2003

Can Primaquine Therapy for Vivax Malaria be Improved?

J. Kevin Baird
U.S. Naval Medical Research Unit # 2, jkevinbaird@yahoo.com

Karl H. Rieckmann
Australian Army Malaria Institute

Vivax series:

Can primaquine therapy for vivax malaria be improved?

J. Kevin Baird[1] and Karl H. Rieckmann[2]

[1]US Naval Medical Research Unit #2, American Embassy Jakarta, Fleet Post Office, Asia-Pacific 96520-8132, USA.
[2]Australian Army Malaria Institute, Weary Dunlop Drive, Gallipoli Barracks, Enoggera, QLD 4051 Australia.

The incidence and range of endemic malaria caused by *Plasmodium vivax* has expanded during the past 30 years. This parasite forms hypnozoites in the liver, creating a persistent reservoir of infection. Primaquine (PQ), introduced 50 years ago, is the only drug available to eliminate hypnozoites. However, lengthy treatment courses and follow-up periods are not conducive to assessing the effectiveness of this drug in preventing relapses. Resistance to standard therapy could be widespread. Studies are urgently needed to gauge this problem and to determine the safety, tolerability and efficacy of shorter courses and higher doses of PQ.

Plasmodium vivax causes malaria in ~ 80 million people annually, predominantly in Asia, the Western Pacific and the Americas [1]. Although the incidence and geographic range of endemic vivax malaria retreated substantially between 1945 and 1970, expanding risk of vivax malaria marks the period 1970 to today [2–6]. Almost half of North America and large tracts of South America, Europe and Asia stand receptive to endemic vivax malaria, including latitudes as far north as Newfoundland in Canada, Sweden in Europe, and Manchuria in Asia. In the southern hemisphere, Argentina and Australia are also receptive [7]. In temperate regions, seasonally abundant anopheline vectors transmit infection, and the parasite lies latent in the liver through seasons in which vector activity cannot endure. In the tropics, *P. vivax* exploits the same capability, but tends to relapse quickly because feeding activity by competent vectors often occurs all year round. Latent stages of *P. vivax* in the liver constitute an important reservoir of infection. Attacking that reservoir demands specific chemotherapy to kill the latent liver stages. Primaquine (PQ) is the only drug available for this purpose and its appropriate application constitutes a crucial weapon against resurgent vivax malaria.

Relapse

The cycle of invasion, development within, and rupture of red blood cells by merozoites, trophozoites and schizonts causes clinical malaria. Hypnozoites lie dormant until they develop to mature liver-stage schizonts containing thousands of individual merozoites. The schizont bursts. Merozoites spill into the bloodstream and infect red blood cells. The ensuing course of clinical malaria is called a relapse. Among the species of *Plasmodium* that infect humans, only *P. vivax* and *Plasmodium ovale* form hypnozoites and cause relapse. The likelihood of relapse by *P. vivax*, and the duration between primary parasitemia and relapse, varies, apparently in relation to latitude and seasonal abundance of anopheline vectors. In general, strains from temperate regions are less likely to relapse ($\sim 30\%$ risk) and tend toward longer latency (> 6 months). Tropical strains usually relapse ($\sim 80\%$ risk), often on multiple occasions (three or more), and begin doing so within a couple of weeks after primary parasitemia [8,9]. Exceptions do routinely occur. For example, risk of relapse by *P. vivax* in India seems inexplicably low for a subtropical environment (between 5% and 15%).

Patients experiencing the debilitating fevers, chills, nausea, vomiting and malaise associated with vivax malaria obtain relief by taking chloroquine (CQ) or quinine. These drugs attack the blood stages, but exert no known direct effect against the liver stages of the parasite. PQ is the only drug that can eradicate parasites from the liver.

PQ as an antimalarial drug

PQ was first synthesized in the USA during the Pacific war (1941–1945) as part of a massive undertaking of antimalarial drug development [10,11]. PQ is an analogue of pamaquine, the first 8-aminoquinoline drug to be produced during an earlier antimalarial drug development program in Germany during the 1920s [12].

Unlike other widely used antimalarial drugs, PQ exerts a broad spectrum of activity against various stages of the parasite. It kills both latent and developing asexual stages in the liver, and sterilizes the sexual blood stages (gametocytes). A standard regimen clears the blood of asexual trophozoites of *P. vivax* [13–15], but fails to affect the same stages of *Plasmodium falciparum* [16–18]. Neither its complex metabolism nor mechanism of activity is fully understood [19]. A wide variety of metabolites, some of them highly reactive hydroxylated species, apparently disrupt parasite mitochondrial membranes. This could account for the relative susceptibility of parasite stages with a paucity of mitochondria [20].

PQ offers a wide range of clinical applications. In many endemic regions, a single 45 mg dose of PQ is administered

---

with standard therapy for falciparum malaria as a measure to block transmission [21]. PQ taken daily effectively prevents infection by *P. falciparum* and *P. vivax* [22–26]. Travelers can take presumptive therapy following travel to prevent relapse. Anti-relapse therapy following diagnosis of vivax malaria constitutes the conventional use of PQ.

How effective is anti-relapse therapy?

Standard anti-relapse therapy is generally considered to be a single daily adult dose of 15 mg PQ base for 14 days. This well-tolerated regimen [27–29] emanated from early experimental clinical studies showing that many strains of *P. vivax* are nearly completely susceptible to a total dose of 210 mg PQ. In other trials performed at the same time, it was realized that infections with the Chesson strain, isolated from an American soldier infected in New Guinea [30], required at least 22.5 mg daily (total dose of 315 mg PQ) to prevent subsequent relapse [27,31,32]. Standard therapy against Chesson *P. vivax* achieved only ~80% efficacy. Because many infections acquired in Southeast Asia and the Southwest Pacific area show similar tolerance of standard PQ therapy (~80% efficacy) [15,33–36], a regimen of 30 mg daily for 14 days (420 mg total dose) is widely recommended [21,35–37]. It is important to point out that virtually all of the data showing that standard PQ therapy works well (>90% efficacy) is at least 40 years old. The same is true even of the 30 mg daily regimen with the exception of two relatively recent studies from Thailand [15,34].

An alternative regimen for PQ-tolerant infections is the intermittent, weekly administration of 45 mg PQ for 8 weeks (360 mg total dose of PQ). This is based on early observations by Alving *et al.* [31] that this regimen mitigated the hemolytic effects of PQ in individuals with the less severe A⁻ variant (the most common mutant genotype in sub-Saharan Africa) of glucose-6-phosphate dehydrogenase (G6PD) deficiency. The 8-week regimen also appeared to be more effective than a daily dose of 15 mg against infections with the Chesson strain [31]. We are not aware of recent data demonstrating the efficacy of this regimen.

These long courses of treatment and follow-up do not encourage assessment of the efficacy of PQ. Consequently, little information is available about the efficacy of such regimens against naturally acquired infections, or about the prevalence or extent of hypnozoites that tolerate or resist standard PQ therapy.

Can PQ treatment be improved?

Shorter regimens improve compliance. The major disadvantage of prolonged daily or weekly courses of drug administration is patient compliance. In a series of studies with American soldiers repatriated from Vietnam, the odds for relapse in groups that were not supervised during standard PQ therapy was 4.4 times greater than in the supervised groups [38–40] (Fig. 1). Compliance with a 14-day regimen is a problem.

In many endemic countries, 15 mg PQ per day for 5 days (75 mg total dose) has long been used to prevent relapse. However, recent well-controlled clinical trials in Pakistan
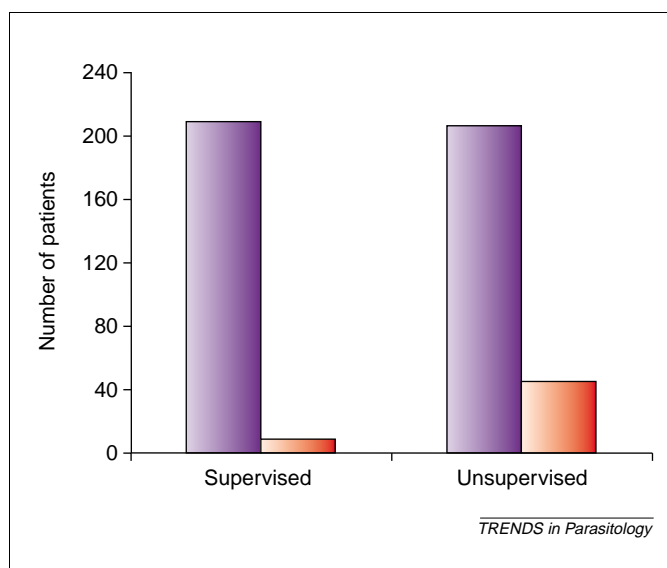

Fig. 1. Relapse of *Plasmodium vivax* in American soldiers repatriated from Vietnam. These American soldiers were given supervised or unsupervised standard primaquine (PQ) therapy of 15 mg daily for 14 days. Patients were followed for 4–12 months after therapy. The number of patients who experienced a relapse (purple bars) or no relapse (red bars) are indicated. The odds ratio for relapse among unsupervised soldiers was 4.4 (95% confidence interval = 2.2 to 8.3; $P < 0.0001$). Adapted from data in Refs [38–40].

[41] and India [42] showed this short, low-dose regimen to be ineffective. Both studies demonstrated almost no effect on the risk of relapse. Nonetheless, we believe that similarly abbreviated treatment courses that deliver an adequate total dose could prove highly effective.

Pre-clinical studies in nonhuman primates showed that the total dose of PQ, rather than schedule of dosing, determined the efficacy of treatment [43]. Clinical studies corroborated that view [31,44]. A total dose of 360–420 mg PQ delivered over a period of 7 days, 14 days or 8 weeks prevented relapse of the PQ-tolerant Chesson strain of *P. vivax* equally effectively. All strains of *P. vivax* except the Chesson strain proved susceptible to a total dose of 210 mg PQ in experimental challenge studies conducted 50 or more years ago. Recent demonstrations of susceptibility to standard PQ therapy, without potentially serious confounding factors such as re-infection or recrudescence, are not available. Two studies from Thailand represent important exceptions demonstrating poor performance of the 210 mg total dose delivered over 14 days [15,34]. A higher dose than 210 mg of PQ might be necessary in areas of established tolerance or resistance (e.g. Southeast Asia and the Southwest Pacific).

Higher doses could improve efficacy. In areas where a total dose of 210 mg is still effective, this dose could be administered over as few as three days (30 mg, twice a day for three days, and once on the fourth day). However, in the Asia and Pacific regions, for an apparently increasing number of vivax infections, the 210 mg or even the 315 mg dose no longer cures ([15,21,33–36]; J.K. Baird and K.H. Rieckmann, unpublished). Treatment with a total dose of 420 mg (or 6 mg kg⁻¹ for a person weighing 70 kg) would almost certainly achieve higher cure rates than the 210 mg standard. This total dose, given as 60 mg daily for 7 days to 11 subjects [44], was just as effective as

30 mg daily for 14 days, or 45 mg weekly for 8 weeks, and was more effective than 15 mg daily for 14 days against the Chesson strain. Provided tolerance is good, higher daily doses for a shorter period of time would almost certainly improve patient compliance.

Tolerability and safety of high dose PQ

Clayman *et al.* [45] gave a range of single doses of PQ to fasted volunteers. They reported abdominal distress in 5%, 10%, 35% and 100% of subjects given 15 mg, 30 mg, 45 mg or 90 mg of PQ, respectively. Doses of 120 mg (in 18 subjects) or 240 mg (in 5 subjects) caused immediate and severe abdominal cramping. However, the same report describes complete relief from these effects, even at the highest doses applied, when PQ was administered with food. Administration of 30 mg PQ daily with a snack for 16 to 52 weeks was as well tolerated as the placebo in prophylactic trials [22–24,26].

Although gastrointestinal complaints were not a very prominent feature in volunteers receiving daily doses of 60 mg [15,44], further studies in various ethnic groups are needed to determine the tolerability and safety of such doses administered over a period of 3–7 days. The same would of course apply to higher daily doses given over a shorter period of time. Such studies should include monitoring for any potential cardiac, hepatic, renal and hematological toxicity.

PQ causes mild methemoglobinemia in normal subjects given standard therapy. Peak levels of ~5% methemoglobinemia are typical during PQ therapy, and sometimes reach up to 15% in normal subjects. Methemoglobinemia of <20% does not cause symptoms or signs in most people. Methemoglobinemia in subjects given 30 mg daily for 20 weeks or 52 weeks was no more pronounced than in subjects receiving standard therapy of 15 mg daily for 14 days [22,26]. PQ-induced methemoglobinemia thus appears mild and self-limited for most people. The impact of higher doses over shorter periods on methemoglobinemia has not been evaluated, although Clayman *et al.* [45] did not report signs or symptoms of methemoglobinemia in the subjects they exposed to very high doses of PQ (up to 240 mg). Some people suffer an inborn deficiency of methemoglobin reductase and are sensitive to PQ-induced methemoglobinemia (2–30% with long-term weekly 45 mg of PQ, see Ref. [37]).

What about G6PD deficiency?

PQ causes acute intravascular hemolysis in people having a genetic deficiency of glucose-6-phosphate dehydrogenase (G6PD). Many dozens of variants of this abnormality occur in varying degrees of frequency among most human populations [46]. It is especially common among people originating from highly malaria-endemic regions, for example, sub-Saharan Africa, where 5–10% of people typically express the trait. Each variant carries between 0% and 100% normal enzyme activity. The level of residual G6PD activity does not always correlate with the severity of drug-induced hemolysis. PQ could cause a mild, self-limited hemolysis of senescent erythrocytes, as in the African A⁻ variant, or a relatively severe and dangerous hemolysis, as in the Mediterranean B⁻ variant. In the

absence of definitive evidence of either G6PD-normal status or demonstrated tolerability in a given variant, PQ should not be administered. This restricts the use of PQ in the setting of interventions against epidemic or endemic vivax malaria. An inexpensive and reliable point-of-care diagnostic kit would solve this problem. The available NADP⁺ spot test (Sigma Chemical Co., St. Louis, MO, USA), among others, provides a reliable and relatively inexpensive (<US$1) diagnostic test, but requires a laboratory setting and skilled hands. Further efforts are needed to develop affordable and simple field kits for identifying individuals that are susceptible to PQ hemolysis.

How should alternative PQ regimens be evaluated?

The effectiveness of PQ treatment regimens should be assessed in different ethnic groups. Such studies must also monitor and document the safety and tolerability of the treatment regimens, especially for gastric discomfort and methemoglobinemia. Initially, experimental regimens should be administered only to G6PD-normal, non-pregnant individuals.

Health care providers or responsible members of the patient's family should directly observe therapy. Ideally, compliance would be signature-affirmed by both the patient and the monitor. Unsupervised therapy, especially over a long period, comes with high risk of poor compliance.

Assessment of the efficacy of PQ treatment should be done in patients who have returned to non-endemic areas and are willing to undergo directly observed therapy followed by lengthy periods of follow-up (at least 2 months, preferably 18 months). The efficacy of PQ therapy usually cannot be assessed confidently in patients residing in endemic areas because re-infection cannot be ruled out. However, patients returning to large cities in endemic areas are very unlikely to be re-exposed to malaria (except in and around the Indian sub-continent where *Anopheles stephensi* transmits malaria within cities). Likewise, re-infection might be excluded in patients residing at high altitudes where anopheline mosquitoes do not occur, despite abundance at lower altitudes.

Companion blood schizonticides in PQ therapy

A diagnosis of vivax malaria usually prompts therapy with both chloroquine (CQ) and PQ because CQ has traditionally been the drug of choice for aborting an acute attack of vivax malaria. However, in 1989, resistance to CQ was first documented in *P. vivax* from Papua New Guinea [47]. Since then, CQ resistance has been shown to occur in Asia [21,48–51] and the Americas [52,53]. In eastern Indonesia, the risk of therapeutic failure approaches 80% within 28 days [51].

Unrecognized resistance to CQ could create the false impression of ineffective PQ therapy. Conversely, ordinarily effective CQ levels (>100 ng ml^{-1}) persist in the blood for about a month and will suppress relapse due to ineffective PQ therapy. This might lead to the false impression of effective PQ therapy. The therapeutic response to CQ represents a potentially powerful confounding factor in assessing PQ efficacy (Fig. 2).

Because quinine is rapidly excreted (almost completely within 24 h), the drug does not have the effect of
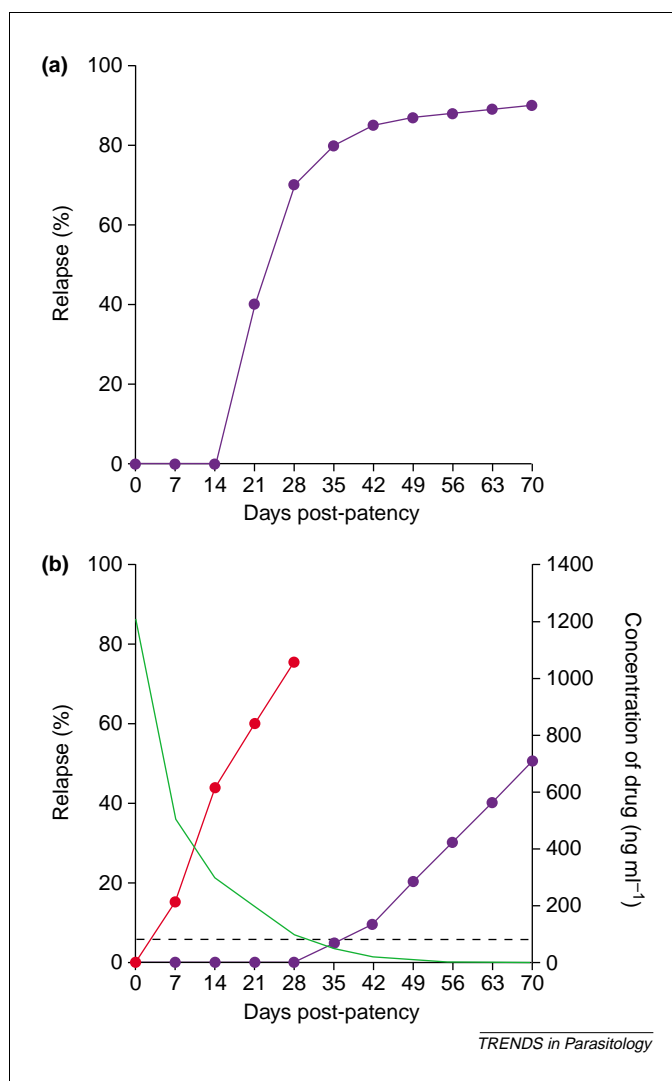
Fig. 2. Relapse of tropical Pacific *Plasmodium vivax* after standard therapy with quinine and chloroquine. (a) Quinine is a rapidly eliminated drug that does not suppress relapses. Relapses commenced ~16 days after patency of the original infection, and most patients relapsed within 45 days from the onset of patent parasitemia (post-patency). (b) Chloroquine (CQ) therapy has a different impact on the timing of relapses or recrudescences in tropical Pacific vivax malaria. CQ-sensitive *P. vivax* (CSPV) (purple line) remains suppressed for ~30 days by persisting concentrations of CQ plus desethylchloroquine (CQ + DCQ; green line) that are higher than the minimum effective concentration (MEC; broken black line). Relapse (or recrudescence) caused by CQ-resistant *P. vivax* (CRPV; red line) occurs much earlier because parasites are no longer suppressed by drug concentrations higher than the MEC (for sensitive parasites). Data adapted from Ref. [60].

suppressing subsequent relapse. The available data point to Day 16 post-patency of the primary parasitemia as the earliest relapse and, for tropical *P. vivax* from the western Pacific region, most have relapsed at least once by Day 45. By contrast, onset of recurrent parasitemia after CQ treatment of CQ-sensitive *P. vivax* (CSPV) infections is suppressed because the blood CQ plus desethylchloroquine (CQ + DCQ) levels remain above the minimal effective concentration (MEC) (~100 ng ml^{-1}). CQ-resistant *P. vivax* (CRPV) infections rapidly develop recurrent (in some cases persistent) parasitemia in the face of ordinarily effective CQ + DCQ levels. Recurrence of parasitemia within one month after treatment is due to either a recrudescence (persisting blood stages) or a relapse (persisting liver stages) of a CRPV infection.

In areas where resistance to CQ occurs, it is difficult to distinguish recrudescence from relapse after CQ and/or PQ treatment. Therefore, we recommend supervised treatment with quinine and PQ to minimize uncertainties surrounding the curative efficacy of PQ. There is much data to support the supposition that quinine therapy completely eliminates the blood stages of *P. vivax* [54]: no recrudescence occurred among volunteers challenged with blood stages and treated with quinine. Quinine is excreted far more rapidly than CQ, and MECs of quinine persist for less than one day after treatment. Therefore, a recurrence of parasitemia following adequate compliance with quinine plus PQ therapy would almost certainly represent a relapse and thus failed PQ therapy.

Interactions between blood schizonticides and PQ in eliminating liver stages could confound the interpretation of outcomes of PQ therapy. A series of experimental challenge studies [27,32] demonstrated apparent synergy between blood schizonticides, such as CQ or quinine with PQ, in preventing relapse. Whereas CQ and quinine alone exert no discernible effect upon the ability of hypnozoites to cause relapse [54], these drugs profoundly improved the performance of PQ in doing so [27,32]. When PQ was not administered concurrently with CQ or quinine, it performed very poorly. We are not aware of any hypothesis explaining this phenomenon. The apparently impaired efficacy of PQ as monotherapy against hypnozoites is neither widely cited nor recognized. Administering PQ concurrently with CQ or quinine might help ensure that anti-relapse therapy is not impaired, as illustrated in Fig. 3.

Novel PQ treatment regimens

The resurgence of vivax malaria in many parts of the world emphasizes the importance of having a more effective cure for the disease. An inadequate attack on the hypnozoite reservoir of infection would almost certainly contribute to further deterioration of the malaria situation. Gauging the adequacy of widely applied regimens of PQ therapy thus constitutes an imperative in formulating rational interventions against endemic vivax malaria. The available data shed little light on this question in almost any area of the world. Relapse after PQ therapy is widely reported [35,36,55–59], but it is difficult to ascertain the primary determinant of therapeutic failure (i.e. poor patient compliance with the lengthy treatment regimens or the presence of PQ-tolerant or PQ-resistant parasites).

The operational necessity for evaluating PQ therapy in malaria control practice should be exploited to also evaluate novel new regimens of PQ that deliver higher doses over shorter periods. In the past, higher doses and shorter courses of treatment have not been evaluated because of the perception that PQ is often not well tolerated by the gastrointestinal tract. This perception could be due to the fact that little attention has been paid to the importance of taking the drug with food. The severe hemolytic reactions observed in some individuals with a G6PD deficiency also tempers efforts to evaluate alternative regimens using higher doses of PQ. That danger is real. Although most G6PD-deficient individuals experience only a mild and self-limiting hemolysis after taking PQ (even with as much as 30 mg daily taken over many weeks
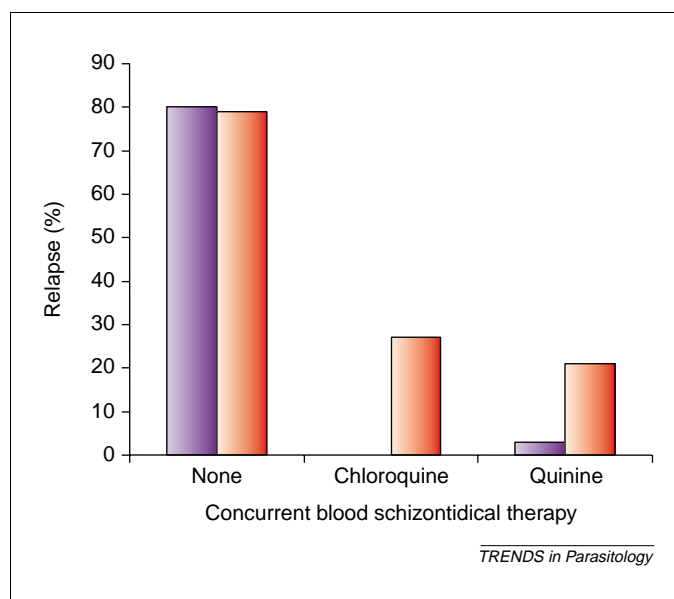
Fig. 3. Clinical data demonstrating the failure of primaquine when given without blood schizonticides. In a randomized study by Alving *et al.* [31], three groups of volunteers were bitten by batches of mosquitoes similarly infected with the Chesson strain of *Plasmodium vivax*. After developing malaria, the volunteers were treated with a total dose of 210 mg of primaquine (PQ) base. One group received a course of quinine treatment before PQ therapy, whereas the other two groups each received concurrent quinine or chloroquine (CQ) therapy (started on same day as PQ). Without concurrent quinine or CQ, relapse after standard PQ therapy (210 mg total dose) was 79% (red bars). When the total dose of PQ was increased to 315 mg by Edgecomb *et al.* [27] (purple bars), the therapeutic performance improved dramatically when the drug was administered with quinine (97% efficacy, *n* = 31), but 80% of subjects relapsed without concurrent quinine during the follow-up period of a year after treatment.

[31]), among the rare G6PD variants, the reaction to PQ (and other drugs) can be life threatening. Development of a point-of-care G6PD deficiency diagnostic test, especially one that identifies those at risk of severe hemolysis, would constitute a tremendous advance that will markedly improve the use of PQ as a tool against the broadening encroachment of vivax malaria.

Ideally, PQ would be replaced by a drug that is well tolerated, safe without special diagnostics, and easily administered over a brief period. The US Army and GlaxoSmithKline have a PQ analog named Tafenoquine™ in Phase III clinical trials. This drug shows promise in addressing some of the pitfalls of PQ therapy, but it is not yet available. In the meantime, PQ already rests on the shelves of most pharmacies and clinics in endemic areas of the world, and every effort should be made to use it effectively. When aiming for higher doses over shorter periods of time, toxicity and safety become paramount concerns that should be evaluated carefully in at least several ethnic groups.

Conclusions

PQ is widely available and affordable in the endemic developing world. It is the only available drug that can eliminate hypnozoites, an important latent reservoir of infection. However, the effectiveness of PQ in preventing relapses has not been assessed adequately because of practical difficulties associated with lengthy treatment courses and follow-up periods. Shorter regimens or higher doses, or both, could markedly improve the ease of

administration and efficacy of PQ. We recommend using quinine therapy when assessing the efficacy of PQ, with either standard or novel PQ regimens. Realizing the full potential of PQ in an endemic setting, however, would require a point-of-care diagnosis of G6PD deficiency. Evaluation of such drug regimens and supporting devices are urgently needed in a variety of ethnic groups to effectively attack an expanding reservoir of infection and encroaching endemic risk.

References

1 Mendis, K. *et al.* (2001) The neglected burden of *Plasmodium vivax* malaria. *Am. J. Trop. Med. Hyg.* 64 (Suppl 1), 97–106
2 Sharma, V.P. (1999) Current scenario of malaria in India. *Parassitologia* 41, 349–353
3 Chai, J.Y. (1999) Re-emerging *Plasmodium vivax* in the Republic of Korea. *Korean J. Parasitol.* 37, 129–143
4 Roper, M.H. *et al.* (2000) The epidemiology of malaria in an epidemic area of the Peruvian Amazon. *Am. J. Trop. Med. Hyg.* 62, 247–256
5 Barcus, M.J. *et al.* (2002) Epidemic malaria in the Menoreh Hills of Central Java. *Am. J. Trop. Med. Hyg.* 66, 2877–2892
6 Sleigh, A.C. *et al.* (1998) Resurgence of vivax malaria in Henan Province, China. *Bull. WHO* 76, 265–270
7 de Zulueta, J. (1987) Changes in the geographical distribution of malaria throughout history. *Parasitologia* 29, 1937–2005
8 Garnham, P.C. (1988) Hypnozoites and relapses in *Plasmodium vivax* and in vivax-like malaria. *Trop. Geogr. Med.* 40, 187–195
9 Cogswell, F.B. (1992) The hypnozoites and relapse in primate malaria. *Clin. Microbiol. Rev.* 5, 26–35
10 Sweeney, A.W. (2000) Wartime research on malaria chemotherapy. *Parassitologia* 42, 337–345
11 Greenwood, D. (1995) Conflicts of interest: the genesis of synthetic antimalarial agents in peace and war. *J. Antimicrob. Chemother.* 36, 857–872
12 Carson, P.E. (1984) 8-Aminoquinolines. In *Antimalarial Drugs II* (Peters, W. and Richards, W.H.G., eds) pp. 121–837, Springer-Verlag
13 Pukrittayakamee, S. *et al.* (1994) Blood stage antimalarial efficacy of primaquine in *Plasmodium vivax* malaria. *J. Infect. Dis.* 169, 932–935
14 Baird, J.K. *et al.* (1995) Treatment of chloroquine-resistant *Plasmodium vivax* with chloroquine and primaquine or halofantrine. *J. Infect. Dis.* 171, 1678–1682
15 Wilairatana, P. *et al.* (1999) Efficacy of primaquine regimens for primaquine-resistant *Plasmodium vivax* in Thailand. *Am. J. Trop. Med. Hyg.* 61, 973–977
16 Arnold, J. *et al.* (1955) The antimalarial action of primaquine against the blood and tissue stages of falciparum malaria. *J. Lab. Clin. Med.* 46, 391–397
17 Basco, L.K. *et al.* (1999) *In vitro* activity of primaquine against the asexual blood stages of Plasmodium falciparum. *Ann. Trop. Med. Parasitol.* 93, 179–182
18 Baird, J.K. *et al.* (2002) Therapeutic efficacy of chloroquine combined with primaquine against *Plasmodium falciparum* in Northeastern Papua, Indonesia. *Am. J. Trop. Med. Hyg.* 66, 6597–6660
19 Brueckner, R. (2001) 8-Aminoquinolines. In *Antimalarial Chemotherapy: Mechanisms of Action, Resistance and New Directions in Drug Discovery* (Rosenthal, P.J., ed.), pp. 151–1237, Humana Press
20 Warhurst, D.C. (1984) Why are primaquine and other 8-aminoquinolines particularly effective against the mature gametocytes and the hypnozoites of malaria? *Ann. Trop. Med. Parasitol.* 78, 165
21 World Health Organization, (2001) *The Use of Antimalarial Drugs: Report of an Informal Consultation*, WHO/CDS/RBM/2001.33, Geneva. pp. 141
22 Fryauff, D.J. *et al.* (1995) Randomized, placebo-controlled trial of

primaquine for prophylaxis of falciparum and vivax malaria in Indonesia. *Lancet* 346, 1190–1193

23 Weiss, W.J. *et al.* (1995) Daily primaquine is effective for prophylaxis against falciparum malaria in Kenya: Comparison with mefloquine, doxycycline, and chloroquine plus proguanil. *J. Infect. Dis.* 171, 1569–1575

24 Soto, J. *et al.* (1998) Primaquine prophylaxis against malaria in nonimmune Colombian soldiers: efficacy and toxicity. *Ann. Intern. Med.* 129, 241–244

25 Schwartz, E. and Regev-Yochay, G. (1999) Primaquine as prophylaxis for malaria in nonimmune travelers: a comparison with mefloquine and doxycycline. *Clin. Infect. Dis.* 29, 1502–1506

26 Baird, J.K. *et al.* (2001) Randomized, parallel placebo-controlled trial of primaquine for malaria prophylaxis in Papua, Indonesia. *Clin. Infect. Dis.* 33, 1907–1997

27 Edgcomb, J.H. *et al.* (1950) Primaquine, SN 13272, a new curative agent in vivax malaria: a preliminary report. *J. Natl. Malaria Soc.* 9, 285–292

28 Alving, A.S. *et al.* (1953) Korean vivax malaria. II. Curative treatment with pamaquine and primaquine. *Am. J. Trop. Med. Hyg.* 6, 970–976

29 Coatney, G.R. *et al.* (1953) Korean vivax malaria V. Cure of the infection by primaquine administered during long-term latency. *Am. J. Trop. Med. Hyg.* 6, 985–988

30 Ehrman, F.C. *et al.* (1945) *Plasmodium vivax* Chesson strain. *Science* 101, 377

31 Alving, A.S. *et al.* (1960) Mitigation of the hemolytic effect of primaquine and enhancement of its action against exoerythrocytic forms of the Chesson strain of *Plasmodium vivax* by intermittent regimens of drug administration. *Bull. WHO* 22, 621–631

32 Alving, A.S. *et al.* (1955) Potentiation of the curative action of primaquine in vivax malaria by quinine and chloroquine. *J. Lab. Clin. Med.* 46, 301–306

33 Collins, W.E. and Jeffery, G.M. (1996) PQ resistance in *Plasmodium vivax*. *Am. J. Trop. Med. Hyg.* 55, 243–249

34 Bunnag, D. *et al.* (1994) High dose primaquine in primaquine resistant vivax malaria. *Trans. R. Soc. Trop. Med. Hyg.* 88, 2187–2219

35 Doherty, J.F. *et al.* (1997) Treatment of *Plasmodium vivax* malaria – time for a change? *Trans. R. Soc. Trop. Med. Hyg.* 91, 76

36 Luzzi, G.A. *et al.* (1992) Treatment of primaquine-resistant *Plasmodium vivax* malaria. *Lancet* 340, 310

37 Clyde, D.F. *et al.* (1981) Clinical problems associated with the use of primaquine as a tissue schizonticidal and gametocytocidal drug. *Bull. WHO* 59, 391–395

38 Martelo, O.J. *et al.* (1969) Malaria in American soldiers. *Arch. Intern. Med.* 123, 383–387

39 Fisher, G.U. *et al.* (1970) Malaria in soldiers returning from Vietnam. Epidemiologic, therapeutic and clinical studies. *Am. J. Trop. Med. Hyg.* 19, 27–39

40 Kaplan, M.H. and Bernstein, L.S. (1974) Improved therapy for Vietnam acquired vivax malaria. *Mil. Med.* 6, 4447–4448

41 Rowland, M. and Durrani, N. (1999) Randomized controlled trials of 5 and 147 days primaquine therapy against relapses of vivax malaria in an Afghan refugee settlement in Pakistan. *Trans. R. Soc. Trop. Med. Hyg.* 93, 641–643

42 Gogtay, N.J. *et al.* (1999) Efficacies of 5- and 14-day primaquine regimens in the prevention of relapses in *Plasmodium vivax* infections. *Ann. Trop. Med. Parasitol.* 93, 809–812

43 Schmidt, L.H. *et al.* (1977) Radical cure of infections with *Plasmodium cynomolgi*: A function of total 8-aminoquinoline dose. *Am. J. Trop. Med. Hyg.* 26, 1116–1128

44 Clyde, D.F. and McCarthy, V.E. (1977) Radical cure of Chesson strain vivax malaria in man by 7, not 14, days of treatment with primaquine. *Am. J. Trop. Med. Hyg.* 26, 562–563

45 Clayman, C.B. *et al.* (1952) Toxicity of primaquine in Caucasians. *J. Am. Med. Assoc.* 149, 1563–1568

46 Beutler, E. (1994) G6PD deficiency. *Blood* 84, 3613–3636

47 Rieckmann, K.H. *et al.* (1989) *Plasmodium vivax* resistant to chloroquine? *Lancet ii*, 1183–1184

48 Baird, J.K. *et al.* (1991) Resistance to chloroquine by *Plasmodium vivax* in Irian Jaya, Indonesia. *Am. J. Trop. Med. Hyg.* 44, 547–552

49 Murphy, G.S. *et al.* (1993) Vivax malaria resistant to treatment and prophylaxis with chloroquine. *Lancet* 341, 96–100

50 Than, M. *et al.* (1995) Development of resistance to chloroquine by *Plasmodium vivax* in Myanmar. *Trans. R. Soc. Trop. Med. Hyg.* 89, 307–308

51 Baird, J.K. *et al.* (1997) *In vivo* resistance to chloroquine by *Plasmodium vivax* and *Plasmodium falciparum* at Nabire, Irian Jaya, Indonesia. *Am. J. Trop. Med. Hyg.* 56, 627–631

52 Phillips, E.J. *et al.* (1996) Failure of combined chloroquine and high-dose primaquine therapy for *Plasmodium vivax* acquired in Guyana, South America. *Clin. Infect. Dis.* 23, 1171–1173

53 Alecrim, M.G. *et al.* (1999) *Plasmodium vivax* resistance to chloroquine and mefloquine in the Brazilian Amazon region. *Rev. Soc. Bras. Med. Trop.* 32, 67–68

54 Wiselogle, F.Y. (1945) *A Survey of Antimalarial Drugs: 1941–1945*, 2 vols. J.W. Edwards

55 Smoak, B.L. *et al.* (1997) *Plasmodium vivax* infections in U.S. Army troops: Failure of primaquine to prevent relapse in studies from Somalia. *Am. J. Trop. Med. Hyg.* 56, 231–234

56 Isaac-Renton, J.L. *et al.* (1983) Drug resistance in malaria: three cases and a review. *Can. Med. Assoc. J.* 129, 454–457

57 Henderson, A. *et al.* (1986) Polyresistant malaria in Ghurka soldiers returning from Papua New Guinea: Treatment and prevention. *J. R. Army Med. Corps* 132, 37–41

58 Rombo, L. *et al.* (1987) Seven patients with relapses of *Plasmodium vivax* or *P. ovale* despite primaquine treatment. *Trop. Med. Parasitol.* 38, 49–50

59 Arias, A.E. and Corredor, A. (1989) Low response of Colombian strains of *Plasmodium vivax* to classical antimalarial therapy. *Trop. Geogr. Med.* 40, 21–23

60 Baird, J.K. *et al.* (1997) Diagnosis of resistance to chloroquine by *Plasmodium vivax*: timing of recurrence and whole blood choroquine levels. *Am. J. Trop. Med. Hyg.* 56, 621–626