

Primaquine Resistant *Plasmodium Vivax* Malaria - A Therapeutic Challenge

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ABSTRACT

Although *P.vivax* infection has been referred to as "benign" malaria symptoms are frequently severe and debilitating leading to significant morbidity and economic losses especially in cases of relapsing illness. Standard treatment of *P.vivax* malaria includes chloroquine, followed by primaquine (PQ) terminal prophylaxis. Reports of true PQ failure and subsequent *P.vivax* relapse are unusual as most suspected cases are ascribed to poor patient adherence, recrudescence of a chloroquine-resistant strain or *P.vivax* reinfection. We report a case of *P.vivax* malaria relapse, after therapy with standard dose of chloroquine and PQ, and again on three occasions despite quinine and various regimens of PQ in a patient who contracted malaria from travelling to Brazil. We also explore treatment options for this serious therapeutic challenge.

CASE REPORT

A 34 year old man was admitted to hospital with a 4 day history of headache, myalgia, fever and profuse vomiting. He had been admitted to another hospital three months before with similar symptoms, after returning from a six weeks holiday in Brazil where he had travelled to the Amazon River basin. He was treated for *P.vivax* malaria then with chloroquine followed by two weeks of daily 15 mg PQ. He had taken Atovaquone-proguanil as malaria prophylaxis during his travel and completed the course two weeks after his return.

He was not on any regular medications and admitted to being compliant with his previous malaria treatment. On admission his temperature was 38.5 C, Pulse rate was 110 beats per minute and his blood pressure was 100/67 mmHg. Cardiovascular, respiratory, gastrointestinal and neurological examination was unremarkable. Blood tests showed a white cell count of 4.8 L^{-1} , haemoglobin of 13.4 g dL^{-1} and a platelet count of 107 L^{-1} . Renal and liver function tests were within normal limits. C-reactive protein was raised at 154 mg/L. Peripheral blood smears showed presence of scanty malarial parasites of several stages of development consistent with *P.vivax*. Glucose-6-Phosphate dehydrogenase screening test was normal. Blood cultures were negative and the chest X-ray did not reveal any abnormality.

He was initially commenced on intravenous Quinine 600mg 8 hourly because he appeared extremely unwell and as he was vomiting profusely. Quinine was also chosen to cover possible recrudescence of a chloroquine resistant strain of *P.vivax* although he had responded to chloroquine 3 months before. This was switched to oral Quinine 2 days later. Repeat blood films did not show any malaria parasites after the second day. He was discharged home on the fourth day and was advised to complete a total 7 days of Quinine and to start Primaquine 15mg daily for 4 weeks after.

He was readmitted to hospital 3 months after his discharge (6 months after his first episode) with symptoms of fever and vomiting. He denied any foreign travel since his first admission. Thin blood film again showed all stages of *P.vivax* parasites, with 1% parasitaemia. Malaria antigen test was positive for *P. vivax* and the PCR test was also only positive for *P.vivax*. He was commenced on intravenous Quinine again mainly due to severe vomiting. This was later changed to oral Quinine when his vomiting settled. Malaria parasites were undetectable on blood films after the fourth day. He was discharged home after he completed 7 days of Quinine, and was advised to take 45 mg Primaquine once weekly for 8 weeks. He was reviewed at the out patient clinic 4 weeks after his discharge and he reported feeling well and admitted to being strictly compliant with the treatment. Also repeat blood film was negative for malaria parasites at this stage.

He was readmitted to hospital once again 10 weeks after his discharge (8.5 months after his first episode) with similar symptoms. He had finished his Primaquine course 2 weeks before. Thin blood films showed early trophozoites of *P. vivax*, with a parasite load of 0.15%. A malaria antigen tests were again positive for *P. vivax* and PCR test only confirmed *P. vivax*. Immunoglobulin and complement tests were normal. He was again commenced on Quinine and the blood film was negative for malaria parasites after 2 days. He was discharged home, and this time advised to take 30 mg of Primaquine for 2 weeks after completing 7 days of Quinine.

He was reviewed at the out patient clinic for 12 months after his discharge and he did not have any further relapses of *P. vivax* malaria.

DISCUSSION

Malaria is an ancient disease that has influenced human evolution and history. It remains a major public health problem although it was initially discovered in 1897.¹ Of the four species of malaria that can infect humans, most experimental attention is directed toward *P. falciparum*. However, a second species of malaria, *P. vivax*, also has a major adverse impact on global health, accounting for up to 80 million cases annually. It is responsible for over 50% of malaria outside Africa, notably in Southeast Asia and Central and South America, and has a particularly strong impact on the Indian subcontinent.²

Unlike *P. falciparum* malaria, *P. vivax* causes relapses which derive from persistent liver stages (hypnozoites) of the parasite.³ The likelihood of relapse by *P. vivax*, and the duration between parasitaemia and relapse varies in relation to latitude and seasonal abundances of anophiline vectors. In the temperate regions, 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. Drugs used to treat *P. vivax* malaria such as chloroquine or quinine attack the blood stages of the parasite, but exert no known direct effect against the liver stages of the parasite. PQ is the only drug available for this purpose and its appropriate use may help prevent relapses. PQ was first synthesised in United States of America during the Pacific war (1941-1945) as part of a massive undertaking of antimalarial drug development.⁴

Unlike other anti-malarial 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 sterilises the sexual blood stages (gametocytes). A standard regimen also clears the blood of asexual trophozoites of *P. vivax*. Neither its complex metabolism nor mechanism of activity is fully understood. 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.⁴

Standard anti-relapse therapy is generally considered to be a single daily adult dose of 15 mg of PQ base for 14 days. This well tolerated regimen amounted from early experimental clinical studies showing that many strains of *P. vivax* are nearly completely susceptible to a total dose of 210mg PQ. It is important to point out that initially all the data showing that standard PQ therapy works well (>90% efficacy) is at least 40 years old. Even before food and drug administration approval of PQ in the United States of America, in 1951, PQ failure was documented in experimental cases of the Chesson (tropical) *P. vivax* strain. Additional reports soon followed, citing dosing differences as the likely reason for *P. vivax* relapse.⁵ A regimen containing 30 mg daily for 14 days is widely recommended for these cases, because infections acquired in south-east Asia and southwest pacific area show an efficacy of only about 80% to PQ therapy.^{4,6}

An alternative regimen for PQ tolerant infections is the intermittent, weekly administration of 45 mg PQ for eight weeks (360 mg total dose of PQ). This is based on early observations by Alving *et al.*⁷ Eight week regimen also appeared to be more effective than a daily dose of 15 mg against infections with a Chesson strain.⁴

Clinical studies have supported the view that the total dose of PQ, rather than schedule of dosing, determined the efficacy of treatment. A total dose of 360-420 mg PQ delivered over a period of 7 days, 14 days or 8 weeks prevented relapse of PQ tolerant Chesson strain of

P. vivax equally effectively.^{4,8} One of the major disadvantages of prolonged daily or weekly course of drug administration is patient compliance. Shorter regimens could improve compliance and higher doses could improve efficacy.

PQ causes acute intravascular haemolysis in people having a genetic deficiency of G6PD. Many dozens of variants of this abnormality occur in varying degrees of frequency among most human populations. In the absence of definitive evidence of either G6PD- normal status or documented tolerability in a given variant, PQ should not be administered.

Tolerability and safety of high dose PQ is an issue that needs to be considered. Clayman *et al*? gave a range of single dose of PQ to fasted volunteers. They reported abdominal distress in 5%, 10%, 35%, and 100% of subjects given 15mg, 30mg, 45mg or 90mg of PQ, respectively. The same report describes complete relief from these effects, even at the highest dose applied when PQ was administered with food. However further studies in various ethnic groups are needed to determine the tolerability and safety of such high doses administered over a short period.

PQ causes methemoglobinaemia in normal subjects given standard therapy. Methemoglobinaemia of <20% does not cause symptoms or signs in most people. Methemoglobinaemia in subjects given 30mg daily for 20 weeks or 52 weeks was no more pronounced than in subjects receiving 15mg daily for 14 days.^{10,11} PQ induced methemoglobinaemia thus appears mild and self limiting in most people. The impact of higher doses over shorter periods on methemoglobinemia has not been evaluated.

When high dose regimens of PQ fail suppressive doses of chloroquine, 300mg/week for several months to years could be considered to prevent relapses.⁵ Ideally an alternative to PQ should be found that is well tolerated, safe and easily administered over a brief period. A new synthetic analogue of PQ, originally called WR 238605, was developed by the Walter Reed Army Institute of Research. It is now known by the generic name tafenoquine.¹² Findings in the first human study with tafenoquine and preclinical studies reveal that the drug was superior to PQ in efficacy with lower toxicity and a longer half life.¹³

In summary most cases of *P. vivax* relapses are attributed to poor compliance, recrudescence of chloroquine resistant strains or reinfection of *P. vivax*. Our patient was compliant with his treatment; did not travel to a malaria region after his first episode of *P. vivax* infection, and therefore did not have any chance of re-infection; was not infected with a chloroquine resistant strain as evident by his response to chloroquine when it was used during the first attack and further relapses despite using quinine in subsequent attacks. He had three relapses despite using different PQ regimes as terminal prophylaxis. He was initially treated with a standard terminal prophylaxis regimen of primaquine (15mg/day for 14 days-total dose 210mg). He then received 15mg/day for 28 days (total dose 420mg), followed by 45mg/week for 8 weeks (total dose 360mg). However his relapses were only prevented after using 30mg of PQ over 14 days (total dose 420 mg). Thus it may be worthwhile considering the use of shorter regimens and higher doses of PQ for terminal prophylaxis as this could improve the ease of administration, compliance and efficacy of PQ. We recommend 30 mg PQ over 14 days as terminal prophylaxis for *P. vivax* malaria in keeping with a recent publication by David *et al*.¹³ Further studies are however needed to assess the safety and tolerability of using higher doses over a period shorter than 14 days. If high dose PQ regimens fail, long term chloroquine prophylaxis could be considered.

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