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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 codeveloped 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 (IC_{50}) 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 IC_{50} 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 IC_{50} 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-adaptated *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 IC_{50} values between 0.3 μM and 14 μM (1, 2, 13). In this study, there was no difference in the tafenoquine mean IC_{50} 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, r^2, 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).

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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

Drug	Result for isolates (95% CI)[a]										
	Djibouti			Libreville, Gabon			Dielmo and Ndiop, Senegal			Total	
	No. of isolates	Mean IC_{50} (95% CI)	% of resistance (95% CI)	No. of isolates	Mean IC_{50}	% of resistance	No. of isolates	Mean IC_{50}	% of resistance	No. of isolates	Mean IC_{50}
Tafenoquine	22	2.68 (2.00–3.58) μM	ND	87	4.65 (3.72–5.79) μM	ND	53	5.06 (3.99–6.41) μM	ND	162	4.43 (3.82–5.14) μM
Primaquine	22	7.28 (5.14–10.3) μM	ND	85	7.48 (6.52–8.59) μM	ND	53	5.74 (4.79–6.90) μM	ND	160	6.82 (6.15–7.59) μM
Chloroquine	29	334 (230–485) nM	93 (77–99)	118	376 (325–435) nM	93 (87–97)	54	104 (75–143) nM	56 (41–69)	201	261 (224–311) nM
Quinine	29	264 (202–345) nM	0 (0–11)	78	393 (308–406) nM	12 (5–21)	51	256 (208–316) nM	6 (1–16)	158	303 (272–337) nM
Amodiaquine	29	10.2 (8.2–12.8) nM	0 (0–12)	118	18.0 (16.2–20.0) nM	0 (0–12)	54	11.0 (9.5–12.7) nM	0 (0–12)	201	14.0 (12.8–15.3) nM
Halofantrine	12	3.17 (2.75–3.66) nM	0 (0–12)	118	0.85 (0.73–0.98) nM	2 (0.2–6)	55	1.4 (1.10–1.77) nM	5 (1–15)	185	1.07 (0.94–1.22) nM
Mefloquine	0			114	7.73 (6.71–8.89) nM	3 (0.5–7)	55	10.45 (8.04–13.58) nM	15 (6–27)	169	8.53 (7.50–9.68) nM
Artesunate	0			85	2.42 (1.93–3.03) nM	0 (0–4)	52	1.85 (1.51–2.27) nM	0 (0–7)	137	2.20 (1.87–2.58) nM
Atovaquone	28	1.25 (0.94–1.66) nM	0 (0–12)	84	3.24 (2.74–3.84) nM	0 (0–4)	51	4.93 (3.95–6.15) nM	0 (0–7)	163	3.13 (2.73–3.61) nM
Doxycycline	20	6.40 (4.54–9.04) μM	ND	85	6.50 (4.95–8.53) μM	ND	53	12.88 (10.81–15.35) μM	ND	158	8.17 (6.89–9.66) μM
Cycloguanil	27	22 (9–55) nM	11 (2–29)	38	343 (166–706) nM	53 (36–69)	54	256 (143–460) nM	56 (41–69)	119	161 (104–251) nM
Pyrimethamine	26	88 (21–184) nM	8 (9–25)	39	2,213 (927–5,272) nM	64 (47–79)	54	1,374 (736–2,570) nM	56 (41–69)	119	881 (547–1,422) nM

[a] 95% CI, 95% confidence interval (IC_{50} 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; cyloguanil, 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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