

# Drug Combinations for the Treatment of Falciparum Malaria in Thailand

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## INTRODUCTION

Multidrug resistant falciparum malaria is a serious problem in Thailand and therapeutic failures to all existing antimalarials are well documented. New drug development takes years before the drug can be registered for use in man. Therefore studies of currently available drugs with appropriate rationales for use could be beneficial to combat this infection. Two measures have been advocated, modification in dosage (1,2) and the use of drug combinations (3,4).

## RATIONALE FOR DRUG COMBINATIONS IN MALARIA

Until recently when synthetic drugs have been available, a single component has been widely used for treating most infections. Monotherapy has been generally accepted because the dose can be easily controlled and drug interactions can be avoided. However, with the emergence of multidrug resistant falciparum malaria, the rationale for using a single compound warrants change. The mechanism of action of different drugs varies, and they can act in different biosynthetic pathways of the plasmodium parasite. Drug combinations can act as additively or in a synergistic way to kill the pathogen. They may also prevent the development of resistance. Some diseases, such as tuberculosis and leprosy, have been successfully treated with drug combinations. In the treatment of malaria, mixtures of active components have been used for centuries. In China

more than 2000 years, an oriental remedy extracted from Qinghao plant (*Artemisia anual* L.) has been used for treatment of chills and fever, presumed to be malaria infections (5). In South America more than 400 years ago, a mixture of cinchona alkaloid extracted from barks of cinchona tree (known as "Peruvian bark extract") was introduced for treating malaria symptoms. During the Second World War, a mixture of cinchona alkaloids was manufactured as a tablet (Totaquine<sup>R</sup>) containing mainly quinine, quinidine and cinchonidine, and used successfully in the treatment of malaria (6). With the deteriorating situation of multidrug resistant falciparum malaria in Thailand (7), attempts have been made to delay the resistance by the use of certain drug combinations. Some suitable combinations have proved effective *in vitro*, in animal malarias and in man.

### 1. Combination of para-aminobenzoic acid (PABA) antagonist and dihydrofolic acid reductase (DHFR) inhibitor together with other compounds.

The principle use of the two combinations are blocking the formation of nucleoproteins of the plasmodium at two different levels by inhibition of synthetase (PABA antagonists) and of reductase of dihydrofolic acid (DHFR inhibitors). PABA antagonists include sulfonamide and sulfone groups; one example of a DHFR inhibitor is pyrimethamine. Drug combinations in this group has been manufactured had marketed in a single tablet and used extensively in the treatment of malaria. Those commonly in use are Fansidar<sup>R</sup>

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(sulfadoxine + pyrimethamine), Metakelfin<sup>R</sup> (sulfalene + pyrimethamine) and Maloprim<sup>R</sup> (dapson + pyrimethamine). These drugs have been used successfully in the treatment of malaria, including chloroquine-resistant falciparum malaria (8). Over the years resistance has developed in many parts of the world. In some areas of Thailand, these drug combinations are now ineffective (9-11).

The demonstration that a combination of sulfadoxine-pyrimethamine and chloroquine delays the development of resistance to the individual compounds, in *Plasmodium berghei* infection in mice, can be explained by their synergistic effect. Peters (12) advocated the extensive use of chloroquine together with Fansidar<sup>R</sup> for chemoprophylaxis in areas where multidrug resistant falciparum malaria exists. Although this combination could not prevent drug resistance, it has some beneficial effect because of the additional protection against concomitant *P. vivax* infection. Another combination which was tested on an empirical basis in Thailand is sulfadoxine-pyrimethamine plus tetracycline. In the treatment of uncomplicated falciparum malaria, the cure rates in 1981-1982 for Fansidar<sup>R</sup> 3 tablets plus tetracycline 1 gm per day, for 7 days, in adult patients admitted in the Bangkok Hospital for Tropical Diseases was 75% (9) and patients treated in a field study was 82% while Fansidar<sup>R</sup> 3 tablets cured only 22% of patients admitted to the hospital in the same period. Unfortunately, with high level multidrug resistant falciparum malaria at the present time, the combination has limited use.

## 2. Combination of chloroquine or amodiaquine with antibiotics (tetracycline or erythromycin).

The use of antibiotic combinations in the treatment of malaria is derived from *in vitro* and animal malaria studies. Kaddu *et al*, (13) demonstrated that minocycline, a tetracycline derivative, has some action against both chloroquine-sensitive and chloroquine-resistant *P. berghei* in mice. Tetracycline alone is a weak antimalarial (14). However it has an additive effect when used with chloroquine. In the Bangkok Hospital for Tropical Diseases, the cure rate of chloroquine 1500 mg base given over 3 days was 0% in 1981 and it has not been used as a single drug for treatment since then. The cure rate increased to 75% in the same year when tetracycline 1 gm per day given for 7 days was added to the chloroquine (9). This combination gave even higher cure rate of 90%, in 1981, when used in the field. However, a

study in eastern Thailand in 1983 revealed that this combination appeared ineffective with clinical deterioration in 2 out of the first 5 studies patients who had RIII resistance (15).

Erythromycin has been known to have antiplasmodial activity since 1912 (16). It is active *in vitro* against both animal and human malarias (17-18). Erythromycin alone is not very effective against *P. berghei* infections in mice, but in combination with chloroquine it has a synergistic effect against chloroquine-resistant strains (16,19). The use of erythromycin with chloroquine was tested in the hope that this combination might prove effective against chloroquine-resistant strains of *P. falciparum*, particularly in children and pregnant women in whom tetracycline is contraindicated. However, a study in eastern Thailand in 1983 revealed that this combination produced only a 19% cure rate in uncomplicated malaria (15,20).

Amodiaquine was introduced into clinical use nearly 40 years ago. In recent years, resistance to the drug has developed in parallel to the distribution of chloroquine resistance. However, its cure rates improve when used together with tetracycline. In the Bangkok Hospital for Tropical Diseases in 1983, the combination of amodiaquine 1500 mg base given over 3 days, together with tetracycline 1 gm per day for 7 days, cured 86% of patients suffering from uncomplicated falciparum malaria (9). Another study in Central Thailand, in 1981, reported a cure rate of 96% (Noeypatimanond *et al*, 1983). The combination of amodiaquine and erythromycin has an additive effect *in vitro*, but in patients suffering from uncomplicated falciparum malaria this combination proved ineffective (22).

## 3. Combination of quinine and other compounds.

The total extracts of cinchona alkaloids have been used in the treatment of malaria for several centuries. The mixture, Totaquine<sup>R</sup>, containing varying proportions of each of the cinchona alkaloids has been used widely in many endemic regions (6). More recently individual alkaloids have been purified and a single active component is advocated. The first case of quinine resistance was reported from Brazil (23) where 25.5 gm base given over 21 days failed to cure the infection. Increased resistance has already appeared in Thailand and adjacent areas such as Kampuchea and Vietnam (24-25). In the Bangkok Hospital for Tropical Diseases in 1979, only 86% of patients treated with quinine for

7 days were completely cured (9). In an attempt to improve the cure rate, many combinations of quinine and other compounds were tested.

A combination of quinine, quinidine and cinchonine in equal ratio (1:1:1) has proved superior to quinine in treating *P. berghei* infection in mice, and it was 4 times more effective *in vitro* than the individual compounds. There was no evidence of cross resistance between the three components of the combination (26-28). The combination has proved to be at least as effective as quinine alone in one open and two double-blind trials in acute uncomplicated falciparum malaria (29-30).

In 1972, studies in Thailand showed that cure rates of short courses of quinine (1-3 days) were improved by adding tetracycline (3-10 days) (31-32). These findings could be explained by *in vitro* and pharmacokinetic studies. It has been shown that additive effects are obtained when tetracycline or erythromycin is added to quinine (19,33). Quinine levels were significantly higher in patients treated with quinine-tetracycline than those treated with quinine alone (34). Since 1980, quinine given for 7 days, combined with tetracycline 1 gm/day for 7 days, has become standard treatment in the hospitals for adults suffering from uncomplicated falciparum malaria in Thailand. This combination gave cure rates approaching 100% when it was first introduced (9,35). However, the combination has given a cure rate of only 90% in adult patients admitted to the Bangkok Hospital for Tropical Diseases in 1980-1991 (36). In one study in eastern Thailand, the most serious area for multidrug resistant falciparum malaria, a combination of quinine with erythromycin failed to improve the cure rate of quinine alone (20).

Sequential treatment of quinine with other antimalarials were also tested. In one study, quinine given for 2-3 days followed by mefloquine 1,000 mg, divided into two doses given 6 to 24 hours apart, cured all 35 patients (37). However, this sequential combination has not been widely accepted because of anxiety concerning the cardiotoxicity of the two drugs, which are both quinoline-methanols. Quinine 1,800 mg per day given for 7 days followed by sulfadoxine-pyrimethamine (Fansidar<sup>R</sup>) 3 tablets cured only 76% of adult patients admitted in the Bangkok Hospital for Tropical Diseases (9).

#### 4. Combination of mefloquine and other compounds.

Both *in vitro* studies and animal models of malaria have revealed that resistance develops rapidly to mefloquine

when used alone (38). The addition of sulfadoxine plus pyrimethamine to mefloquine delayed mefloquine resistance. In addition, it was demonstrated that the three components showed an additive effect (39). In an effort to delay development of resistance to mefloquine, the World Health Organization and Hoffman La Roche Co. advocated the combination of mefloquine and sulfadoxine-pyrimethamine (Fansimef<sup>R</sup>). This drug has been registered for use by this trade name in Thailand since 1984. In 1983-1986 a single dose of Fansimef<sup>R</sup> 3 tablets (contained a total of mefloquine 750 mg and sulfadoxine 1500 mg and pyrimethamine 75 mg) cured 98% adult patients admitted in the Bangkok Hospital for Tropical Diseases (40) and 98% adult patients in the western part of Thailand (41). The adding of sulfadoxine-pyrimethamine to mefloquine did not improve cure rate significantly. In 1987-1988, mefloquine 750 mg in combination with sulfadoxine 1500 mg and pyrimethamine 75 mg (Fansimef<sup>R</sup>) and mefloquine 750 mg alone (Larium<sup>R</sup>) were studied in a randomised trial in the western part of Thailand and the cure rates were 96% and 93% respectively (42). There were some doubts on the use of these combination in areas where sulfadoxine-pyrimethamine resistance had already become established. The risk and benefit of the combination was open to criticism. Above all the pharmacokinetic properties of the three components do not match ideally. It now seems reasonable to use mefloquine alone as a single component in areas where widespread resistance to sulfadoxine-pyrimethamine exists.

In 1985, Rahman and Warhurst demonstrated that an additive effect of mefloquine plus tetracycline was obtained on *P. falciparum* isolates studied *in vitro*. This information encouraged us to test the combination in the hope that it may increase cure rates. We have treated adults patients suffering from uncomplicated falciparum malaria with mefloquine 1,250 mg divided into 2 doses 6 hours apart, together with tetracycline 1 gm per day for 7 days, and compared it with a standard regimen of quinine-tetracycline for 7 days. The cure rate of mefloquine-tetracycline was as effective as quinine-tetracycline (94% vs 98% respectively) with very few side effects (43). A further study in 1992, using mefloquine 1,250 mg together with doxycycline 200 mg per day for 7 days, reported a cure rate of 96% (44). Therefore, the combination of mefloquine with either tetracycline or doxycycline is an alternative regimen for treating multidrug resistant falciparum malaria.

### 5. Combination of artemisinin derivatives and other compounds.

Artemisinin derivatives which are commonly used include artesunate and artemether. Artesunate, given orally or intravenously, and artemether intramuscular injection have been licensed in Thailand. Their action on killing parasites is rapid, with more than 90% parasitaemias cleared during the first 24 hours of administration. Unfortunately recrudescence rates are high, ranging from 10 to 100%, depending on doses and duration of treatment (45-47). Even with the recommended dose (600 mg total dose of artesunate given over 5 days), a cure rate of only 88% was obtained in a very recent study (3). To overcome such high recrudescence rates, sequential treatment with mefloquine, or combination with antibiotics such as tetracycline or doxycycline have been tried. In recent studies, the sequential treatment of artesunate (600 mg given over 5 days) followed by mefloquine (1,250 mg given in 2 doses 6 hours apart) gave 100% cure rates both in acute and recrudescing falciparum malaria (3,4). This sequential treatment is safe and is recommended for acute uncomplicated falciparum malaria and for those who fail with other regimens. The rationale for this sequential treatment is that artesunate clears the parasitaemia, whilst mefloquine prevents recrudescence, but it avoids the potential double toxicity of the two components. Because of the excellent results of the sequential treatment, a half-dose regimen (artesunate 300 mg given over two and a half days followed by 750 mg mefloquine) was tested subsequently and produced a cure rate of 90% (48). This is acceptable when compared to other commonly available drugs for treating acute uncomplicated falciparum malaria in Thailand. A randomised trial of short course therapy of artesunate followed by mefloquine in 2 days compared with a high dose of mefloquine (25 mg/kg divided into 2 doses 6 hours apart) revealed cure rates of 92% vs 74% respectively (49). Studies, both *in vitro* and in animal malaria, have demonstrated a synergistic effect with the combination of artemisinin and mefloquine (50-51); clinical trials using this combination are underway.

### 6. Combination of primaquine and others.

The rationale for use of primaquine in combination with other antimalarials is that it acts on a different stage of the parasites life cycle.

In falciparum malaria, a single dose of primaquine (30 mg base) is routinely prescribed with other anti-

malarials, for adult patients suffering from acute uncomplicated falciparum malaria, in Thailand. Primaquine is given on the first day of treatment, in order to prevent spread of the infection, because of its gametocytocidal action. Primaquine is also given on the first day of treatment when combined with blood schizontocides such as quinine-tetracycline, mefloquine or mefloquine-sulfadoxine-pyrimethamine. In addition, primaquine (30 mg base) is also given with sulfadoxine-pyrimethamine for presumptive treatment at malaria clinics in Thailand. In other countries such as in Malaysia and in Central America, primaquine, combined with amodiaquine or chloroquine, was used for mass drug administration against *P. falciparum* in semi-immune populations (52).

In vivax malaria, a 14 days course of primaquine 15 mg base per day together with chloroquine 1.5 gm base given over 3 days in adult patients, is routinely prescribed both at malaria clinics and in the hospitals in Thailand. The purpose of adding primaquine is to eliminate the trophozoites in liver so that relapse does not occur.

### SUMMARY

With the emergence of multidrug resistant falciparum malaria in Thailand, various drug combinations have been tested. Drug combinations for the treatment of adult patients suffering from uncomplicated falciparum malaria include quinine-tetracycline for 7 days, or sequential treatment of artesunate (600 mg given over 5 days) followed by mefloquine (1,250 mg divided into 2 doses 6 hours apart) are recommended. The sequential treatment is highly recommended for those who failed from other treatment regimens. Other combinations such as a short course sequential treatment of artesunate (300 mg given over 2.5 days) followed by a single dose of 750 mg mefloquine, or a combination of mefloquine 1,250 mg together with tetracycline 1 gm per day or doxycycline 200 mg per day for 7 days are alternative treatment regimens with acceptable cure rates. The simultaneous administration of artesunate and mefloquine, in various doses and duration of treatment, is currently being investigated. Until proven otherwise, the drug combinations are still recommended for all adult patients suffering from acute uncomplicated falciparum malaria contracted in multidrug resistant areas. In severe malaria and malaria in children, the drug combinations need further investigation.

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