In-vitro activity of primaquine against the asexual blood stages of *Plasmodium falciparum*

Primaquine, an 8-aminoquinoline, has been shown to inhibit the development of the hepatic stages (hypnozoites and schizonts), gametocytes, and asexual, intra-erythrocytic forms of malarial parasites (Peters and Robinson, 1987). This triple action is unique among antimalarial drugs. Primaquine is widely used for its anti-hypnozoite action (i.e. to prevent relapses of *Plasmodium vivax* or *P. ovale* infection) and interest in its use as a causal prophylactic, to eliminate the liver schizonts of all four *Plasmodium* species infecting man, before they mature to invade the erythrocytes, has increased in recent years (Fryauff et al., 1995). Primaquine may also be prescribed as a gametocide to patients in areas with low levels of transmission.

The blood schizonticidal action of primaquine was initially studied in six healthy volunteers who were inoculated with a chloroquine-sensitive strain of *P. falciparum* (P-F-6/Panama) before treatment with the drug at doses of 30 or 45mg/day for 14 days.
maquine is 7.4-, 10-, and 47-fold less active than quinine [195 (167–227) nM], chloroquine [141 (104–192) nM], and monodesethylamodiaquine [30.8 (26.4–35.9) nM], respectively. The synthetic aminoalcohols—mefloquine [13.0 (9.4–18.0) nM] and halofantrine [1.74 (1.32–2.30) nM]—and artemisinin derivatives—artesunate [1.16 (0.78–1.73) nM] and dihydroartemisinin [1.27 (0.98–1.64) nM]—are approximately 100–1000 times more active than primaquine. Some of the isolates, which were pyrimethamine-resistant, gave similar IC₅₀ for pyrimethamine and primaquine but the others had lower IC₅₀ for pyrimethamine (see Fig.).

Bhasin and Trager (1987), using the HB3/Honduras clone of P. falciparum, found that 1 μg primaquine/ml (i.e. 2.1 μM) was required to inhibit approximately 50% of asexual parasite growth in vitro. Although this IC₅₀ value falls within the range found in the present study, several methodological differences (parasite growth assessed by microscopical examination, exposure for 96 h and use of only three drug concentrations in the earlier study) preclude direct comparison of the results of the two investigations. In another study, using six, culture-adapted strains of P. falciparum and the same drug assay as in the present study (except for the higher initial parasitaemias of 1%–2%), primaquine was found to be more potent against the chloroquine-resistant strains (IC₅₀ = 0.59–0.71 μM) than against the chloroquine-sensitive (IC₅₀ = 5.5–14 μM) (Geary et al., 1987). Although these IC₅₀ are similar to those in the present study, none of the present isolates exhibited IC₅₀ of >2.5 μM. However, as in the study of Geary et al. (1987), the geometric mean IC₅₀ (and CI) of the present chloroquine-resistant isolates [1.30 (1.14–1.48) μM] were significantly lower than those of the chloroquine-sensitive isolates.
Although primaquine is principally metabolised into a carboxylic acid derivative in man (Breckenridge et al., 1987), the full and complex process of its human metabolism, which yields numerous metabolic products, has not been fully elucidated. Some of the metabolites exhibit higher activities against the hepatic stages of malarial parasites than primaquine itself and may be associated with drug-induced haemolysis in patients with glucose-6-phosphate-dehydrogenase deficiency (Strother et al., 1981; Baird et al., 1986; Bates et al., 1990). The blood schizonticidal activities of the metabolites were not determined in the present study.

In the P. berghei rodent model, primaquine itself has been found to possess a high activity against the asexual intra-erythrocytic parasites, whereas the carboxylic acid metabolite appears to be essentially devoid of blood schizonticidal action (Peters and Robinson, 1987). Further studies are needed to define the various roles of primaquine metabolites in man.

In conclusion, primaquine is less active in vitro than the standard blood schizonticides (chloroquine, amodiaquine, pyronaridine, quinine, mefloquine, halofantrine, artesinin derivatives, atovaquone and pyrimethamine), which have IC50 against the blood schizonts of drug-sensitive isolates, of <500 nM (quinine) or even <100 nM (others) (Ringwald et al., 1996). However, the blood schizonticidal activity of primaquine in vitro is superior to that of the antibiotics used in antimalarial chemotherapy, such as doxycycline and clindamycin (Divo et al., 1985; Basco and Le Bras, 1993). Although the results of in-vitro studies should not be extrapolated to in-vivo conditions, and clinical studies are needed to confirm the present results, the moderate blood schizonticidal activity observed here may indicate that primaquine alone may not be curative against P. falciparum infections. However, drug combinations exhibiting synergistic effects with primaquine may render this 8-aminoquinoline useful against the asexual blood stages of P. falciparum.

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