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Optimal Dose and Timing of Primaquine Administration for Falciparum Malaria Transmission Blockade

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Artemisinin combination therapy (ACT) is the first-line anti malarial treatment for falciparum malaria in many malaria endemic countries. Apart from action on asexual stage of falciparum malaria, artemisinin derivatives also kill young gametocytes and thereby reduce the number of mature infective gametocytes [1]. Since artemisinin derivatives have no effect to mature gametocytes, in 2010 WHO recommended to add a single dose primaquine (0.75 mg base/kg) to ACT for uncomplicated falciparum malaria as an antigametocyte drug, and therefore, substantially lowered the transmission risk [2]. Addition of primaquine to an ACT shortened estimated gametocyte circulation times from 4.6 and 5.0 days respectively, to 0.5 days [3,4]. Some countries use 30 mg (0.5 mgbase/kg) and the others use 45 mg (0.75 mg base/kg) adult dose of primaquine on either the first day or the last day of an ACT. In 2012, WHO recommended a single dose of 0.25 mg base/kg in blocking transmission and mentioned this dose was unlikely to cause serious toxicity in subjects with any glucose-6-phosphate dehydrogenase deficiency (G6PD) variant [5]. Therefore a single dose of 0.25 mg base/kg primaquine should be given to all patients (except for pregnant women and infants <1 year of age) with parasitologically confirmed *P. falciparum* malaria on the first day of treatment, in addition to an ACT, in (1) areas threatened by artemisininresistance where single doseprimaquine as a gametocytocide for *P. falciaprum* malaria is not being implemented and (2) elimination areas that have not yet adopted primaquine as a gametocytocide for *P. falciparum* malaria. Moreover WHO mentioned that a lower single dose of primaquine (0.25 mg base/kg) might be given without G6PD testing [5]. WHO also recommended the current policies of some countries where already use a 0.75 mg base/kg single dose of primaquine in the treatment of *P. falciparum* malaria could be continued until more information on the efficacy of the lower dose is available. Therefore the current issues of primaquine administration for blocking transmission of uncomplicated *P. falciparum* malaria are the optimal dose and the proper timing of primaquine administration.

Dose of primaquine: Relation of primaquine dose to hemolysis and G6PD activity should be characterized during acute malaria illness [6]. Primaquine doses added to ACT lower than 0.5-0.75 mg base/kg may provide sufficient blocking transmission and may be safer than the current WHO recommended doses. Recently Eziefula AC showed that 0.4 mg base/kg primaquine had similar gametocytocidal efficacy to the reference 0.75 mg base/kg primaquine dose, but a dose of 0.1 mg base/kg was inconclusive for non-inferiority and suggested further trials into the efficacy and safety of doses of primaquine between 0.1 mg base/kg and 0.4 mg base/kg (including the dose of 0.25 mg base/kg recently recommended by WHO in 2012) of the potential for widespread use of the drug to block falciparum malaria transmission [7].

Timing of primaquine administration: Primaquine is readily absorbed from gastrointestinal tract. Peak plasma concentrations occur around 1-2 hours after administration and then decline, with elimination half-life of 3-6 hours [2]. Primaquine used on the first day of ACT can kill mature gametocytes on the first day of treatment and may be more advantage than to give primaquine on day 3 of ACT or later since some patients after taking antimalarial drugs return to work in malaria endemic area on the first day of treatment and may have risk to transmit gametocytes to anopheles if primaquine is not given on the first day of ACT. However some doctors prefer to give primaquine on day 3 of ACT or later since many patients have nausea and vomiting on the first day and primaquine may cause increased gastrointestinal adverse effects if the patients have fever and nausea from acute malaria on the first day. Patients may better tolerate if primaquine is given on day 3 of ACT or later. Moreover many doctors do not give primaquine to the patients at all if the patient does not return to malaria endemic area since gametocytes will disintegrate few weeks later. Piyaphanee showed the longest interval between admission and the first appearance of gametocytes was 192 hours [8]. The median gametocyte clearance time was 163 hours (range 12-806 hours) in patients in whom gametocytemia resolved; however 9.8% of patients still had gametocytemia on day 28 of discharge without primaquine treatment. Gametocytemia was generally present within the first 24 hours of admission and emerged in only 1.9% of patients later after completed 2-3 days of ACT without primaquine treatment. Smithuis showed that after additional single dose primaquine (0.75 mg base/kg) given to falciparum malaria with ACT treatment, gametocyte clearance accelerated substantially after primaquine administration [9]. However, gametocytes were still found on days 7, 14, and 21 of treatment; therefore if those patients with gametocytemia returned to malaria endemic area, they could transmit gametocytes to anopheles. The latter study showed that single dose primaquine added to ACT might not be enough to completely kill gametocytes, particularly if mature gametocytes emerged after the first day of ACT and single dose primaquine treatment, eg. at 192 hours (or day 8) after starting of treatment. Adding more than single dose of primaquine, intermittent or continuous primaquine administration to ACT [10,11] for certain days may be needed to kill all or nearly all mature gametocytes to completely block falciparum malaria transmission but such information needs further studies.

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