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Primaquine for Prevention of Malaria in Travelers

J. Kevin Baird
US Naval Medical Research Center Detachment, Lima, Peru, jkevinbaird@yahoo.com

David J. Fryauff
Naval Medical Research Center, Silver Spring

Stephen L. Hoffman
Sanaria, Gaithersburg, Maryland

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J. Kevin Baird,[1] David J. Fryauff,[2] and Stephen L. Hoffman[3]

[1]US Naval Medical Research Center Detachment, Lima, Peru; and [2]Naval Medical Research Center, Silver Spring, and [3]Sanaria, Gaithersburg, Maryland

An expanding risk and range of endemic malaria threatens travelers. Primaquine is an old drug recently demonstrated to offer effective prophylaxis. Clinical trials conducted in Indonesia, Kenya, and Colombia showed that a primaquine base (30 mg per day) had protective efficacy against *Plasmodium falciparum* and *Plasmodium vivax* of 85%–93%. Among 339 children (age, >8 years) and adults taking this regimen for 12–52 weeks, there was no greater risk of adverse symptomatic events among primaquine users than among recipients of placebo in double-blind studies. Among 151 subjects evaluated after 20 or 52 weeks of daily primaquine therapy, methemoglobinemia was found to be mild (<13%; typically <6%) and transient (duration, <2 weeks). We consider primaquine base (0.5 mg/kg per day consumed with food) to be safe, well-tolerated, and effective prophylaxis against malaria for nonpregnant persons and those with normal glucose-6-phosphate dehydrogenase levels. Primaquine's major advantage over most drugs for chemoprophylaxis is that it does not have to be taken before entering or beyond 3 days after leaving a malarious area.

INTRODUCTION

Malaria often kills exposed and unprotected travelers. During the past 30 years, the risk of infection and range of endemic malaria has increased [1]. Worsening resistance to affordable antimalarials globally and the general collapse of vector control in areas in Asia and the Americas where malaria is endemic largely explain the resurgence [2]. Increasing travel to exotic locations amplifies risk to the traveling public. The options for travelers are limited by safety and protective efficacy of drugs available for chemoprophylaxis, but practicality also impacts effectiveness. For example, drugs that cost too much, that persons cannot tolerate, or that are inconvenient to administer are associated with a high probability of inadequate compliance.

Most antimalarials available for chemoprophylaxis, such as chloroquine, mefloquine, and doxycycline, work by killing blood-stage parasites. This "suppressive" mode of activity explains the necessity of both loading doses (to achieve protective plasma levels) and the 4 weeks of therapy after exposure (to kill parasites that later emerge from the liver). Until recently, all available antimalarials worked this way. The dosing requirements thus inconvenienced travelers who were facing departure on short notice or who were going on brief trips.

One means of protecting persons with brief exposure to malaria is causal prophylaxis. Causal drugs prevent malaria by killing parasites as they develop in the liver. This precludes loading and postexposure dosing, because invading parasites enter the liver within an hour. A fixed combination of atovaquone and proguanil (Malarone; GlaxoSmithKline) has causal prophylactic activity against *Plasmodium falciparum* [3]. It is not yet known whether it has causal prophylactic activity against *Plasmodium vivax* [4]. Primaquine (figure 1), the 8-aminoquinoline drug used since 1950 to prevent relapse of malaria, has causal prophylactic activity against both *P. falciparum* and *P. vivax*.

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Reprints or correspondence: CAPT J. Kevin Baird, US Naval Medical Research Center Detachment, Unit 3800, American Embassy, Lima, APO AA 34031 USA (baird@nmrcd.med.navy.mil).

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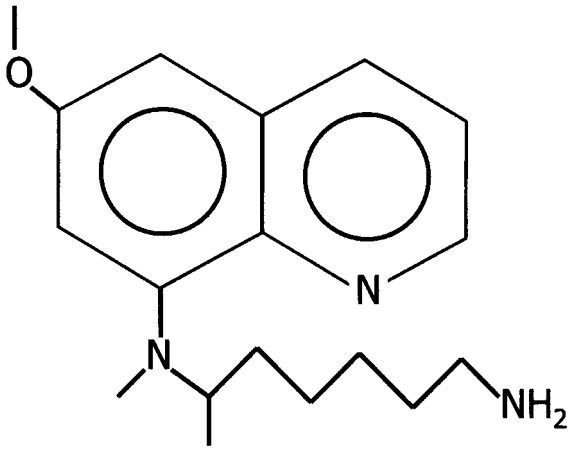

Figure 1. The chemical structure of primaquine

Only primaquine is licensed for prevention of relapse. It exerts potent activity against liver stages of plasmodia. Diagnosis of a relapsing malaria prompts health care providers to administer primaquine therapy. Health care providers often prescribe presumptive therapy to returning travelers and repatriated persons. This is terminal prophylaxis. The US Army's developers of primaquine explored its use as a primary causal prophylactic during early clinical trials [5, 6], but chloroquine, an effective and convenient prophylaxis with weekly dosing, eclipsed primaquine for prophylaxis. Primaquine was later combined with chloroquine in a single tablet, the "C-P pill," and administered weekly as chemoprophylaxis against malaria in US troops during the war in Vietnam [7, 8].

During the 1990s, we studied the use of primaquine for prevention of malaria [9–11]. We required a regimen that was practical for persons who would have brief exposure to malaria, as occurs when Navy ships harbor. The early clinical data on primaquine pointed to a solution, so we executed studies in Indonesia [9, 11] and Kenya [10] that demonstrated its safety, tolerability, and efficacy. Soto et al. [12] corroborated those findings in a study of Colombian soldiers. Schwartz and Regev-Yogtay [13] reported superior effectiveness of primaquine, compared with mefloquine or doxycycline, for prophylaxis of Israeli travelers. We recently completed a clinical trial of daily primaquine prophylaxis in Indonesian Papua [14], again demonstrating good efficacy, safety, and tolerability.

This article consolidates the key clinical observations regarding primaquine for prophylaxis against malaria. An examination of its safety, tolerability, and protective efficacy suggests that daily primaquine should be one of the instruments available for protecting travelers from malaria. That role and the potential pitfalls are identified and discussed.

ACTIVITY OF PRIMAQUINE

Coccidian sporozoa of the genus *Plasmodium,* the plasmodia, cause malaria. Their complex life cycle (figure 2) includes stages separated by host, tissue, form, function, and susceptibility to drugs. Drugs that kill asexual blood-stage plasmodia (e.g., chloroquine or mefloquine) exert no apparent effect against plasmodia during either asexual liver stages or sexual blood stages. Primaquine, in contrast, exerts activity against asexual parasites of *P. vivax* in the liver and blood [15], as well as against sexual blood forms, but it lacks activity against the asexual blood stages of *P. falciparum* [6, 16, 17]. The recommended clinical application of primaquine includes another drug to kill asexual blood-stage plasmodia. Health care providers in areas where malaria is not endemic use primaquine almost exclusively against hypnozoites, the asexual liver-stage plasmodia responsible for relapse. In regions of endemicity, a single dose of primaquine is prescribed with *P. falciparum* to sterilize the sexual blood-stage plasmodia and, in principle, to prevent transmission of the infection [18].

Early clinical trials of primaquine offer firm evidence of activity against asexual liver-stage plasmodia. However, little is known of this mechanism of primaquine. Its complex metabolism generates many forms within the liver [19, 20], including volatile quinonimines [21]. Some studies have demonstrated disruption of parasite mitochondrial membrane [22, 23]. Early researchers documented a peculiar property: the total dose of primaquine determined activity independent of the regimen of administration [24]. A dose of 420 mg base prevented relapse of infection with the Chesson strain of *P. vivax* when administered over 7 days or 8 weeks [25, 26]. This extraordinary observation, and the lack of a hypothesis that could explain it, reflects the very poor degree to which the activity against the latent liver stages of infection is understood. The very rapid elimination of primaquine (half-life, 4–6 h) deepens the mystery of the efficacy of lengthy dosing regimens for this drug.

Primaquine prophylaxis differs from therapy in subtle but critical aspects. A therapeutic regimen administered over 1–8 weeks delivers a total dose that kills parasites within the liver. A prophylactic regimen, in contrast, eliminates parasites soon after invasion. For example a single 30-mg dose of primaquine administered 1–3 days after sporozoite challenge prevents infection with *P. falciparum,* whereas the same dose given on day 5 exerts no activity [6]. The key determinant of prophylactic activity is not total dose but the single dose administered 2–72 h after challenge.

EARLY CLINICAL TRIALS AS A CAUSAL PROPHYLACTIC

In 1954, Arnold et al. [5] described the prevention of malaria using primaquine. They applied the James regimen (i.e., daily

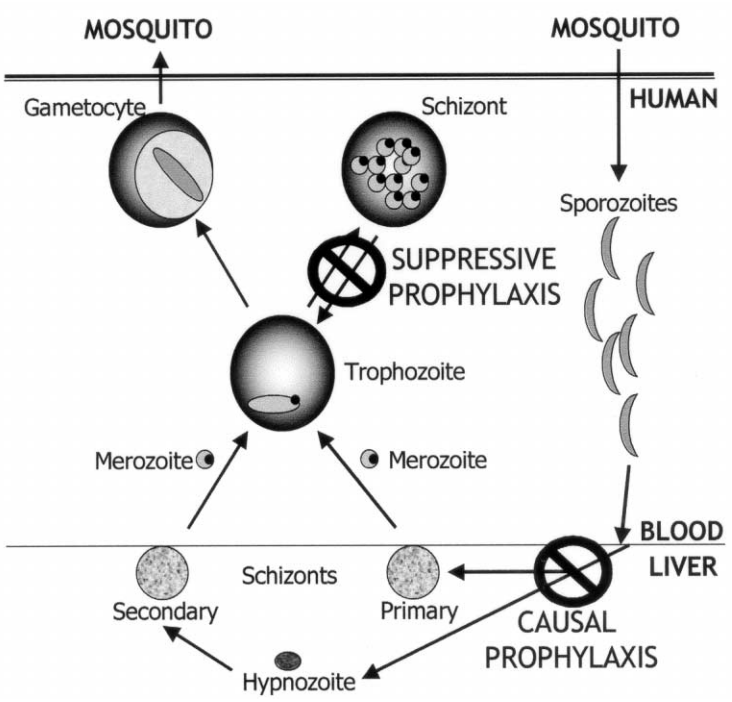

Figure 2. The life cycle of plasmodia that cause malaria in humans and the sites of vulnerability to suppressive and causal prophylactics

doses the day before, the day of, and for 6 days after challenge) with experimental sporozoite challenge with Chesson strain *P. vivax*. Thirty adult men were assigned to 3 treatment groups (10, 15, or 30 mg per day). The proportions of protected subjects after 190–450 days of follow-up were 30%, 20%, and 100%, respectively (table 1).

Arnold et al. [6] later demonstrated that primaquine had causal prophylactic activity against Panama P-F-6 strain *P. falciparum*. The James regimen of 30 mg of primaquine per day provided complete protection for 5 subjects. Three other subjects were challenged with Thailand JHK strain *P. falciparum* and were protected. Arnold and colleagues subsequently limited dosing to the day of challenge and for 4 days after the challenge for 9 subjects, and all were protected.

A complex experiment revealed that the first 24–72 h after infection was the primaquine-susceptible stage of parasite development in the liver. Again evaluating 10-, 15-, and 30-mg doses, the investigators administered drug on days 1, 3, or 5 after sporozoite challenge [6]. For single doses given on the day after challenge, only the 30-mg doses proved to be effective, protecting 10 of 10 subjects. The same dose administered on day 3 protected 9 of 10 subjects, and, on day 5, it protected none of the 10 subjects. *P. falciparum* in its early stages in the liver appeared to be susceptible to single doses of primaquine; however, maturation to day 5 provided tolerance (table 1). Powell et al. [27] reported essentially similar findings.

Alving and colleagues [28] evaluated single doses with experimental challenge by Chesson *P. vivax*. They administered 60–180-mg doses at 24, 12, or 4 h before challenge or on day 3, 5, or 7 after challenge. Doses of 180 or 120 mg given 12 or 4 h before challenge showed 89% efficacy, but no other single dose or schedule proved to be more than 20% efficacious. This experiment missed the critical dosing period of 1–2 days after challenge, because it intended to prove efficacy of weekly primaquine in the C-P pill [29]. It remains unclear whether a single 30-mg dose of primaquine given within 48 h after challenge suffices to prevent vivax malaria.

TERMINAL PROPHYLAXIS

A presumptive regimen of primaquine therapy (typically, 15 mg per day for 14 days immediately after travel to a malarious area) is known as "terminal prophylaxis" [18]. Like the C-P pill [29], the rationale and application of this regimen have no relation to the causal prophylactic activity of primaquine.

RECENT CLINICAL TRIALS OF PRIMAQUINE AS A CAUSAL PROPHYLACTIC

The US Navy initiated clinical trials of primaquine for prophylaxis in Indonesia and Kenya during the early 1990s. An operational requirement for a practical regimen of prophylaxis for brief exposure drove this work. The US Navy often puts several thousand people ashore in malarious areas for brief periods. Protection of these people with available drugs, such as mefloquine or doxycycline, often proves to be impractical.

Table 1. Protective effect of primaquine against the Panama P-F-6 strain of *Plasmodium falciparum* and the Chesson strain of *Plasmodium vivax*.

Plasmodium, primaquine daily dose in mg	Day(s) of dosing[a]	No. of subjects		No. of untreated controls/ no. who were infected	Protective efficacy, % (95% CI)
		Challenged	Protected		
Plasmodium falciparum					
10	1	10	2	10/10	20 (3–56)
10	3	10	4	…	40 (12–74)
10	5	10	0	…	0 (0–31)
15	1	10	4	10/10	40 (12–74)
15	3	10	9	…	90 (56–99)
15	5	10	0	…	0 (0–31)
30	1	10	10	10/10	100 (69–100)
30	3	10	9	…	90 (56–99)
30	5	10	1	…	10 (0.3–45)
30	0, 1–4	9	9	NR	100 (66–100)
30	−1, 0, 1–6	5	5	…	100 (48–100)
P. vivax					
10	−1, 0, 1–6	10	7	10/10	70 (35–93)
15	−1, 0, 1–6	10	8	10/10	80 (44–98)
30	−1,-0, 1–6	10	10	10/10	100 (69–100)
30	0, 1–4	12	10	"All"	83 (52–98)

NOTE. Protective effect of primaquine against the Panama P-F-6 strain of *P. falciparum* was reported in [6], and the protective effect against the Chesson strain of *P. vivax* was reported in [5]. NR, not reported.

[a] Day 0 is the day of challenge with infected mosquitoes.

Primaquine used as a causal prophylactic offered a possible solution [30].

Two trials conducted simultaneously in Indonesia and Kenya in 1992–1993 explored an alternate-day dosing regimen of 30 mg for adults and 15 mg for children [9, 10]. In Indonesia, Javanese transmigrants received either primaquine or chloroquine prophylaxis the day of arrival in the Arso region of hyperendemicity in northeastern Papua (formerly known as Irian Jaya). After 16–20 weeks, 30 (56%) of 54 subjects taking chloroquine acquired malaria, compared with 5 (11%) of 45 who received primaquine. Four of the 5 infections were due to *P. falciparum,* and the other was due to *P. vivax*. The protective efficacy of primaquine relative to chloroquine was 73% (95% CI, 32%–90%) for *P. falciparum,* 90% (95% CI, 44%–98%) for *P. vivax,* and 80% (95% CI, 56%–92%) for either species. In Kenya, 39 children received 15 mg of primaquine 3 times per week, and 39 others received placebo. Although parasitemia was appreciably delayed in the primaquine group, all 78 subjects developed patent falciparum malaria (efficacy, 0%). These trials demonstrated 2 important facts: (1) alternate-day regimens did not provide adequate protection against *P. falciparum,* and (2) the tolerability of this regimen of primaquine proved, to the surprise of the investigators, to be superior to weekly doses of chloroquine and to be equal with placebo. The stage was thus set for evaluating the safety, tolerability, and efficacy of daily primaquine therapy for prophylaxis.

Two subsequent trials [10, 11] were initiated in 1993. In Kenya (table 2), 32 children received 15 mg of primaquine per day, and 8 (25%) developed patent *P. falciparum* malaria, compared with all 34 subjects (100%) who received a placebo. The protective efficacy of 85% (95% CI, 67%–94%) for primaquine compared well with the 84%, 77%, and 54% efficacies of daily prophylaxis with doxycycline, mefloquine, and chloroquine plus proguanil, respectively, observed in the same study. In Indonesia, 125 Javanese transmigrants in the Arso region were randomized to 3 treatment arms: 30 mg of primaquine per day (43 subjects), a daily dose of placebo (42 subject), and weekly doses of chloroquine (40 subjects) for 52 weeks. Three subjects who received primaquine developed patent malaria (7%), compared with 26 subjects (62%) who received placebo and 21 (53%) who received chloroquine. The risk of falciparum and vivax malaria was approximately equal among subjects who received placebo (46% and 54% of infections, respectively). The protective efficacy of primaquine relative to placebo was 92% (95% CI, 35%–99%) for *P. falciparum,* 86% (95% CI, 50%–96%) for *P. vivax,* and 89% (95% CI, 69%–96%) for either species (table 3). The protective efficacy of chloroquine relative to placebo was 21% (95% CI, 0%–63%) for *P. falciparum,* 10%

Table 2. Protective efficacy of daily 15-mg doses of primaquine against *Plasmodium falciparum* in Kenyan children and adolescents, compared with other antimalarials and placebo.

Variable	Treatment arm				
	Primaquine (n = 32)	Doxycycline (n = 32)	Mefloquine (n = 30)	Chloroquine plus proguanil (n = 37)	Placebo (n = 34)
No. of person-years at risk	6.6	6.2	5.8	6.5	4.2
No. of infections	8	8	11	24	34
Protective efficacy, % (95% CI)	85 (67–94)	84 (67–95)	77 (56–91)	54 (21–74)	…

NOTE. Data are from [9].

(95% CI, 0%–52%) for *P. vivax*, and 15% (95% CI, 0%–43%) for either species.

In 1997, a randomized, double-blind, placebo-controlled trial of 30 mg of primaquine prophylaxis per day involving 176 Colombian soldiers [12] corroborated the findings from Indonesia and Kenya. Daily 30-mg doses of primaquine (122 subjects) or placebo (54 subjects) were administered for 16 weeks (commencing 1 day before exposure and continuing for 1 week afterward). Two subjects (2%) who received primaquine developed falciparum malaria, compared with 11 subjects (20%) who received placebo. Six subjects (5%) who received primaquine developed vivax malaria, compared with 13 subjects (24%) who received placebo. The protective efficacy of primaquine against *P. falciparum* was 94% (95% CI, 75%–99%), and it was 85% (95% CI, 57%–95%) against *P. vivax*. The protective efficacy of primaquine against either species was 89% (95% CI, 75%–96%). Table 3 presents the statistical data from this trial.

During 1999 and 2000, a trial of primaquine (30 mg per day) for prophylaxis was conducted in the Armopa region of northeastern Papua, Indonesia [14]. The Javanese subjects were randomized to inclusion or exclusion (ratio, 3:1) in a double-blind, placebo-controlled trial of daily atovaquone-proguanil reported elsewhere [31]. The 97 excluded volunteers accepted participation in an open-label trial of primaquine prophylaxis. The 2 trials were conducted simultaneously in the same villages by the same research team, and the attack rate in the placebo group in the atovaquone-proguanil trial was applied to estimate protective efficacy among subjects receiving primaquine (or a parallel placebo). Prophylaxis with 30 mg of primaquine per day (97 subjects) or a placebo (149 subjects) was administered for 20 weeks. Two subjects (2%) who received primaquine developed falciparum malaria, compared with 23 subjects (15%) who received placebo. No subject who received primaquine developed vivax malaria, compared with 16 subjects (13%) who received placebo. The protective efficacy of primaquine against *P. falciparum* was 88% (95% CI, 48%–97%), and it was >92% (95% CI, 77%–99%) for *P. vivax*. The protective efficacy of primaquine against either species was 93% (95% CI, 71%–98%). Table 3 lists the essential statistics from this trial.

SAFETY AND TOLERABILITY

Some experts regard primaquine as too toxic for use as a prophylactic [32]. Hepatic and cardiac lesions appear in experimental animals given lethal doses of primaquine, but this pathology has not appeared in humans [33]. The 3 dominant issues of safety and tolerability of primaquine are gastrointestinal discomfort, methemoglobinemia, and hemolysis in people who have an inborn deficiency of glucose-6-phosphate dehydrogenase (G6PD). Critical analysis of the available data reveals that primaquine is safe and well-tolerated in people considered good candidates to receive it.

Clayman et al. [34] described epigastric pain in 5%, 10%, 35%, and 100% of fasted subjects given a single 15-, 30-, 45-, or 90-mg oral dose of primaquine, respectively. Immediate cramping occurred in subjects given 120-mg and 240-mg doses. Stomach upset associated with primaquine is well documented and widely cited. However, Clayman et al. [34] described fed subjects who had almost no GI complaints, "even at the highest doses administered" (p. 1566). The recent clinical trials of primaquine included a requirement for dosing with a snack or meal, and gastrointestinal complaints were no more frequent among subjects given primaquine than among those who received placebo (table 4). Primaquine taken with a light snack rarely elicited complaints.

Standard primaquine therapy elevates methemoglobin levels to ~4% in most healthy subjects [35]. Methemoglobin levels of <20% are almost always tolerated without symptoms or signs [36], and observed subjects taking primaquine rarely complain of shortness of breath and have not, to our knowledge, ever exhibited signs of cyanosis. People who have an inborn deficiency in methemoglobin reductase are very susceptible to primaquine-induced methemoglobinemia [36, 37]. Two trials from Indonesia documented methemoglobin levels in subjects taking primaquine after 50 and 20 weeks [11, 14]. The mean methemoglobin levels in those studies, 8.5 g/L (range, 2–19 g/L) and 5.1 g/L (range, 2–12 g/L), respectively, were not significantly different from these measurements for 30 subjects on the day after administration of 15 mg of primaquine per day for 14 days (6.1 g/L; range, 1–15 g/L) (table 5) [35]. Baird et

Table 3. Efficacy of daily 30-mg doses of primaquine for prophylaxis of adults in randomized, placebo-controlled trials in Indonesia and Colombia.

Variable	Study		
	Fryauff et al. [11]	Soto et al. [12]	Baird et al. [14]
Age of subjects, years	>15	18–42	14–60
Duration of prophylaxis, weeks	52	16–18	20
No. of subjects in treatment arm			
Primaquine	43	122	97
Placebo	42	54	149
No. of *Plasmodium falciparum* infections			
Primaquine arm	1	2	2
Placebo arm	12	11	23
P. falciparum protective efficacy, % (95% CI)	94 (61–99)	94 (78–99)	88 (48–97)
No. of *Plasmodium vivax* infections			
Primaquine arm	2	6	0
Placebo arm	14	13	16
P. vivax protective efficacy, % (95% CI)	90 (65–99)	85 (57–95)	>92 (>37–99)
No. of all malaria cases			
Primaquine arm	3	8	2
Placebo arm	26	24	39
All malaria protective efficacy, % (95% CI)	92 (79–99)	89 (75–96)	93 (71–98)

al. [14] observed subjects for 28 days after receipt of their last dose of primaquine and found that methemoglobin levels returned to normal in all subjects by day 15. Prolonged dosing with 30 mg of primaquine per day does not elevate methemoglobin levels to more than the levels observed during 14 days of standard 15-mg daily therapy. The highest methemoglobin level recorded among 115 subjects given 30 mg per day for many weeks was 13%. Methemoglobin levels do not approach the threshold (>20%) associated with clinical symptoms or signs during prolonged daily dosing, and methemoglobinemia resolves within 2 weeks.

Primaquine is dangerous for people with G6PD deficiency [38]. Clinical risk depends on the variant and, presumably, residual G6PD activity. Most Africans and African Americans have ~20% normal G6PD activity (~10% of African Americans have A− variant G6PD), and primaquine causes mild and self-limited anemia. In such people, primaquine destroys only senescent RBCs, and further hemolysis does not occur, even in the face of continuous dosing [26]. More rare variants (with <5% residual G6PD activity) are associated with life-threatening acute intravascular hemolysis [39–42]. The safe use of primaquine requires screening for G6PD deficiency. Several standard qualitative laboratory tests, which cost less than $1 each and require little technical skill (e.g., the $NADP^+$ spot test), are available from Sigma Chemical Company.

GAPS IN KNOWLEDGE ABOUT PRIMAQUINE PROPHYLAXIS

Although it has been demonstrated to be safe, tolerable, and effective in clinical trials of healthy, nonpregnant, and G6PD-normal adults and children, some questions remain concerning primaquine prophylaxis. No trial included children aged <8 years. Most trials administered primaquine daily for 12–20 weeks, and no field trials have assessed brief regimens. Finally, field trials have not evaluated risk of relapse after exposure, and the effective duration of postexposure regimens is unclear.

Prophylaxis for small children is a problem. Doxycycline cannot be used, and the subtle neurologic side effects of mefloquine that occur in some adults are difficult to evaluate in

Table 4. Relative risk (RR) for gastrointestinal (GI) complaints associated with daily 30-mg doses of primaquine prophylaxis, compared with placebo.

GI complaint	RR (95% CI), by study		
	Weiss et al. [10][a]	Fryauff et al. [11][b]	Baird et al. [14][b]
Nausea	0.29 (0.19–0.45)	0.62 (0.42–1.5)	0.79 (0.46–1.4)
Vomiting	NR	0.72 (0.44–1.8)	1.51 (0.59–3.4)
Abdominal pain	0.56 (0.36–0.73)	0.69 (0.58–1.4)	1.4 (0.86–2.2)

NOTE. NR, not reported.
[a] Study is from Kenya
[b] Study is from Indonesia.

Table 5. Methemoglobin levels on the last day of primaquine therapy or prophylaxis.

Variable	Study		
	Fletcher et al. [35]	Fryauff et al. [11]	Baird et al. [14]
Study site	Thailand/United Kingdom	Indonesia	Indonesia
Dosage (duration)	15 mg/day (14 days)	30 mg/day (50 weeks)	30 mg/day (20 weeks)
No. of subjects	30	31	84
Methemoglobin level, mean g/L (range)	6.1 (1–15)	8.5 (2–19)	5.1 (2–12)

young children. The availability of safe, well-tolerated, and effective prophylactics for this age group would provide sorely needed alternatives. Primaquine being prohibited in pregnant women stems from inability to ascertain G6PD status of the fetus. Primaquine therapy is routinely prescribed to small children with malaria, and it is considered safe at any age, provided that normal G6PD status is demonstrable. This experience incidentally proves that primaquine prophylaxis of 2 weeks' duration is safe for this age group.

Primaquine prophylaxis for older children and adults has not been evaluated for >52 weeks' duration. The evaluated safety of most drug regimens rarely exceeds a few months, and primaquine is no exception; however, the perceived role of this drug does not include long-term prophylaxis. We do not view a daily regimen of primaquine or any other drug as suited to long-term prophylaxis. The vast majority of likely recipients would not require treatment for more than a few months. Nonetheless, some patients face long-term, unavoidable, high-risk exposure to malaria and may be considered poor candidates to receive an available weekly regimen. Although it is not convenient and has an incomplete long-term dosing safety profile, primaquine should be considered along with other daily regimens as an alternative.

The minimum number of doses necessary to prevent infection and relapse is not known. This issue bears directly on 2 important questions: (1) is primaquine prophylaxis effective over less than 1 week of dosing, and (2) what should be the duration of dosing after exposure? The early clinical trials with *P. falciparum* showed that a single 30-mg dose of primaquine was sufficient to prevent infection. Parallel experiments with *P. vivax* were not performed. The investigators applied the James regimen of dosing on days −1, 0, and 1–6 relative to challenge. A single experiment involving 12 subjects evaluated the same 30-mg dose given on days 0 and 1–4, and 2 subjects were not protected against *P. vivax* (efficacy, 83%; table 1). Corroboration of the results of that experiment would dictate a minimum of 2 daily doses during exposure, combined with ⩾6 doses after exposure, to prevent relapse of *P. vivax* infection. The available evidence does not support a firm recommendation for the duration of postexposure dosing with longer-term prophylaxis. Three days may suffice, but this requires confirmation.

THE NICHE FOR PRIMAQUINE PROPHYLAXIS

Responsible prescribing of prophylaxis includes consideration of the safety, tolerability, and efficacy of the drug. However, prevention of malaria often hinges on convenience to the traveler. Convenience may refer to the timing and simplicity of the dosing schedule, but, for many travelers, it also includes affordability.

The available data demonstrate the safety, tolerability, and efficacy of daily doses of primaquine in nonpregnant children (age, >8 years) and adults with normal G6PD status. Resistance to primaquine at 30-mg daily dosing by liver-stage parasites is not known to occur, and the clinical trials in Indonesia demonstrated efficacy against a backdrop of *P. falciparum* and *P. vivax* that were highly resistant to chloroquine [9, 11, 14].

Primaquine is most convenient for persons undertaking brief travel, compared with standard suppressive prophylactics [43]. Daily dosing with primaquine that commences upon arrival and ceases 3 days after return may substantially diminish the risk of poor compliance with therapy. We consider primaquine or atovaquone-proguanil to be the best choice for travel of ⩽1 month's duration. The study by Schwartz and Regev-Yochay [13] perhaps best substantiates this view for primaquine: among 106 Israeli travelers to Ethiopia who took daily primaquine prophylaxis, 6 (6%) developed malaria after returning home, whereas malaria occurred in 27 (52%) of 52 other travelers who took mefloquine, doxycycline, or chloroquine.

Primaquine is not licensed for use as prophylaxis in the United States. A change in labeled indication requires sanction by the US Food and Drug Administration. However, doing so for primaquine presents an economic challenge. Patent protection expired decades ago. The cost of an application for change of label may exceed $1 million. The organization that bears that cost stands little chance of recovering it in the marketplace. This represents the primary challenge for the licensure of primaquine for prophylaxis.

CONCLUSIONS

Clinical trials of primaquine base (30 mg q.d. for 12–52 weeks) from Indonesia, Kenya, and Colombia conducted during 1993–2000 proved that it was 85%–93% effective against *P. falciparum* or *P. vivax*. No serious adverse events occurred. Taken with food, the regimen caused no more gastrointestinal discomfort than did placebo (only 2 subjects in one trial could not tolerate the regimen). Primaquine caused mild methemoglobinemia (methemoglobin level, ~5%) that resolved within 2 weeks. Methemoglobinemia after 20–54 weeks of treatment was no more pronounced than after completion of standard therapy. Prophylaxis using primaquine carries the decisive advantage of no requirement for either a loading regimen before travel or 4 weeks of treatment after exposure. Primaquine does not have a labeled indication in the United States for prophylaxis, but the available studies support the view that it is safe, well tolerated, and effective in people who are considered good candidates to receive it.

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