

MINI REVIEW

LONG TERM PRIMAQUINE ADMINISTRATION TO REDUCE *PLASMODIUM FALCIPARUM* GAMETOCYTE TRANSMISSION IN HYPOENDEMIC AREAS

Polrat Wilairatana^{1,3}, Noppadon Tangpukdee¹ and Srivicha Krudsood²

¹Department of Clinical Tropical Medicine, ²Department of Tropical Hygiene, ³WHO Collaborating Center for Clinical Management of Malaria, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Abstract. Artemisinin-combination therapies (ACTs) for falciparum malaria reduce gametocyte carriage, and therefore reduce transmission. Artemisinin derivatives act only against young gametocytes, but primaquine acts against mature gametocytes (which are usually present in the circulation at the time the patient presents for treatment). Both artemisinin derivatives and primaquine have short half-lives (less than 1 hour and 8 hours, respectively). Therefore, asexual parasites and young gametocytes may remain after completing ACT. Single dose of primaquine (0.5-0.75 mg base/kg) at the end of ACT can kill only mature gametocytes (if present) but cannot kill young gametocytes (if present). Remaining asexual forms and sequestered young gametocytes remaining after completion of ACT may develop into mature gametocytes 7-15 days later. Some patients have the first appearance of gametocytemia 4-8/day after completion of ACT. Thus, additional doses of primaquine (0.5-0.75 mg base/kg) given 15-18 days after or concurrently with 3 day-ACT respectively or given 15-22 days after or concurrently with 7 day-ACT respectively may be beneficial in killing the remaining mature gametocytes and thus contribute to interruption of *P. falciparum* gametocyte transmission more affectively than giving only a single dose of primaquine just after completing ACT.

Key words: *Plasmodium falciparum*, artemisinin-combination therapies, primaquine, malaria transmission blocking

INTRODUCTION

In 2010 the WHO recommended a single dose of primaquine (0.75 mg base/kg

Correspondence: Dr Polrat Wilairatana, Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, 420/6 Ratchawithi Road, Ratchathewi, Bangkok 10400, Thailand.

Tel: +66 (0) 2354 9159, Fax: +66 (0) 2354 9158

E-mail: tmpwl@mahidol.ac.th

or 45 mg base for a 60 kg adult) to artemisinin combination therapy (ACT) for uncomplicated falciparum malaria as an antigametocyte drug, particularly as a component of pre-elimination or an elimination program. Primaquine markedly reduces circulating gametocytes and sterilizes those remaining (Rieckmann *et al*, 1968). Effective blood schizontocide treatment may leave surviving gametocytes (Lawpoolsri *et al*, 2009). When slow-acting

antimalarials are used, a brief duration of primaquine gametocidal activity precedes elimination of trophozoites which may differentiate into gametocytes. Therefore, a single 45 mg dose of primaquine added as adjunctive therapy for *P. falciparum* infection may not completely block transmission (Baird and Hoffman, 2004).

GAMETOCYTE CLEARANCE AFTER ACT

Artemisinin-combination therapies (ACTs) reduce gametocyte carriage markedly, and therefore reduce transmission since artemisinin derivatives have an effect on young gametocytes (WHO, 2006). Tangpukdee *et al* (2008) studied gametocyte clearance after ACT in uncomplicated malaria and severe malaria. All patients had gametocytes on Day 0 of admission. Oral artesunate and mefloquine were used for 3 days to treat uncomplicated malaria patients and intravenous artesunate was used for 5 days followed by oral mefloquine to treat severe malaria patients. In this study primaquine was not administered. Forty-one point five percent, 13.1, 3.8, 2, and 2% of uncomplicated malaria patients had gametocytemia on Days 3, 7, 14, 21, and 28 after onset of treatment, respectively, and 8.2, 2.7, 0.9, and 0.9% of severe malaria patients had gametocytemia on Days 7, 14, 21, and 28 after onset of treatment, respectively. This study confirms artesunate did not kill all gametocytes by completion of the artesunate treatment course. After completion of 3-day oral ACT or 5-day intravenous ACT, the patient may still transmit malaria due to the presence of gametocytes. Piyaphanee *et al* (2006) studied emergence and clearance of gametocytes in uncomplicated *P. falciparum* malaria with different regimens of ACT (dihydroartemisinin plus mefloquine, dihydroartemisinin-pipera-

quine-trimethoprim, artesunate plus mefloquine, dihydroartemisinin-piperaquine) for 2 or 3 day regimens. Primaquine was not given in that study. The study included patients with and without gametocytemia on Day 0 of treatment. Seventy-two point five percent of the patients had gametocytemia on Day 0. On Days 7 and 14, 10% and <4% of patients still had gametocytemia. Parasitemia at 4, 4.5, and 8 days after admission was found in 0.8, 0.4, and 0.4% of the patients, respectively, after 2 or 3 day ACT regimens. The mean gametocyte clearance time (GCT) was 245.61 hours (~10 days) whereas the maximum (GCT) was 806 hours (~34 days). Therefore, if those patients were in areas with malaria vectors prior to clearance of gametocytes, there is risk of transmission of malaria.

Two studies (Piyaphanee *et al*, 2006; Tangpukdee *et al*, 2008) found primaquine to be beneficial after ACT treatment of uncomplicated falciparum malaria for eradication of gametocytes. If patients entered areas with malaria vectors before primaquine administration, there is a high chance of transmitting gametocytes, since gametocytemia between Day(s) 0 and 3 of ACT was high (98.3%) (Piyaphanee *et al*, 2006). The WHO (2006) recommended where ACT is not used, a single oral dose of primaquine of 0.75 mg base/kg (45 mg base maximal for adults) combined with a fully effective blood schizontocide may be used to reduce transmission if it is possible to achieve high coverage rates for the population infected with malaria. Gametocytemia is still present in some patients even after completion of ACT, therefore primaquine may be beneficial to give in those ACT treated patients. Primaquine and a transmission blocking agent after falciparum malaria treatment has been widely used in Southeast Asia

and South America. The National Antimalarial Drug Policy of Thailand has recommended for more than 10 years, to give primaquine 30 mg single dose after artesunate and mefloquine treatment for uncomplicated malaria regardless of the presence or absence of gametocytemia on blood smear as routine additional treatment after ACT completion. Primaquine at a dose of 30-45 mg has been shown to be very effective against gametocytes of *P. falciparum*. In children, primaquine 0.5-0.75 mg base/kg single dose may be used (Na-Bangchang *et al*, 1993). A single primaquine dose is well tolerated and prior testing for G6PD deficiency is not required (WHO, 2006).

GAMETOCYTEMIA AFTER ACT

Earlier studies addressed the effect of antimalarial drug treatment on gametocytes and most of these studies used microscopy for detection and quantification of gametocytes, but it has been shown that patients without microscopically detectable gametocytes can infect mosquitoes (Githeko *et al*, 1992) and submicroscopic gametocytemia is common (Nassir *et al*, 2005). Schneider *et al* (2006) showed the potential for *P. falciparum* malaria transmission remains high even after treatment with ACT, although the prevalence and density of gametocytes was lower after artesunate and sulfadoxine-pyrimethamine treatment in Kenyan patients. In that study gametocyte prevalence was 86% by quantitative evaluation versus 22% by microscopy. Gametocytemia is detectable by microscopy down to densities of approximately 10-20/ μ l. At least one male gametocyte progeny (eight microgametes) and one female macrogametocyte are required in a mosquito blood meal (approximately 2-3 μ l) for infection to occur. Gametocyte

densities of 1/ μ l can theoretically infect mosquitoes; this is below the density which can be detected by routine microscopy (White, 2008). Thus gametocytemia after ACT as seen in the studies by Piyaphanee *et al* (2006) and Tungpukdee *et al* (2008) is significant since gametocytes may be transmitted after completing ACT without primaquine.

YOUNG AND MATURE GAMETOCYTES

Merozoites emerging from a single schizont developed either into further asexual stages or into gametocytes (Talman *et al*, 2004a,b). Gametocytemia arises 7-15 days after the initial asexual wave (Eichner *et al*, 2001). This maturation period has long been compared to that of the other human malaria species (1-3 days) (Robert and Boudin, 2003). The half-life of mature gametocyte in the blood is generally reported to be 2.4 days (Sinden, 1983). However, a mean circulation time of 6.4 days, which is about twice the expected 3.4 days deduced from a 2.4 day half-life, has been reported (Eichner *et al*, 2001). Some gametocytes have been found to have a longevity of up to 4 weeks in blood circulation (Smalley and Sinden, 1977; Piyaphanee *et al*, 2006; Tungpukdee *et al*, 2008). Young gametocytes may sequester in tissue and take 8-10 days to become mature gametocytes in peripheral circulation, which can be infective to mosquitoes for 10-14 days (WHO, 2006). *P. falciparum* differs from the other human malarias in two important respects: first gametocyte formation is delayed with respect to the peak production of asexual stages, and second, mature gametocytes are resistant to most anti-malarial drugs which affect asexual stages (White, 2008). During infections with *P. vivax*, *P. malariae*, and *P. ovale*, the

asexual and sexual stages appear almost together; in contrast to *P. falciparum*, are sensitive to all drugs which kill asexual stages (Pukrittayakamee *et al*, 2008; White, 2008).

ARTEMISININ DERIVATIVES, PRIMAQUINE, AND GAMETOCYTES

Artemisinin derivatives are hydrolyzed to the active metabolite dihydroartemisinin (DHA), which has an elimination half-life of approximately 45 minutes. Artemisinin derivatives act against young gametocytes. Artemisinin derivatives greatly reduce young sequestered gametocytes but have "little" effect on mature circulating gametocytes and an unknown sporontocidal effect on gametocyte transmission to mosquitoes. DHA destroys immature gametocytes, preventing new infective gametocytes from entering the circulation, but its effect on mature gametocytes is less and 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 against mature gametocytes of *P. falciparum* but has an unknown gametocidal effect and sporontocidal effect on young sequestered gametocytes (WHO, 2006). It is well absorbed and is cleared by hepatic transformation into a more polar metabolite carboxyprimaquine with an elimination half-life of 8 hours (White, 2009). 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) have 3 possible outcomes:

1) After completion of ACT and the

treatment outcome is cure and no asexual parasites or young gametocytes are found, primaquine will kill all mature gametocytes (if present), the patient will have no mature gametocytemia later.

2) After completion of ACT, and some asexual parasites or young sequestered gametocytes (not seen on microscopy) remain, because of the short half-life of artemisinin derivatives, after ACT completion, there will be no remaining DHA in the circulation to kill young gametocytes. A single dose of primaquine given at the end of ACT will kill mature gametocytes but not young gametocytes (if present), the patient will have mature gametocytemia in the circulation 7-15 days later (from young gametocyte development).

3) A single dose primaquine after ACT completion will kill only mature gametocytes on the day of primaquine administration, *eg*, on Day 3 of the 3-day ACT regimen, but will not kill mature gametocytes that first appear after Day 3 of ACT (*ie*, gametocytemia will be found on Days 4, 4.5, 5 or 8, as was seen in Piyaphanee *et al* (2006) since primaquine has short half-life (8 hours).

POSSIBLE WAYS TO REDUCE GAMETOCYTE TRANSMISSION

In the above situations, a daily 45-mg dose of primaquine given for 15 days after ACT completion will kill mature gametocytes that remain after ACT completion and kill mature gametocytes that develop from young gametocytes 7-15 days later. However, if the patient has mild malaria symptoms and wants to go back to an area with malaria vectors while taking ACT, more additional daily doses of primaquine 45 mg base should be given for 3 days or 7 days (depending on the 3-day or 7-day

ACT regimen) “concurrently” with ACT to prevent gametocyte transmission). Therefore the patient may take a daily dose of 0.45 mg base primaquine for 15-18 days with the 3-day ACT regimen or for 15-22 days with the 7-day ACT regimen, if they enter an area with malaria vectors. To avoid gastrointestinal adverse effects of primaquine, the drug should be taken with food. Apart from either a single dose (WHO, 2010) or long primaquine administration another regimen to reduce gametocyte transmission in hypoendemic areas with multidrug-resistant falciparum malaria (eg, Thailand) is to give primaquine 30 mg weekly for 2-3 weeks (Na-Bangchang *et al*, 1993; Wilairatana *et al*, 2010).

A disadvantage of long administration of primaquine is the drug cannot be given to patients with G6PD deficiency. In mild-to-moderate G6PD deficient patients, a single dose of primaquine after ACT completion may be used.

CONCLUSION

To interrupt transmission of falciparum malaria in hypoendemic areas, at the end of a fully effective blood schizontocide with ACT, primaquine 0.5-0.75 mg/kg (30-45 mg base maximal for adults) may be given for 15-18 days or 15-22 days after 3-day ACT or 7 day-ACT regimens, respectively. Long term daily primaquine administration after ACT is more effective in killing gametocytes than a single dose of primaquine given after ACT completion. However, it is unknown whether long term primaquine administration after ACT would result in suppression of infectivity. It appears theoretically possible, since artemisinin derivatives and primaquine act on different stages of gametocytes. Further studies to evaluate this hypothesis are warranted. Primaquine adherence requires good health

service and patient collaboration since the drug has to be taken for many days.

ACKNOWLEDGEMENTS

The authors wish to thank the Faculty of Tropical Medicine, Mahidol University for their assistance with the printing cost.

REFERENCES

- Baird JK, Hoffman SL. Primaquine therapy for malaria. *Clin Infect Dis* 2004; 39: 1336-45.
- Eichner M, Diebner HH, Molineaux L, Collins WE, Jeffery GM, Dietz K. Genetics, sequestration and survival of *Plasmodium falciparum* gametocytes: parameter estimates from fitting a model to malaria therapy data. *Trans R Soc Trop Med Hyg* 2001; 95: 497-501.
- Lawpoolsri S, Klein EY, Singhasivanon P, *et al*. Optimally timing primaquine treatment to reduce *Plasmodium falciparum* transmission in low endemicity Thai-Myanmar border populations. *Malar J* 2009; 8: 159.
- Githeko AK, Brandling-Bennett AD, Beier M, Atieli F, Owaga M, Collins FH. The reservoir of *Plasmodium falciparum* malaria in a holoendemic area of western Kenya. *Trans R Soc Trop Med Hyg* 1992; 86: 355-8.
- Na-Bangchang K, Karbwang J. Clinical pharmacology of primaquine. In: Karbwang J, Wernsdorfer W, eds. *Clinical pharmacology of antimalarials*. 1st ed. Bangkok: Faculty of Tropical Medicine, Mahidol University, 1993: 316.
- Nassir E, Abdel-Muhsin AM, Suliaman S, *et al*. Impact of genetic complexity on longevity and gametocytogenesis of *Plasmodium falciparum* during the dry and transmission-free season of eastern Sudan. *Int J Parasitol* 2005; 35: 49-55.
- Piyaphanee W, Krudsood S, Tangpukdee N, *et al*. Emergence and clearance of gametocytes in uncomplicated *Plasmodium falciparum* malaria. *Am J Trop Med Hyg* 2006; 74: 432-5.

- Pukrittayakamee S, Imwong M, Stepniewska K, Day NPJ, White NJ. The effects of different antimalarial drugs on gametocyte carriage in *P. vivax* malaria. *Am J Trop Med Hyg* 2008; 79: 378-84.
- Rieckmann KH, McNamara JV, Frischer H, Stockert TA, Carson PE, Powell RD. Gametocidal and sporontocidal effects of primaquine and of sulfadoxine with pyrimethamine in a chloroquine-resistant strain of *Plasmodium falciparum*. *Bull World Health Organ* 1968; 38: 625-32.
- Robert V, Boudin C. Biologie de la transmission homme-moustique du *Plasmodium*. *Bull Soc Pathol Exot* 2003; 96: 6-20.
- Schneider P, Bousema T, Omar S, *et al.* (Sub)microscopic *Plasmodium falciparum* gametocytemia in Kenyan children after treatment with sulfadoxine-pyrimethamine monotherapy or in combination with artesunate. *Int J Parasitol* 2006; 36: 403-8.
- Talman AM, Domarle O, McKenzie FE, Arieu F, Robert V. Gametocytogenesis: the puberty of *Plasmodium falciparum*. *Malar J* 2004a; 3: 24.
- Talman AM, Paul RE, Sokhna CS, *et al.* Influence of chemotherapy on the *Plasmodium* gametocyte sex ratio of mice and humans. *Am J Trop Med Hyg* 2004b; 71: 739-44.
- Tangpukdee N, Krudsood S, Srivilairit S, *et al.* Gametocyte clearance in uncomplicated and severe *Plasmodium falciparum* malaria after artesunate-mefloquine treatment in Thailand. *Korean J Parasitol* 2008; 46: 65-70.
- Sinden RE. Sexual development of malaria parasite. *Adv Parasitol* 1983; 22: 153-216.
- Smalley ME, Sinden RE. *Plasmodium falciparum* gametocytes their longevity and infectivity. *Parasitology* 1977; 74: 1-8.
- White NJ. The role of anti-malarial drugs in eliminating malaria. *Malar J* 2008; 7 (suppl 1): S8.
- Wilairatana P, Krudsood S, Tangpukdee N. Appropriate time for primaquine treatment to reduce *Plasmodium falciparum* transmission in hypoendemic areas. *Korean J Parasitol* 2010; 48: 179-82.
- World Health Organization (WHO). Guidelines for the treatment of malaria. 1st ed. Geneva: WHO, 2006: 71, 133-43.
- World Health Organization (WHO). Guidelines for the treatment of malaria. 2nd ed. Geneva: WHO, 2010: xi.