Quinine-Resistant Malaria in Traveler Returning from Senegal, 2007

Bruno Pradines, Thierry Pistone, Khaled Ezzedine, Sébastien Briolant, Lionel Bertaux, Marie-Catherine Receveur, Daniel Parzy, Pascal Millet, Christophe Rogier, and Denis Malvy

We describe clinical and parasitologic features of in vivo and in vitro Plasmodium falciparum resistance to quinine in a nonimmune traveler who returned to France from Senegal in 2007 with severe imported malaria. Clinical quinine failure was associated with a 50% inhibitory concentration of 829 nmol/L. Increased vigilance is required during treatment follow-up.

Resistance of Plasmodium falciparum to antimalarial drugs is one of the most worrisome problems in tropical medicine. Quinine remains the first-line antimalarial option for treatment of patients with complicated malaria in Europe and Africa. However, emergence of quinine resistance has been sparsely documented (1). Maximizing the efficacy and longevity of quinine as a drug to control malaria will critically depend on pursuing intensive research into identifying in vitro markers and implementing active in vivo and in vivo surveillance programs such as those supported by the World Antimalarial Resistance Network. Such molecular markers are needed to monitor temporal trends in parasite susceptibility (2). We report quinine-resistant P. falciparum malaria in a patient who returned to France from Senegal.

The Patient

A 17-year-old white man from France spent 2 months (April and most of May) in Dielmo, Senegal, where malaria is highly endemic and shows intense perennial transmission (3). He did not use antimalarial prophylaxis or protection against mosquitoes. After returning to France, he was admitted to the Bordeaux University Hospital Cen-
involved in chloroquine resistance (K76T), and the dihydropteroate synthase gene, which encodes the sulfadoxine target (A437G), identified the resistant allele in our isolate (6). There was no mutation in codon 268, which encodes the atovaquone target (4). The isolate had only 1 copy of the *P. falciparum* multidrug resistance (*Pfmdr1*) gene and a mutation in codon 184, which suggested in vitro susceptibility to mefloquine (7). Amplification of DNA from parasites obtained on day 0 and preserved on fixed and stained thin blood films by a modification of the procedure of Edoh et al. (8) was not successful.

**Conclusions**

Quinine remains a reliable treatment for patients with complicated or severe *P. falciparum* malaria outside southern Asia. Clinical failure with quinine used alone or in combination with clindamycin is common in Africa. In our case-patient, a correlation between the results of the in vivo and in vitro assessments was demonstrated at day 27. Because of the lack of reliable data on the correlation between quinine IC$_{50}$ and clinical failure, arbitrary IC$_{50}$ cutoff values were chosen for in vitro quinine resistance (300 nmol/L, 500 nmol/L, or 800 nmol/L) (9).

Quinine resistance appears to share common characteristics with chloroquine resistance. It is associated with mutations in the *pfmdr1* (10) and *pfcr* (11) genes. Nevertheless, the mechanism of quinine resistance is still unknown. In addition to the *pfmdr1* and *pfcr* genes, other genetic polymorphisms such as microsatellite length variations in the *P. falciparum* sodium/hydrogen exchanger (*pfhE-1*) gene (5) and mutations in the *P. falciparum* multidrug resistance protein gene may contribute to quinine resistance (12).

We report an association of clinical failure of quinine treatment with an IC$_{50}$ of 829 nmol/L, a mutation in codon 76 of the *pfcr* gene, and an ms4760–18 profile for *pfhE-1* composed of 2 DNNND repeats. Isolates of *P. falciparum* with ≥2 DNNND repeats may be associated with reduced susceptibility to quinine. Henry et al. (5) reported that 2 DNNND repeats were associated with quinine IC$_{50}$ values ranging from 300 nmol/L to 700 nmol/L, and that 3 repeats were associated with an IC$_{50}$ >600 nmol/L. However, the 3 strains with IC$_{50}$’s >800 nmol/L had ≥2 DNNND repeats (6). Our results are consistent with these data.

*P. falciparum* resistance levels may differ depending on malaria transmission and drug pressure. Data from Senegal are fragmentary and were obtained by in vitro susceptibility studies conducted with isolates reported to have decreased in vitro susceptibility to quinine (6). Our patient had traveled to Dielmo, Senegal, where in vitro surveillance of antimalarial drug susceptibility has been conducted since 1996. During 1996–2005, the overall prevalence of isolates with IC$_{50}$ >800 nmol/L for quinine was <6%: 1% in 1996, 4% in 1997, 0% in 1998, 6% in 1999, and 0% in 2005 (13). Quinine was used for 96.4% of the treatments administered in Dielmo during 1990–1995 (14). This drug has since been replaced by chloroquine, sulfadoxine-pyrimethamine, and artemisinin-based combination therapies.

We report a patient with clinical failure associated quinine resistance in a traveler to Senegal. Our results are consistent with those of a recent review of the Uganda Malaria Surveillance Project that reported a higher risk for selecting quinine-resistant parasites associated with a 7-day quinine treatment course (15). Thus, resistance to quinine should be monitored in West Africa. Although such clinical failure of therapy is rare, increased vigilance is required during treatment follow-up, and surveillance of the parasite population should also be increased.

Dr Pradines is a senior researcher at the Research Unit in Parasitological Biology and Epidemiology of the Institute for Tropical Medicine of the French Army, Le Pharo, Marseille, France. His primary research interests are the epidemiology and population genetics of malaria.

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**Table. In vitro susceptibility of 3 Plasmodium falciparum isolates to 12 antimalarial drugs, France***

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study isolate</th>
<th>3D7</th>
<th>W2</th>
<th>Cutoff value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinine</td>
<td>829 nmol/L</td>
<td>157 nmol/L</td>
<td>574 nmol/L</td>
<td>&gt;800 nmol/L</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>472 nmol/L</td>
<td>21 nmol/L</td>
<td>392 nmol/L</td>
<td>&gt;100 nmol/L</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>10.4 nmol/L</td>
<td>49.3 nmol/L</td>
<td>39.3 nmol/L</td>
<td>&gt;30 nmol/L</td>
</tr>
<tr>
<td>Lumezantrine</td>
<td>19 nmol/L</td>
<td>29 nmol/L</td>
<td>35 nmol/L</td>
<td>&gt;150 nmol/L</td>
</tr>
<tr>
<td>Monodesethylamodiaquine</td>
<td>47 nmol/L</td>
<td>17 nmol/L</td>
<td>162 nmol/L</td>
<td>&gt;60 nmol/L</td>
</tr>
<tr>
<td>Dihydroartemisinin</td>
<td>1.1 nmol/L</td>
<td>2.5 nmol/L</td>
<td>3.0 nmol/L</td>
<td>&gt;10.5 nmol/L</td>
</tr>
<tr>
<td>Atovaquone</td>
<td>13.3 nmol/L</td>
<td>4.1 nmol/L</td>
<td>3.6 nmol/L</td>
<td>&gt;350 nmol/L</td>
</tr>
<tr>
<td>Cycloguanil</td>
<td>70 nmol/L</td>
<td>&lt;10 nmol/L</td>
<td>1191 nmol/L</td>
<td>&gt;500 nmol/L</td>
</tr>
<tr>
<td>Pyrimethamine</td>
<td>354 nmol/L</td>
<td>&lt;50 nmol/L</td>
<td>9139 nmol/L</td>
<td>&gt;2000 nmol/L</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>12.8 μmol/L</td>
<td>10.5 μmol/L</td>
<td>13.5 μmol/L</td>
<td>&gt;35 μmol/L</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>24 μmol/L</td>
<td>48 μmol/L</td>
<td>39 μmol/L</td>
<td>ND</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>39 μmol/L</td>
<td>108 μmol/L</td>
<td>126 μmol/L</td>
<td>ND</td>
</tr>
</tbody>
</table>

*P. falciparum strains 3D7 and W2 were used as controls. ND, not determined.
References


Address for correspondence: Khaled Ezzedine, Centre René Labusquière, Tropical Disease Branch, PPF Parasitologie, Université Victor Segalen Bordeaux 2, 146 Rue Léo Saignat, 33076 Bordeaux CEDEX, France; email: khaled.ezzedine@chu-bordeaux.fr