A single dose of 45 mg primaquine is routinely given for *Plasmodium falciparum* malaria in endemic areas to reduce the risk of transmission. Primaquine markedly reduces circulating gametocytes and sterilizes those remaining [1]. Effective blood schizontocidal treatment may leave surviving gametocytes [2]. When slow-acting antimalarials are used, brief duration of primaquine gametocidal activity precedes elimination of trophozoites which may differentiate to gametocytes. A single 45-mg dose of primaquine adjunctive to therapy for *P. falciparum* infection may not completely block transmission [3].

WHO (2006) mentioned that artemisinin-combination therapies (ACT) reduce gametocyte carriage, and therefore reduce transmission. Artemisinin derivatives will act against only young gametocytes whereas primaquine acts on mature gametocytes which are present usually in the circulation at the time when the patient presents for treatment. Both artemisinin derivatives and primaquine have short half-lives, less than 1 hr and 7 hr, respectively. Therefore, asexual parasites or young gametocytes remain after completed ACT. A single dose of primaquine (0.50-0.75 mg base/kg) at the end of ACT can kill only mature gametocytes but cannot kill young gametocytes (if present). Remaining asexual forms after completion of ACT course, e.g., artesunate-mefloquine for 3 days, may develop to mature gametocytes 7-15 days later. Thus, an additional dose of primaquine (0.50-0.75 mg base/kg) given 2 weeks after ACT completion may be beneficial for killing remaining mature gametocytes and contribute to more interruption of *Plasmodium falciparum* transmission than giving only 1 single dose of primaquine just after completing ACT.

If the patients entered to endemic areas after completion of 3-day ACT course for uncomplicated malaria or after 5 days' intravenous artesunate treatment in severe malaria, some patients still have gametocytemia and could transmit gametocytes to mosquitoes. Piyaphanee et al. [6] studied emergence and clearance of uncomplicated *P. falciparum* malaria with different regimens of ACT (dihydroartemisinin plus mefloquine, dihydroartemisinin-piperaquine-trimethoprim, artesunate plus mefloquine, dihydroartemisinin-piperaquine) in either 2 or 3 days. Primaquine was not given. The study included the patients with and without gametocytemia on day 0 of admission [6]. On day 0, 72.5% of the patients had gametocytemia. On day 7 and 14, 10% and < 4% of the patients had gametocytemia. First appearance of parasitemia at 4, 4.5, and 8 days of admission was found in 0.8%, 0.4%, and 0.4% respectively [6]. Therefore, if those patients entered malaria endemic areas after completion of the
used microscopy for detection and quantification of gameto-
cytes, but it has been shown that patients without microscopically
detectable gametocytes can infect mosquitoes [8] and sub-
microscopic gametocytemia can be common [9]. Detailed quan-
titative studies on submicroscopic gametocytes are now pos-
possible with the recently developed gametocyte-specific \textit{Pfs25} quan-
titative nucleic acid sequence-based amplification (QT-NASBA)
which can detect gametocyte densities above 20 gametocytes
per ml of blood [10]. Schneider et al. [11] showed that the poten-
tial of \textit{P. falciparum} malaria transmission remains high even
after treatment with ACT, although the prevalence and density of
gametocytes is lower after artemisinin and sulfadoxine-pyrimi-
Thane treatment in Kenya patients. In their study, the game-
tocyte prevalence was 86% by a quantitative method compared
with 22% by microscopy [11]. Gametocytemia is detectable by
microscopy down to densities of approximately 10-20/\mu l. At
least 1 male gametocyte’s progeny (8 microgametes) and 1 fe-
\textit{male macrogametocyte are required in a mosquito blood meal
(approximately 2-3 \mu l) for infection to occur. Gametocyte densi-
\textit{ties of 1/\mu l can theoretically infect mosquitoes and this is below
the density which can be detected by routine microscopy [12].
Thus, gametocytemia after ACT treatment as in Tungpukdee
and Piyaphanee’s studies [5,6] were meaningful that gameto-
cytes might transmit after completed ACT without primaquine
treatment.

Merozoites emerging from a single schizont developed either
into further asexual stages or into gametocytes [13,14]. Gameto-
cytemia arises 7-15 days after the initial asexual wave [15]. This
maturation period has long been compared to that of the other
human malaria species \textit{falciparum} 1-3 days [16]. The ratio of gameto-
cytes to asexual stages in \textit{P. falciparum} is less than \textit{1:10; a recent
study showed a much lower ratio (1 : 156) [15]. The half-life of
mature gametocyte in the blood is generally reported to be 2.4
days [17]. However, mean circulation time of 6.4 days which is
about twice the expected 3.4 days deduced from a 2.4 half-life
was reported [15]. Some gametocytes have been found to have
the longevity of up to 4 weeks in blood circulation [18]. Field
and Shute [19] first described 5 different maturation stages of
\textit{P. falciparum} gametocytes which were further characterized by
light microscopy and later by electron microscopy [19]. Young
gametocytes may be sequestered in tissues and they take 8-10
days to become mature gametocytes in the peripheral circula-
tion which can be infective to mosquitoes for 10-14 days [4].
\textit{P. falciparum} differs from the other human malarias in 2 impor-
tant respects; first, the gametocyte formation is delayed with
respect to the peak production of asexual stages, and second,
mature gametocytes are resistant to most of the antimalarial drugs, which affect asexual stages [12].

In infections with *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale*, the asexual and sexual stages appear almost together, and in contrast to *P. falciparum*, they are sensitive to all drugs which kill the asexual stages [12,20]. Artemisinin is a sesquiterpene lactone peroxide. The derivatives of artesunate and artemether are hydrolyzed to the active metabolite dihydroartemisin (DHA) which has an elimination half-life of approximately 45 min. Artemisinin derivatives and to a far lesser extent, chloroquine will act against young gametocytes. Artemisinin derivatives greatly reduce young sequestered gametocytes and have “little” effects to mature circulating gametocytes and unknown sporontocidal effects of gametocytes to mosquitoes. They destroy immature gametocytes, preventing new infective gametocytes from entering the circulation, but their effects on mature gametocytes are less and so they will not affect the infectivity of those already present in the circulation at the time a patient presents for treatment.

Primaquine is an 8-aminoquinoline and has actions greatly against mature gametocytes of *P. falciparum* but has unknown gametocytocidal effects and sporontocidal effects to young sequestered gametocytes [4]. It is well absorbed and is cleared by hepatic transformation to more polar metabolite carboxy-primaquine with an elimination half-life of 7 hr. Primaquine is the only drug known to act on mature infective gametocytes in circulation and accelerates gametocyte clearance, as opposed to artemisinins which mainly inhibit gametocyte development. If a single 45-mg dose of primaquine is added to therapy for *P. falciparum* infection at the end of ACT, gametocytemia (if present) may be 2 possible outcomes:

1. After completion of ACT and the treatment outcome is cure and no asexual parasite or young gametocytes are found, primaquine will kill all mature gametocytes (if present) and the patient will have no gametocytemia in blood circulation later.

2. After completion of ACT some asexual parasites or young gametocytes may remain.

Regarding the short half-life of artemisinin derivatives, after ACT completion, there will be no remaining DHA in circulation to kill young gametocytes. A single dose of primaquine given at the end of ACT will kill only mature gametocytes but not young gametocytes (if present), and the patient will have mature gametocytemia in blood circulation 7-15 days later (from young gametocyte development). In this situation, if another 45-mg dose of primaquine is given 15 days or 2 weeks after ACT, primaquine will kill mature gametocytes which will develop 7-15 days later. In the patients with retreatment after primary treatment failure, double doses of 45 mg of primaquine may be given; the first dose just after completion of ACT and the second dose at 2 weeks later to ensure eradication of mature gametocytes.

In the future, if tafenoquine (slowly eliminated 8-aminoquinoline) can be used in the clinical practice, it can be given only once after asexual parasite treatment and it is not necessary to be followed by another dose 2 weeks later since tafenoquine has a terminal elimination half-life of 2 weeks. The drug is more efficacious than primaquine.

In conclusion, to interrupt transmission of falciparum malaria in the population in hypoendemic areas, at the end of a fully effective blood schizontocide ACT, primaquine 0.50-0.75 mg/kg (30-45 mg base maximal for adults) may be given twice; at the end of ACT and again 2 weeks later. At present, it is unknown whether the use of single or double doses of primaquine after ACT completion would result in a further suppression of infectivity. However, it appears possible in principle, since artemisinin derivatives and primaquine act on different stages of gametocytes. Further studies to prove this hypothesis are warranted. Adherence to the second primaquine dose, if used, needs good health services and good patients’ collaboration.

REFERENCES


