinine might be considered because doses of 10 mg/kg body weight produce concentrations well above that needed to inhibit the in vitro growth of P. falciparum parasites. However, this may not be suitable in areas where quinine resistance is increasing, as in south-east Asia, and might even enhance the development of quinine resistance in the African situation.

Quinidine. Quinidine had three- to fourfold higher activity than quinine. This is probably not equivalent to a higher degree of efficacy in vivo as quinidine gives about three times lower concentrations than quinine in equivalent doses (23, 28). In areas like

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See footnote a on page 460.
Liberia where quinine has retained sufficient activity, it is probably to be preferred for antimalarial therapy as it has less cardiotoxic affinity and therefore possibly fewer side-effects on the heart than quinidine.

Conclusion
Quinine remains a highly efficient antimalarial drug in Liberia even after the appearance of chloroquine-resistant *P. falciparum* strains and changes in the susceptibility to quinine. As short as two days of therapy with quinine (10 mg/kg body weight twice daily) appeared to be efficacious in 15 children tested. A 3-day course may therefore be expected to safely provide radical cures in a larger sample and may be an alternative treatment for semi-immune individuals in endemic areas with a certain degree of chloroquine resistance. This dosage represents a 60% cost reduction compared with the 7-day course and is expected to have a higher rate of compliance.

That chloroquine-resistant parasites are less susceptible to quinine, although not to the point of showing a resistance pattern, may be an indication of a further development towards *P. falciparum* resistance to quinine in Africa. It is therefore essential to continuously monitor the susceptibility of *P. falciparum* to quinine in different parts of Africa, preferably using both standardized *in vivo* and *in vitro* tests.

Acknowledgements
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Résumé
Sensibilité de *Plasmodium falciparum* à différentes doses de quinine *in vivo*, et à la quinine et la quinidine *in vitro*, par rapport à la chloroquine, au Libéria

*Plasmodium falciparum* chloroquinorésistant s’est rapidement étendu à Yekepa après son apparition en 1988. Les sensibilités *in vivo* et *in vitro* à la quinine et à la quinidine, comparées à la sensibilité à la chloroquine, ont été étudiées en recherchant le nombre de jours de traitement nécessaires pour une guérison radicale, et en mesurant, en même temps, les concentrations de quinine.

Les concentrations minimales inhibitrices (CMI) pour la maturation des schizontes, dans tous les tests *in vitro* réussis, étaient de $5.12 \times 10^{-6}$ mol/l pour la quinine et de $1.28 \times 10^{-5}$ mol/l pour la chloroquine, montrant que les 50 isolats étudiés étaient sensibles aux deux médicaments. La Cl$_{50}$ et la Cl$_{90}$ étaient de 0,22 et de $0,78 \times 10^{-6}$ mol/l pour la quinine, et de 0,07 et $0,26 \times 10^{-6}$ mol/l pour la chloroquine. L’inhibition *in vitro* de parasites par $1,6 \times 10^{-6}$ mol/l de chloroquine était obtenue pour 31 isolats sur 47, 16 (34%) étant résistants. La Cl$_{50}$, la Cl$_{90}$ et la CMI moyenne géométrique pour la quinine étaient environ deux fois supérieures pour les isolats chloroquinorésistants que pour ceux qui étaient sensibles à la chloroquine ($P = 0,006$).

Des enfants infectés par *P. falciparum* ($n = 64$) ont été répartis au hasard dans quatre groupes et traités par la quinine (10 mg/kg de poids corporel, deux fois par jour), pendant 1 jour (3 doses), 2 jours, 4 jours, et 7 jours respectivement. Les 59 enfants qui ont tous terminé l’étude n’avaient plus de parasitémie au jour 4, mais 5 sur 15 de ceux traités avec seulement trois doses ont présenté une récidive de parasitémie entre le jour 7 et le jour 14, qui a été considérée comme une rerudescence. Dans les autres groupes, des récidives de parasitémie n’ont eu lieu qu’entre les jours 17 et 28, et ont été considérées comme des réinfections. Les concentrations sanguines moyennes de quinine chez 12 malades le quatrième jour du traitement étaient de 17,0, 12,2 et $8,4 \times 10^{-6}$ mol/l, 2, 6 et 12 heures respectivement après la dernière dose. Ces concentrations étaient bien supérieures aux valeurs de la CMI *in vitro*.

La quinine reste un antipaludéen extrêmement efficace au Libéria, même après l’apparition de souches de *P. falciparum* chloroquinorésistantes; le traitement de 3 jours, qui semble un schéma efficace dans une population semi-immune, représente une réduction de coût de 60% par rapport au traitement de 7 jours, et il est vraisemblable que son taux d’observance sera plus élevé. Le fait que des parasites chloroquinorésistants soient moins sensibles à la quinine, mais pas au point de faire preuve d’une réelle résistance, peut être l’indication d’une nouvelle extension de la résistance de *P. falciparum* à la quinine en Afrique. Il est de ce fait indispensable de surveiller continuellement la sensibilité de *P. falcipa- rum* à la quinine dans différentes parties d’Afrique.

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