



Commentary

Assessing Gametocyte Carriage in Treated Asymptomatic Falciparum Carriers in Africa



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In this issue of *EBioMedicine*, Okebe et al. have published a paper from The Gambia on the antigametocyte effects of three doses (0.2, 0.4 & 0.75 mg base/kg body weight) of single dose primaquine (PQ) combined with dihydroartemisinin piperazine (DHAPP) in asymptomatic carriers of *P. falciparum*, a key target group for malaria elimination (Okebe et al., 2016). They included individuals aged at least one year without symptoms or fever who: (i) were carriers of *Plasmodium falciparum* (detected by slide microscopy), (ii) did not have glucose-6-phosphate dehydrogenase deficiency as detected by the fluorescent spot test, and (iii) had haemoglobin (Hb) concentrations of ≥ 8 g/dL. DHAPP was dosed on study days (D) 0, 1 and 2 and PQ delayed ≥ 1 h after the last DHAPP dose. The primary end point was D7 gametocyte carriage, determined by quantitative nucleic acid sequence-based amplification of Pfs25 mRNA female gametocytes. Secondary end points included mosquito infectivity on D7, assessed by membrane feeding assays (MMFAs), and the decline in Hb concentrations.

This study is one of several studies from a consortium that are assessing/have assessed the antigametocyte efficacy and the transmission blocking effects of PQ. Like the study of Goncalves et al., Okebe et al. have included an assessment of mosquito infectivity in a subset (Goncalves et al., 2016).

This study showed that all PQ doses produced marked and similar declines in gametocyte carriage on D7 and D14 and that these declines were significantly greater than DHAPP alone. A chi-squared for trend was significant for a dose dependent effect on D7. The final sample size was insufficient to demonstrate non-inferiority of either the 0.2 or 0.4 mg/kg PQ arms vs. the 0.75 mg/kg dose (the dose first recommended by WHO) but this is not a limitation. The high efficacy of all three PQ doses suggests that the 0.2 mg/kg dose is already high on the PQ dose response curve for gametocytocidal effects.

Gametocyte carriage has been an efficacy end point in antimalarial drug studies but it is crucial to realise that gametocytaemia is a weak surrogate marker of mosquito infectivity. Gametocyte density has been shown to correlate with mosquito infectivity in untreated individuals in a non-linear relationship (Jeffery and Eyles, 1955) (Churcher et al., 2012). Post treatment, the relationship is more difficult to define (Beavogui et al., 2010) but Dicko et al. found no relationship following treatment with PQ combined with DHAPP (Dicko et al., 2016).

Okebe et al.'s study has reconfirmed the findings from Goncalves et al. that mosquito infectivity is low in individuals with low gametocytaemias who have been treated with an artemisinin based combination treatment (ACT) with or without PQ. Both studies used the same MMFA protocol but performing MMFAs is challenging. They require optimal conditions to maintain healthy mosquitoes, are less sensitive than direct mosquito feeding and measure infectivity at one time point. Moreover, the number of mosquitoes used by Okebe et al. was low, lower than that of Goncalves et al., and considerably lower than the numbers used by Dicko et al. Thus, they may have underestimated infectivity in all the treatment arms. One limitation is the lack of a baseline infectivity assessment so a treatment effect cannot be quantified.

The tolerability of these PQ doses, dosed at 48 h, in otherwise healthy, G6PD normal individuals with adequate Hb concentrations was, as expected, good. D3 was the day of the nadir Hb concentration and most of the declines in the D3 Hb concentrations would have been malaria related. The Hb dynamics between these asymptomatic individuals and patients with acute uncomplicated falciparum malaria overlap – a point that may not be widely appreciated.

Where do these results leave us regarding future research and policy?

Okebe et al.'s trial was not designed to assess PQ safety in G6PD deficient individuals. The main PQ related toxicity feared by policy makers in such individuals is acute haemolytic anaemia. However, safety data on single low dose (SLD) PQ dosed at 0.25 mg/kg in asymptomatic/well individuals are accumulating and are reassuring. In Thailand, mean Hb declines of $\sim 5\%$ and $\sim 1\%$ were seen in G6PD deficient and normal individuals, respectively, when SLDPQ was given with DHAPP as mass drug administration (Bancone et al., 2016). The SAFEPRIM I and II studies have been completed in Africa and are not yet published. The indications are that there are no safety signals but more work is needed to include anaemic children and adults.

The knowledge gap that demands an adequately powered trial is the safety of SLDPQ in children with acute uncomplicated malaria when

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dosed on D0 (PQ has been dosed at 48 h by the consortium studies). Such a trial, that has few exclusion criteria to maximise its generalisability, is planned for 2017 under the sponsorship of Oxford University.

Low infectivity was found in these low gametocytaemic, asymptomatic individuals on D7. The trial was not designed nor powered to answer the question whether PQ combined with DHAPP increases the anti-infectivity efficacy in such individuals nor do we know how infectious these individuals were at baseline. Goncalves et al. found appreciable pretreatment infectivity in their study but they recruited asymptomatic individuals with patent gametocytaemia.

To determine the optimal PQ dose in asymptomatic *P. falciparum* carriers, a large, dose-ranging trial would be needed with mosquito infectivity as the efficacy end point. Alternatively one could simply assess the WHO recommended SLDPQ dose of 0.25 mg/kg looking for an “added value” of PQ. It is very unlikely that PQ will achieve complete transmission blocking but if it achieves “high” efficacy and adds value over an ACT alone, it would be an attractive option for malaria elimination.

Disclosure

The author declared no conflicts of interest.

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