In Vitro Activity of Tafenoquine against the Asexual Blood Stages of Plasmodium falciparum Isolates from Gabon, Senegal, and Djibouti

Antimalarial drugs, when used as monotherapies, are rapidly losing their effectiveness. One promising new drug is the antimalarial 8-aminoquinoline tafenoquine (SB-252263 [formerly WR-238605]), a new synthetic primaquine analogue developed by the U.S. Army and GlaxoSmithKline, which has been shown effective not only against the liver stages, gametocytes, and sporozoites of Plasmodium falciparum (4), but also against the blood stages of the parasite (13). Tafenoquine demonstrated significant protection against P. falciparum infection in Gabon, Ghana, and Kenya (6, 7, 12). Tafenoquine has been reported to be well tolerated, with only mild gastrointestinal effects (8).

Isolates were collected in 1999 from malaria patients from Libreville (Gabon, Central Africa), Dielmo and Ndiop (Senegal, West Africa), and Djibouti (East Africa). The isotopic, microdrug susceptibility test used was described previously (10).

The 50% inhibitory concentration (IC50) values for tafenoquine were in the range 0.9 to 9.7 µM in Djibouti, 0.6 to 33.1 µM in Gabon, and 0.5 to 20.7 µM in Senegal. The geometric mean IC50 was 2.68 µM in Djibouti, versus 4.62 µM in Gabon and 5.06 µM in Senegal (Table 1). Tafenoquine was found to possess marked blood schizonticidal activity in P. falciparum in areas with high percentages of multidrug-resistant parasite populations. There was no difference in the tafenoquine mean IC50 values between Dielmo-Ndiop and Libreville, even though the levels of reduced susceptibility for chloroquine, mefloquine, cycloguanil, and pyrimethamine were different. Conversely, tafenoquine was significantly more active in Djibouti than in Gabon or Senegal (P = 0.016). The results of these in vitro tests were comparable with those reported by other authors in culture-adapted P. falciparum clones and strains (2, 11).

Published in vitro data for the blood schizonticidal activity of primaquine in P. falciparum show a range of IC50 values between 0.3 µM and 14 µM (1, 2, 13). In this study, there was no difference in the tafenoquine mean IC50 values between the three areas (P = 0.111). Tafenoquine is more active in vitro than primaquine, wherever the area. Tafenoquine exerts a blood schizonticidal activity 4 to 100 times higher than that of primaquine in the Plasmodium berghei and Plasmodium yoelii mouse model (9). Tafenoquine had a half-life that is more than 50 times longer than that of primaquine (3, 5). The difference in kinetics results in more prolonged, high concentrations of tafenoquine in the blood. These properties permit weekly dosing for prophylaxis and short-term or single-dose therapy for radical cure.

Only 3.5% of the variation of response to tafenoquine is explained by response variation to primaquine. The coefficients of determination, r2, ranging from 0.001 to 0.113, are too weak to consider that cross-resistance may exist between tafenoquine and standard antimalarial drugs. Since correlation analysis provides an insight into the mode of action and cross-susceptibilities between different drugs, these data may be seen as an indication of the relative independence of tafenoquine from the susceptibility of P. falciparum to standard antimalarial drugs.

In conclusion, these data permit definition of the baseline of in vitro susceptibility to tafenoquine before its use and will allow the monitoring of its resistance or its reduced susceptibility when tafenoquine will be commonly used. Given its greater schizonticidal activity, tafenoquine is a promising candidate as a short treatment for P. falciparum and Plasmodium vivax malaria. However, the potential side effects of tafenoquine, such as the production of methemoglobin and the risk of hemolysis in glucose-6-phosphate dehydrogenase-deficient patients, have to be taken into consideration (14).

The authors thank for their participation the populations and medical staffs of Libreville, Dielmo, Ndiop, and Djibouti. We thank W. K. Milhous from the Walter Reed Army Institute of Research and S.

### Table 1. In vitro susceptibilities and prevalence of resistance or reduced susceptibility of wild isolates of Plasmodium falciparum from Djibouti, Gabon, and Senegal to the drugs shown

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of isolates</th>
<th>Mean IC50 (95% CI)</th>
<th>% of resistance</th>
<th>Mean IC50 (95% CI)</th>
<th>% of resistance</th>
<th>Mean IC50 (95% CI)</th>
<th>% of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Djibouti</td>
<td></td>
<td></td>
<td>Libreville, Gabon</td>
<td></td>
<td>Dielmo and Ndiop, Senegal</td>
<td>Total</td>
</tr>
<tr>
<td>Tafenoquine</td>
<td>22</td>
<td>2.68 (2.08–3.58) µM</td>
<td>ND</td>
<td>87</td>
<td>4.65 (3.72–5.79) µM</td>
<td>ND</td>
<td>53</td>
</tr>
<tr>
<td>Primaquine</td>
<td>22</td>
<td>7.28 (5.14–10.33) µM</td>
<td>ND</td>
<td>85</td>
<td>7.48 (6.52–8.59) µM</td>
<td>ND</td>
<td>53</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>29</td>
<td>334 (230–485) µM</td>
<td>93 (77–99)</td>
<td>118</td>
<td>376 (325–435) µM</td>
<td>93 (87–97)</td>
<td>51</td>
</tr>
<tr>
<td>Quinine</td>
<td>29</td>
<td>264 (202–385) µM</td>
<td>0 (0–11)</td>
<td>79</td>
<td>393 (308–486) µM</td>
<td>2 (1–21)</td>
<td>51</td>
</tr>
<tr>
<td>Amodiaquine</td>
<td>29</td>
<td>10.2 (8.2–12.3) µM</td>
<td>0 (0–12)</td>
<td>118</td>
<td>18.0 (16.2–20.0) µM</td>
<td>0 (0–12)</td>
<td>51</td>
</tr>
<tr>
<td>Halofantrine</td>
<td>12</td>
<td>3.17 (2.75–3.96) µM</td>
<td>0 (0–12)</td>
<td>ND</td>
<td>0.95 (0.73–0.98) µM</td>
<td>2 (0–6)</td>
<td>55</td>
</tr>
<tr>
<td>Methoquine</td>
<td>0</td>
<td></td>
<td></td>
<td>114</td>
<td>7.73 (6.71–8.89) µM</td>
<td>3 (0.5–7)</td>
<td>55</td>
</tr>
<tr>
<td>Artesunate</td>
<td>0</td>
<td>85</td>
<td></td>
<td></td>
<td>2.42 (1.93–3.03) µM</td>
<td>0 (0–4)</td>
<td>52</td>
</tr>
<tr>
<td>Atovaquone</td>
<td>28</td>
<td>1.25 (0.94–1.66) µM</td>
<td>0 (0–12)</td>
<td>84</td>
<td>3.34 (2.74–3.94) µM</td>
<td>0 (0–4)</td>
<td>51</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>20</td>
<td>6.40 (4.54–9.04) µM</td>
<td>0 (0–12)</td>
<td>38</td>
<td>6.50 (4.95–8.53) µM</td>
<td>ND</td>
<td>53</td>
</tr>
<tr>
<td>Cycloguanil</td>
<td>27</td>
<td>22 (9.5–55) µM</td>
<td>11 (2–29)</td>
<td>38</td>
<td>343 (166–706) µM</td>
<td>ND</td>
<td>53</td>
</tr>
<tr>
<td>Pyrimethamine</td>
<td>26</td>
<td>88 (21–184) µM</td>
<td>8 (0–25)</td>
<td>39</td>
<td>2,233 (927–2,572) µM</td>
<td>64 (47–79)</td>
<td>119</td>
</tr>
</tbody>
</table>

*95% CI, 95% confidence interval (IC50 or resistance). The cutoff values, defined statistically (+2 standard deviations above the mean and/or after correlation with clinical failures) for in vitro resistance or reduced susceptibility were as follows: chloroquine, 100 nM; quinine, 800 nM; mefloquine, 30 nM; halofantrine, 6 nM; amodiaquine, 80 nM; artesunate, 10.5 nM; atovaquone, 1,900 nM; cycloguanil, 500 nM; and pyrimethamine, 2,000 nM. The cutoff values for in vitro reduced susceptibility to tafenoquine, primaquine, and doxycycline have not yet been determined (ND).
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