GLOBAL MALARIA PROGRAMME

World Health Organization

Policy brief on single-dose primaquine as a gametocytocide in *Plasmodium falciparum* malaria

January 2015

Contents

Background

Primaquine has been used since the early 1950s and is the most widespread 8-aminoquinoline antimalarial medicine. It has been used extensively in radical treatment of *Plasmodium vivax* and *P. ovale* malaria and as a single-dose gametocytocide in falciparum malaria. The main limitation to its use has been its haemolytic toxicity: 8-aminoquinoline antimalarial agents produce dose-dependent acute haemolytic anaemia (AHA) in individuals deficient in glucose-6-phosphate dehydrogenase (G6PD) in an inherited X-linked genetic disease. The prevalence of G6PD deficiency varies between 5% and 32.5% in malaria-endemic areas of Africa and Asia, and its geographical distribution overlaps with the distribution of malaria.

Use of primaquine as a gametocytocide has great potential for reducing the transmission of falciparum malaria in low-transmission settings and can therefore prevent the transmission of artemisinin-resistant falciparum malaria. In the 2010 edition of the *Guidelines for the treatment of malaria*, WHO recommended addition of primaquine at a dose of 0.75 mg base/kg (45 mg base adult maximal dose) to treatment regimens in programmes for reducing *P. falciparum* transmission, "provided the risks of haemolysis in G6PD deficient patients are considered". Population benefits of reducing malaria transmission by a gametocytocidal medicine can be achieved only if a very high proportion of infected individuals receive these medicines. As there is often uncertainty about the prevalence and severity of G6PD deficiency and testing for this condition at points of care is usually not available, fear of primaquine-induced AHA has limited implementation of this recommendation. The adoption by countries of single-dose primaquine as a *P. falciparum* gametocytocide is variable, and there is some variation in the doses recommended and their timing with regard to administration of artemisinin-based combination therapy (ACT).

WHO convened an Evidence Review Group in August 2012 to review the WHO policy on use of single-dose primaquine as a gametocytocide in *P. falciparum* malaria. The objectives of the meeting were to: review the evidence from both published literature and unpublished studies on the efficacy and safety of single-dose primaquine when used as a *P. falciparum* gametocytocide; to prepare draft responses to questions identified by the WHO Secretariat and the Malaria Policy Advisory Committee (MPAC) on use of primaquine; to formulate recommendations for a policy statement on use of primaquine as a single-dose gametocytocide given with ACT; and to identify gaps in knowledge and prioritize the research agenda.[1]

1. The full report of the Evidence Review Group on the safety and effectiveness of single-dose primaquine as a *P. falciparum* gametocytocide is available on the WHO Global Malaria Programme website at: http://www.who.int/malaria/mpac/sep2012/primaquine_single_dose_pf_erg_meeting_report_aug2012.pdf

In September 2012, the MPAC supported the findings of the review, and the Technical Expert Group on Malaria Chemotherapy adapted the recommendations for inclusion in the third edition of the WHO *Guidelines for the treatment of malaria*, as outlined in the subsequent section.

WHO recommendation

The review of evidence on the safety and effectiveness of primaquine as a gametocytocide for *P. falciparum* malaria indicated that a single dose of primaquine at 0.25 mg base/kg is both effective in blocking transmission and unlikely to cause serious toxicity in individuals with any of the G6PD-deficiency variants. Thus, WHO recommends:

> In low transmission areas, give a single dose of 0.25 mg/kg primaquine with ACT to patients with *P. falciparum* malaria (except pregnant women, infants aged < 6 months and breastfeeding women of infants aged < 6 months) to reduce transmission. Testing for G6PD deficiency is not required.

Population benefits of reducing malaria transmission with gametocytocidal medicines such as primaquine can be achieved only if a very high proportion of treated patients receive these medicines and if there is not a large transmission reservoir of asymptomatic parasite carriers. This strategy is therefore likely to be effective only in areas of low-intensity malaria transmission.

Considerations for implementation of the new recommendation

Administration

- A single dose of primaquine at 0.25 mg base/kg should be given to all patients with parasitologically confirmed *P. falciparum* malaria, except for pregnant women, women in the first 6 months of breastfeeding and children less than 6 months of age, because there are insufficient data on the safety of its use in these populations.
- The single dose of primaquine should be added on the first day of ACT administration.[2] No data are available on optimum timing, but public health considerations and practicalities favour directly observed therapy on the first day of ACT administration to ensure transmission blocking as early as possible during an infection as well as compliance with the single-dose treatment.
- Tolerability can be improved by taking primaquine with food.
- A medical history of haemolysis should be sought, and such individuals should be advised to monitor signs of severe AHA, such as dark urine (e.g. aided by a colour chart), and to seek medical advice if the urine becomes dark.

Risk for acute haemolytic anaemia (AHA) associated with a single dose of primaquine

- G6PD-normal individuals have a very low risk for severe adverse effects. Primaquine is well tolerated at doses up to 45 mg if taken with food.
- In G6PD-deficient individuals, the risk for AHA associated with a dose of 45 mg primaquine is 100%, although the severity of AHA varies and haemolysis is sub-clinical in the majority of cases. The severity of AHA depends on the dose of primaquine and the G6PD variant; the variation is greatest among heterozygous females, as they have a variable proportion of G6PD-deficient red cells in their blood. As the regimen of 15 mg/day for 14 days has been used extensively in radical cure and mass drug administration without G6PD screening, it is expected that a single

2. See Annex 1 for data on the dose–response relation of 8-aminoquinolines with the transmissibility of falciparum malaria.

15-mg adult dose (0.25 mg base/kg) of primaquine will not cause clinically significant haemolysis in G6PD-deficient individuals.

Need for testing for G6PD deficiency before single low-dose primaquine administration

- Clinically significant haemolysis is not expected to occur in either G6PD-normal or -deficient individuals given a single 15-mg adult dose (0.25 mg base/kg) of primaquine. Therefore, there is no need for systematic testing for G6PD deficiency before administering a single dose of 0.25 mg primaquine base per kg body weight.

Detection of primaquine-induced haemolysis in patients of unknown G6PD status in the field

- Patients and their caregivers should be informed about the risk for AHA, be instructed to monitor urine colour and to stop use of the medicine and seek medical advice if the urine becomes dark. Young children should be carefully monitored.
- Health workers should be trained, with the support of appropriate job-aids, to recognize symptoms and to determine when to refer patients for further assessment. The symptom checklist includes back pain, dark urine, jaundice, fever, dizziness and breathlessness.

Management of side-effects

- Stop administration of primaquine (if multiple doses are being given).
- Give oral hydration.
- Refer to an inpatient facility.
- Undertake a clinical assessment.
- Check haemoglobin or haematocrit.
- Check plasma or serum creatinine or urea (blood urea nitrogen) if possible.
- Give a blood transfusion, if needed, according to the following guidelines:
  - haemoglobin < 7 g/dL: transfuse
  - haemoglobin < 9 g/dL with concurrent haemolysis: transfuse
  - haemoglobin 7–9 g/dL or > 9 g/dL and no evidence of concurrent haemolysis: careful fluid management with monitoring of urine colour.

Expected benefits

- Primaquine, given to patients with confirmed falciparum malaria at a single dose of 0.25 mg/kg on the first day of the treatment with an ACT is effective in blocking the infectivity of gametocytes of *P. falciparum* to malaria vectors. In particular, areas threatened by artemisinin resistance and areas with elimination programmes are expected to benefit from this new recommendation.
- G6PD testing is not available in most malaria-endemic areas, and the unknown G6PD status of individuals has limited the use of primaquine as a gametocytocidal medicine for *P. falciparum* malaria. The new recommendation to administer a single low dose of primaquine, which is not expected to induce clinically significant haemolysis, should be implemented widely in order to reduce the transmission of falciparum malaria, including the spread of resistant strains.

Annex 1. Evidence to support the new WHO recommendation

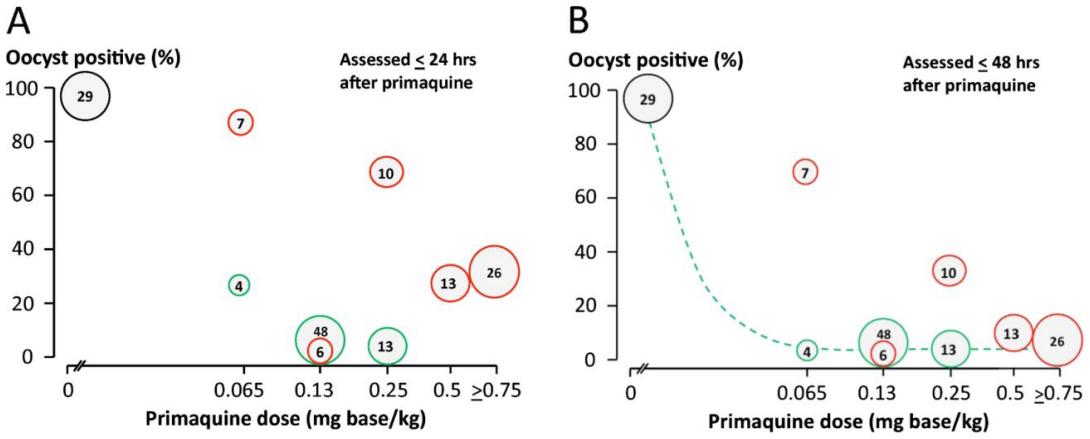
Transmission-blocking effect of primaquine. Of the currently available medicines, only the 8-aminoquinolines and methylene blue have been confirmed to reduce the transmissibility of mature *P. falciparum* gametocytes. Reduction in gametocytaemia has been used as a measure in trials of the effects of antimalarial drugs on transmission, but the relation between gametocyte density and transmissibility is non-linear, complex and affected by several covariates. Moreover, this relation varies substantially among individuals, as some patients may have high densities of young stage V gametocytes, which are not infectious. The reduction in transmissibility, assessed from oocyst numbers and morphology, and consequent sporozoite numbers significantly precede the effect on gametocyte densities. Thus, changes in gametocyte density result in underestimates and are a poor indicator of the transmission-blocking effects of 8-aminoquinoline antimalarial agents (*1*). Definitive assessment therefore requires direct evaluation of infectivity to mosquitoes.

Studies of the effects of 8-aminoquinoline antimalarial agents on the infectivity of *P. falciparum* to anopheline mosquitoes were first reported in 1929. Detailed information from published studies is available on 159 people assessed in different locations with different vectors and exposure to different 8-aminoquinoline drugs. The evidence includes one study in China (kindly provided by Professor Gao Qi) in which 78 individuals received different doses of primaquine and other antimalarial medicines, studies on 31 people who received plasmoquine[1] (before 1950) and 50 people who received primaquine (*2–8*). In these studies (reviewed by White et al. (*9*)), the infectivity to mosquitoes was assessed from oocyst counts and sporozoite rates in the malaria vectors fed to patients who had taken primaquine at different doses and combinations. Some studies also included evaluation of how well fed mosquitoes generated secondary infections in healthy volunteers (infectivity). These studies suggest that doses of 15 mg primaquine alone and 7.5 mg together with an ACT are effective transmission blocking regimens. As administration of 15 mg was not fully effective when given alone without an artemisinin derivative, more data are urgently needed in areas where artemisinin resistance is emerging.

Primaquine-transmission dose-response relation. Characterization of the dose–response or concentration–effect relation is a necessary prerequisite for dose optimization. Data from studies of the transmission-blocking effects of plasmoquine suggest that low doses (10–20 mg) have potent transmission-blocking activity.[2] The dose–response relations show that artemisinin derivatives potentiate the transmission-blocking effects of primaquine and that primaquine at doses as low as 0.125 mg base/kg (adult dose, 7.5 mg) when given with an artemisinin derivative still have near maximal transmission-blocking effects (see Figure 1 and Figure 2). These data support use of a single 0.25-mg base/kg dose as a gametocytocide, given in combination with an ACT.

1. Plasmoquine is the predecessor of primaquine. It was the first 8-aminoquinoline, developed in the mid-1920 for the treatment of malaria, which had gametocytocidal efficacy even at low doses.
2. Pooling of published data on primaquine with the results of unpublished studies conducted in China (kindly provided by Professor Gao Qi) resulted in data sets for 128 individual patients, 78 of whom received primaquine at doses between 3.7 and 15 mg base.

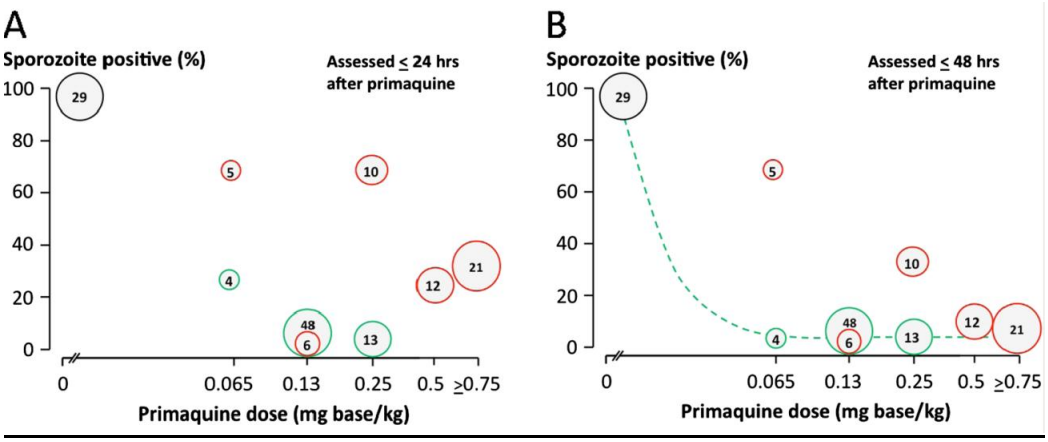
Figure 1. Dose–response relations for primaquine in reducing the infectivity of *P. falciparum*-infected individuals to anopheline mosquitoes



From reference (*9*)

The vertical axis shows the proportion of fed anopheline mosquitoes that were infected. Pooled data from all studies (*1*,*10*). Left: Oocyst formation (proportion of patients who were still infectious to mosquitoes) from blood sampled 24 hours after primaquine dose. Right: Oocyst formation from blood sampled 48 hours after primaquine dose. The groups given primaquine with an artemisinin derivative are shown in green, and those given primaquine with a non-artemisinin derivative or no antimalarial agent are shown in red. In these studies, 29 patients received no primaquine. The size of the circle is proportional to the number of people in each group (shown within).

Figure 2. Dose–response relations for primaquine in reducing infectivity to anopheline mosquitoes, as in Figure 1, with assessment of sporozoite formation



From reference (*9*)

Left: Sporozoite formation assessed from blood sampled 24 hours after primaquine dose. Right: Sporozoite formation assessed from blood sampled 48 hours after primaquine dose. The numbers are not the same as in Figure 1 because sporozoites were not assessed in all studies.

G6PD deficiency and the risk for AHA. The main concern about the safety of primaquine administration is the risk for AHA of G6PD-deficient individuals (reviewed by Beutler & Duparc (*11*)). G6PD-deficient individuals are uniquely vulnerable to oxidative stress, as their erythrocytes do not have alternative pathways for G6PD-dependent NADPH[3] production, and NADPH is essential to maintain their two main antioxidant defences: reduced glutathione and catalase. The severity of AHA depends on many factors, including the dose of primaquine; pre-existing or co-existing morbid conditions, particularly fever and pre-existing anaemia; age (severe AHA tends to be more life-threatening in children) and the G6PD-deficiency

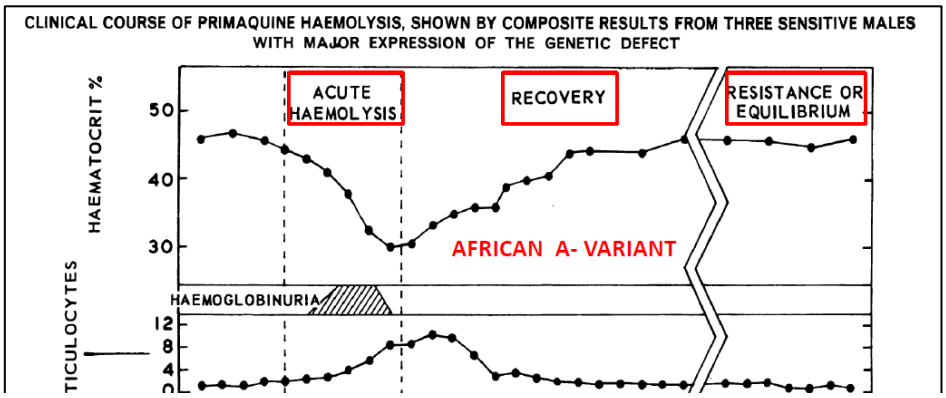
3. NADPH, reduced form of nicotinamide adenine dinucleotide phosphate

variant involved. G6PD variants arise from different mutations in the G6PD gene, which affect the stability of the enzyme in red blood cells. As the mutant enzymes undergo intra-erythrocytic decay more rapidly than the normal enzyme, older red cells are more vulnerable to oxidant haemolysis; however, specific variants of mutant enzymes undergo intra-erythrocytic decay more rapidly than other variants and, therefore, the extent of enzyme deficiency is more extreme with some than with others. With some variants, the G6PD enzyme is very unstable and only a minor proportion of young red blood cells retain residual G6PD activity. With other variants, the intra-erytrocytic decay is slower and newly produced erythrocytes have higher enzyme residual activity and are therefore more resistant to oxidant stress. This results in self-limiting AHA upon repeated daily administration of primaquine or another oxidant challenge. These considerations are relevant to the administration of primaquine at daily doses for 2 weeks as anti-relapse treatment of *P. vivax* but are not relevant to administration of a single primaquine dose as a gametocytocide in *P. falciparum*.

Characterization of haemolysis phases. Alving et al. in 1962 (*12*) reported haemolysis in healthy African–American people, probably with G6PD deficiency variant A-, who were given a course of 30 mg primaquine daily for a long period. As shown in Figure 3, the haematocrit usually started falling on the second day. Haemolysis can be divided into three phases:

- **Phase 1. Acute haemolysis:** an acute phase lasting 7–12 days, in which the haematocrit falls to its lowest and about 30% of the red cell mass is destroyed. The urine is dark, sometimes black, and the bilirubin level rises to 3–5 mg/dL (55–105 µmol/L). If primaquine is stopped during the acute phase, erythrocyte destruction ceases within 48–96 h.
- **Phase 2. Recovery:** even if primaquine is continued, a recovery phase occurs between days 10 and 40, in which reticulocytosis reaches a peak of 8–12%, and the haematocrit slowly returns to normal by the fourth or fifth week.
- **Phase 3. Equilibrium:** a phase in which haemolysis is balanced by increased erythrocyte production, which continues as long as primaquine is given.

Figure 3. Characterization of haemolysis phases in "primaquine-sensitive" (probably G6PD A-) healthy adults exposed to primaquine at 30 mg base daily over an extended period



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