NOTES

Dose-Dependent Resorption of Quinine after Intrarectal Administration to Children with Moderate Plasmodium falciparum Malaria

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The pharmacokinetics of increasing doses of an intrarectal Cinchona alkaloid combination containing 96.1% quinine, 2.5% quinidine, 0.68% cinchonine, and 0.67% cinchonidine (Quinimax) was compared to that of parenteral regimens in 60 children with moderate malaria. Quinine exhibited a nonlinear pharmacokinetics, suggesting a saturation of rectal resorption. When early rejections appeared, blood quinine concentrations decreased by 30 to 50% and were restored by an immediate half-dose administration of the drug. Rectal administration of doses of 16 or 20 mg/kg of body weight led to concentration-time profiles in blood similar to those of parenteral regimens and could be an early treatment of childhood malaria.

Intrarectal administration represents a promising administration route of antimalarial drugs in the field, especially convenient for patients unable to swallow and when parenteral formulations are unavailable. Its efficacy has been demonstrated with artemisinin derivatives for the treatment of moderate to severe Plasmodium falciparum malaria, especially in Southeast Asia (7, 9). In Africa, artemisinin derivatives are not readily available, and quinine remains one of the most widely used antimalarial drugs at the primary health center level. We previously showed that intrarectal administration of various formulations of quinine was as effective as the currently used intramuscular treatment of childhood malaria (2, 3). Nevertheless, a large interindividual variability was observed in quinine bioavailability and concentrations in blood according to the galenic formulation and the administered dose (2, 4, 6). Whatever rectal formulation is used, the drug may be extruded spontaneously without being noticed, leading to a decrease of clinical efficacy. Then, we compared the absorption characteristics of increasing doses of a rectally administered Cinchona alkaloid combination (containing 96.1% quinine, 2.5% quinidine, 0.68% cinchonine, and 0.67% cinchonidine [Quinimax]; Sanofi, Chantilly, France) with those of the currently used parenteral regimens.

This open and randomized study took place in the children’s ward of the Sanou Sourou Hospital, Bobo Dioulasso, Burkina Faso, and was approved by the Ethical Committee of the Burkina Faso Health Ministry. Children with moderate malaria (having more than 1,000 asexual P. falciparum parasites per microliter of blood and requiring a parenteral treatment) were eligible after full informed consent was given by a parent or guardian. Exclusion criteria included severe malaria (cerebral malaria, severe hypoglycemia, or anemia) (19), diarrhea, anatomical abnormalities of the rectum, and antimalarial treatment within the preceding week.

Quinine was administered as a gluconate salt of the Cinchona alkaloid formulation. Sixty children were randomly administered one of the following treatments, repeated for 48 h. Quinine was given either intramuscularly at a dose of 12 mg per kg of body weight every 12 h (IM12), intravenously as a slow infusion of 8 mg per kg over 4 h every 8 h (IV8), or rectally at doses of 8 mg/kg (IR8) or 16 mg/kg (IR16) every 8 h and at 12 mg/kg (IR12) or 20 mg/kg (IR20) every 12 h.

The solution was administered via a plastic syringe after one-third dilution in water. Children were placed in a decubitus position for 5 min and watched closely for the first hour. If rectal solution was expelled, the child was excluded from the study. Early rejections were evaluated for some children excluded from the kinetic study and received a parenteral treatment. The effect of early rejections was evaluated for some children excluded from groups IR12 (n = 6) and IR20 (n = 6). Four children with early rejection after a 20-mg/kg dose received a further half-dose. At 48 h, all the children were able to tolerate oral medication and quinine was given per os to complete a 5-day treatment.

Physical signs, rectal temperature, and parasitemia were recorded at inclusion and once daily until day 7. Two hundred microliters of blood was collected in EDTA tubes before and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, and 24 h after the start of therapy. In the groups receiving quinine twice daily, additional samples were collected at 10 and 12 h. Whole-blood quinine...
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (mean ± standard deviation)</th>
</tr>
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<tbody>
<tr>
<td>Sex (boys/girls)</td>
<td>5/5; 7/3; 4/6; 6/4; 7/3; 4/6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>26 (10–38); 19 (12–35); 20 (13–27); 20 (10–35); 25 (13–35); 18 (12–25)</td>
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<tr>
<td>Age (mo)</td>
<td>99 (24–162); 72 (4–144); 60 (40–122); 60 (24–120); 90 (36–146); 72 (30–120)</td>
</tr>
<tr>
<td>Pulse (beats/min)</td>
<td>103 (90–120); 100 (90–112); 108 (95–110); 99 (88–116); 100 (90–115); 102 (90–120)</td>
</tr>
<tr>
<td>Hemoglobin (g/100 ml)</td>
<td>6.9 (6.5–8.6); 7.3 (6.4–8.9); 6.3 (5.7–8.4); 9.0 (6.5–11.7); 8.9 (6.8–11.3); 8.7 (5.4–10.1)</td>
</tr>
<tr>
<td>Parasitemia (no. of parasites/µl) at:</td>
<td>Admission</td>
</tr>
<tr>
<td></td>
<td>24 h</td>
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<tr>
<td>No. of patients with positive blood at:</td>
<td>Admission</td>
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<tr>
<td></td>
<td>24 h</td>
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<td>72 h</td>
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<td>48 h</td>
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<td>Temperature (°C) at:</td>
<td>Admission</td>
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<tr>
<td></td>
<td>24 h</td>
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<td>48 h</td>
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* Administration was by slow intravenous infusion and by the intramuscular and intrarectal routes in children with *Plasmodium falciparum* malaria. Data are median (range) values, unless stated otherwise.

** TABLE 1. Parasitological and clinical data at admission and after administration of the Cinchona alkaloid combination.**
concentrations were determined by high-performance liquid chromatography with fluorometric detection (16).

Concentrations of quinine in whole blood were fitted by using an iterative least-squares curve-fitting program (APIS) (10). Peak concentrations ($C_{\text{max}}$) and the times to $C_{\text{max}}$ were observed values. The area under the concentration-time curve (AUC) was calculated according to the trapezoidal rule. The bioavailability of the rectal quinine was calculated as the ratio of the rectal AUC from 0 to 8 h ($\text{AUC}_{0-8 \text{ h}}$) to the parenteral AUC$_{0-8 \text{ h}}$. Normally distributed data were compared by parametric tests, and abnormally distributed data were compared by the Kruskal-Wallis test. A $P$ value of $\leq 0.05$ was considered to be statistically significant.

Baseline clinical and biological parameters were comparable among all the groups (Table 1). All the children had recent vomiting, and nine (15.0%) were prostrate. The main clinical symptoms reported were headache (58.3%), abdominal pain (33.3%), and coughing (35.0%).

The concentration-time profiles in whole blood and the pharmacokinetic parameters of quinine are displayed in Fig. 1 and Table 2. Blood quinine $C_{\text{max}}$s were similar for the IM12 and IV8 groups but occurred more quickly after intramuscular administration. The AUC$_{0-8 \text{ h}}$ of quinine in blood was higher after intramuscular injection than after intravenous infusion, but trough concentrations were similar after the first drug administration and at 24 h.

Peak and trough concentrations and AUC$_{0-8 \text{ h}}$s of quinine in blood were lower in the IR8, IR12, and IR16 groups than in the IM12 group but similar for the IR20 and parenteral groups. In the IM12 group, the resorption rate of quinine was higher than in the IV8 and IR8 groups and similar to that of the IR12, IR16, and IR20 groups. The rectal bioavailability of quinine markedly decreased from 96 to 54% when the rectal dose was increased. When early rejection of liquid stools occurred in the first hour of rectal treatment, both the $C_{\text{max}}$s and AUC$_{0-8 \text{ h}}$s of quinine in blood decreased by 30 to 50%. The administration of a further half-dose restored values to levels similar to those observed in patients in the IR20 group who did not reject the treatment (Table 2 and Fig. 2).

The change in pharmacodynamic parameters at 24 h reflects the effect of the two or three first administrations of the Cinchona alkaloid combination (Table 1). Parasitemia and body temperature clearance times were similar in all groups. All children were afebrile at 72 h, had cleared their parasites at 96 h, and remained so until day 7. There were no major adverse events attributable to the administration route or the drugs. After intramuscular administration, all children complained of pain at the injection point. Intrarectal administration was associated with an increasing frequency of mucoid stools.

Most of the parenteral formulations of quinine were acidic (pH, 2.0), leading to local discomfort and a low rate of observance of intramuscular treatment (1). The substitution of the hydrochloride for a gluconate salt and an increase in the pH value to 4.5 improve the local tolerance but may affect the extent of drug distribution (18). The kinetics profiles obtained after intravenous and intramuscular administrations are similar to those previously reported for hydrochloride salt (4, 5). In contrast, after rectal administration of 8 mg/kg, the bioavailability of the gluconate form is higher than that previously observed with the more acidic formulations (3, 5, 6). The main mechanism of rectal absorption is a passive transport that depends mainly on the molecular weight, the lipophilicity, and the degree of ionization of molecules (19). Basic drugs like quinine may be absorbed faster at this higher pH value.

After rectal administration, blood quinine concentrations did not rise proportionally in response to the rectal dose, suggesting a saturability of drug absorption by the human rectal mucosa. This dose-dependent absorption seems to be characteristic of the rectal route because a linear relationship between the dose (4 to 16 mg/kg) and the AUC of quinine was previously observed after oral administration (17). A negative relationship between the dose and the bioavailability was also reported for suppositories of artesunate in Ghanaian children (12) and of chloroquine in healthy subjects (14). Because no argument exists in favor of a saturable transporter in the rectal mucosa, many other biological factors influence the bioavail-
no rejection. no regimens revealed any pharmacodynamic difference. Al-
effective drug concentrations must be rapidly achieved. especially at the onset of treatment of severe malaria, when
absorption with the 16- and 20-mg/kg rectal doses are compara-
se West Africa (13, 15). The rate and the extent of quinine ab-
parasitological and clinical efficacy. Nevertheless, in order to
restores effective concentrations in blood especially in the
isterial initial 24 h, the immediate administration of a half-dose
above the minimum effective concentration.

Such tolerance and pharmacodynamic outcomes require in-
vestigation in larger studies. To provide this information, a
phase III study has recently been completed in Burkina Faso
H. Barennes, T. Balima-Koussoube, E. Kambole, A. Hema,
the treatment of childhood cerebral malaria in Niger. Trans. R. Soc.

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### TABLE 2. Pharmacokinetic parameters of quinine in the blood of children with P. falciparum malaria after administration of the Cinchona alkaloid combination

<table>
<thead>
<tr>
<th>Treatment (no. of children)</th>
<th>Cmax (µg/ml)</th>
<th>Tmax (h)</th>
<th>Kd (h⁻¹)</th>
<th>AUC0–8 h (µg ml⁻¹ h⁻¹)</th>
<th>Bioavailability (%) vs that with:</th>
<th>Trough concn of quinine (µg/ml) at:</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM12 (10)</td>
<td>6.1 (4.5–10.4)</td>
<td>3.0 (1.5–5.0)</td>
<td>1.75 (1.3–2.7)</td>
<td>41.8 (29.9–60.4)</td>
<td>4.5 (3.1–6.7)</td>
<td>IM12</td>
</tr>
<tr>
<td>IV8 (10)</td>
<td>5.9 (3.9–6.7)</td>
<td>4.1* (3.0–6.0)</td>
<td>0.64* (0.50–1.0)</td>
<td>32.8* (23.0–42.2)</td>
<td>4.4 (2.9–5.4)</td>
<td>IV8</td>
</tr>
<tr>
<td>IR8 (10)</td>
<td>4.6* (2.1–6.2)</td>
<td>4.0* (3.0–8.0)</td>
<td>0.96* (0.50–1.40)</td>
<td>26.7* (11.2–36.9)</td>
<td>81 2.8* (0.9–5.3)</td>
<td>IR8</td>
</tr>
<tr>
<td>IR12</td>
<td>No rejection (10)</td>
<td>5.1* (3.3–6.7)</td>
<td>2.5* (1.0–5.0)</td>
<td>1.16 (0.60–1.70)</td>
<td>31.5* (18.2–44.3)</td>
<td>75 64 2.7* (1.2–5.0)</td>
</tr>
<tr>
<td>IR16 (10)</td>
<td>Rejection (6)</td>
<td>3.7* (2.5–4.1)</td>
<td>2.0 (1.5–5.0)</td>
<td>21.7* (17.4–29.9)</td>
<td>52 44 3.2* (1.3–6.6)</td>
<td>IR16</td>
</tr>
<tr>
<td>IR20</td>
<td>No rejection (10)</td>
<td>5.1* (3.6–6.4)</td>
<td>2.5* (1.0–3.0)</td>
<td>1.26* (0.60–1.90)</td>
<td>35.6* (23.5–42.7)</td>
<td>64 54 4.2* (2.6–5.2)</td>
</tr>
<tr>
<td>Rejection (6)</td>
<td>3.8* (2.0–5.2)</td>
<td>1.3 (1.0–5.0)</td>
<td>18.7* (9.4–22.7)</td>
<td>27 23 4.2* (2.7–7.0)</td>
<td>5.0* (2.5–8.5)</td>
<td>IR20</td>
</tr>
<tr>
<td>Rejection + half-dose (4)</td>
<td>6.3 (4.9–8.6)</td>
<td>2.0 (1.0–3.5)</td>
<td>36.4 (30.0–56.7)</td>
<td>27 23</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Values are medians, with ranges in parentheses. Tmax, time to peak concentration in blood; Kd, absorption constant rate; *, P < 0.05 versus values for IM12 group; +, P < 0.05 versus values for IV8 group; *, P < 0.05 versus values for IR8 group; §, P < 0.05 versus values for IR12 group; #, P < 0.05 versus values for group with no rejection.

ability. The spread of a large volume of enemas or multiple suppositories appears not to be limited to the rectal area, and its migration into the ascending colon with more-limited re-
sorption capacity may result in a lower bioavailability (18). The decrease in bioavailability may also be ascribed to the adher-
ence of drug to the stools or its degradation by microorganisms and to the variability in the rectal mucosa blood flow (8, 18).

According to the level of the spread in the rectum, the drug partly avoids first-pass clearance by the liver, but similar concentrations of the 3-hydroxyquine in blood were previously observed after both parenteral and rectal administrations, sug-
gest ing more a loss of aqueous formulation itself than a hepatic
first-pass transformation (5). Nevertheless, this saturability of rectal absorption may limit the rise in blood quinine concentra-
tions often required in areas where strains became resistant, like in Southeast Asia.

The main disadvantage of a rectal route is that the drug may be extruded spontaneously and require careful monitoring (8). The frequency of early rejections of quinine enemas was esti-
bated to be about 20% of children in Togo (1). Rejections decrease the bioavailabilities of the 12- and 20-mg/kg doses by
30 and 50%, respectively, but do not significantly affect the parasitological and clinical efficacy. Nevertheless, in order to
avoid subtherapeutic concentrations in blood during the criti-
cal initial 24 h, the immediate administration of a half-dose restores effective concentrations in blood especially in the
treatment of potentially evolving cases of *P. falciparum* mal-
laria.

Similar concentration-time profiles in blood and pharmaco-
dynamic efficacy were obtained with the recommended intra-
venous regimen at 8-h intervals and the intramuscular schedule
at 12-h intervals widely used in peripheral health centers of
West Africa (13, 15). The rate and the extent of quinine ab-
sorption with the 16- and 20-mg/kg rectal doses are compar-
able to those obtained with the 12-mg/kg intramuscular treat-
ment. Such fast drug delivery may be of clinical relevance, especially at the onset of treatment of severe malaria, when
effective drug concentrations must be rapidly achieved.

Despite a large difference in blood quinine concentrations, no regimens revealed any pharmacodynamic difference. Al-

though it has low bioavailability, the 8-mg/kg rectal regimen
ensured a clearance of parasitemia that was as effective as parenteral treatments. Similarly, in Guinea-Bissau, complete therapeutic efficacy was reported for a single daily 12-mg/kg oral
dose (11). Together, these results confirm that in West
Africa, all these regimens ensured blood quinine concentra-
tions far above the minimum effective concentration.

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