Quinine-Resistant Malaria in Traveler Returning from Senegal, 2007

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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 vitro 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 pfcr1 (11) genes. Nevertheless, the mechanism of quinine resistance is still unknown. In addition to the pfmdr1 and pfcr1 genes, other genetic polymorphisms such as microsatellite length variations in the P. falciparum sodium/hydrogen exchanger (pfhhe-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 pfcr1 gene, and an ms4760–18 profile for pfhhe-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.

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References