



Combination Anti-malarial Therapy and WHO Recommendations

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Abstract

Malaria infection is a major global health problem causing at least 1 million deaths per year. *P. falciparum* parasite in many areas has developed resistance to antimalarial monotherapy. The use of antimalarial combinations will delay the onset and slow the rate of spread of resistance. WHO recommends that all countries experiencing resistance to conventional monotherapies, such as chloroquine, quinine, amodiaquine or sulfadoxine–pyrimethamine, should use combination therapies, preferably those containing artemisinin derivatives or artemisinin-based combination therapies. Other alternative combination therapies are artesunate plus tetracycline or doxycycline or clindamycin and quinine plus tetracycline or doxycycline or clindamycin.

Key words: Malaria, Combination therapy

Introduction

Malaria remains the most important parasitic infection of man. Each year, 300-500 million of the world's population are infected and 1-3 million people die from malaria infection. The development of drug resistance in both falciparum and vivax malaria, the two most important forms of human malaria, will further increase the already massive burden of morbidity and mortality from malaria (Figure 1, Pukrittayakamee & White, 2002; WHO, 2010)

Plasmodium falciparum parasite in many tropical countries has developed resistance to many major antimalarial drugs: chloroquine, sulfadoxine-pyrimethamin, quinine and mefloquine (Figure 2). The artemisinin derivatives have been used extensively in Vietnam and Thailand over the past few years and *P. falciparum* has recently shown reduced in vivo susceptibility to artesunate in western Cambodia as

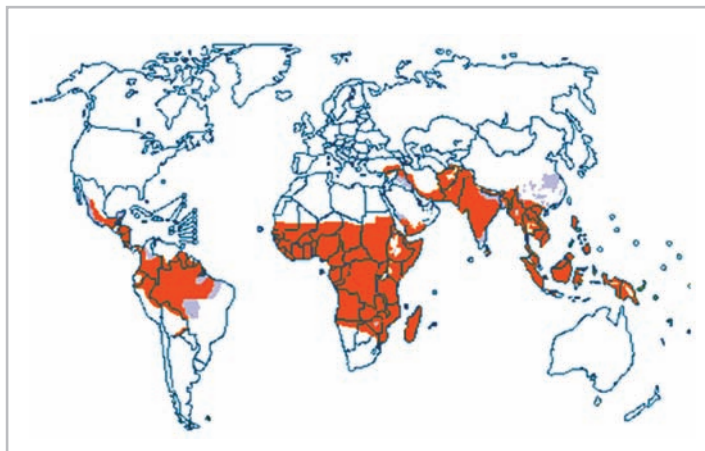


Figure 1 World Malaria Situation (WHO, 2009)

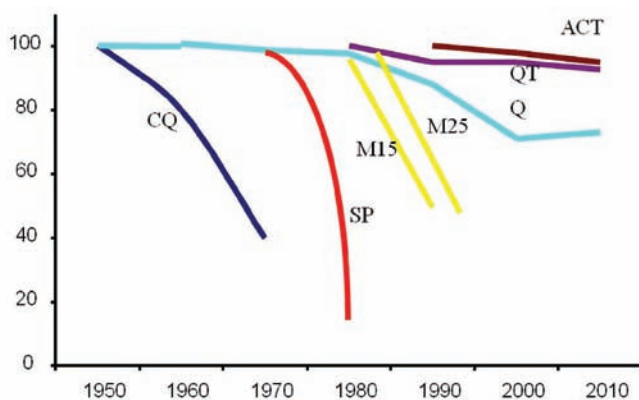


Figure 2 Cure rate of major antimalarial drugs for treatment of falciparum malaria. CQ = chloroquine, SP = sulfadoxine-pyrimetamine, M15 = mefloquine 15 mg/kg, M25 = mefloquine 25 mg/kg, Q = quinine, QT = quinine plus tetracycline, ACT = artemisinin base-combination therapy.



compared to northwestern Thailand (Dondorp et al, 2009). In the last decade *P. vivax* in Indonesia also developed resistance to chloroquine (the cheap and widely available antimalarial drug). High-level chloroquine resistance has been well documented on the northern part of the island of New Guinea and in Sumatra, and there have been sporadic reports from other geographic locations.

The use of antimalarial combinations will delay the onset and slow the rate of spread of resistance—especially when drug resistance mutant alleles are rare. The concept that resistance could be delayed or prevented by combining drugs with different targets was developed first in the treatment of tuberculosis. It has since been adopted widely for the treatment of cancer and HIV infection. Thus combinations will considerably delay the emergence of drug resistance. They also inhibit the spread and further increase of established low-grade resistance.

In the last two decades, there have been several clinical studies on various antimalarial drugs in combination for the treatment of chloroquine resistant falciparum malaria. The choice of combined drugs for uncomplicated falciparum malaria is usually an antimalarial-antibiotic or two antimalarials with short and long half lives. For adult patients, artemisinin-based combination therapy (ACT) and quinine-tetracycline are effective worldwide with > 90% cure rates (Figure 2).

Artemisinin-based combination therapy (ACT)

The artemisinin drugs have considerable advantages over other compounds for use in antimalarial combinations (Pukrittayakamee & White, 2002, WHO, 2010). They are very active and well tolerated, and they reduce parasite numbers more than the other antimalarials by approximately 10,000 fold per asexual cycle. Although there are some minor differences in oral absorption and bioavailability between the different artemisinin derivatives, there is no evidence that these differences are clinically significant in currently available formulations. It is the properties of the partner medicine that determine the efficacy and choice of combination. Resistance to the artemisinins' partner medicines compromises the efficacy of the ACT (Figure 3). The available ACTs already recommended for the treatment of uncomplicated falciparum malaria are artesunate plus mefloquine, artemether plus lumefantrine, artesunate plus amodiaquine and artesunate plus sulfadoxine-pyrimethamine. Other additions to the list of ACTs options for the treatment of uncomplicated falciparum malaria are dihydroartemisinin-piperaquine (Artekin) and pyronaridine-artesunate (Pyramax).

Artesunate plus mefloquine

Since mid-1994 mefloquine has been combined with a 3-day course of artesunate, and there has been no further decline in mefloquine sensitivity. More recently artemisinin and its derivatives in combination with mefloquine, have been very effective. They have accelerated recoveries, increased cure rates, reduced transmissibility and appear also to have delayed the further development of resistance and reduced the incidence of disease. Artesunate plus mefloquine is currently available as blister packs with separate scored tablets containing 50 mg of artesunate and 250 mg base of mefloquine, respectively. A fixed-dose formulation of artesunate and mefloquine is at an advanced stage of development. A target dose of 4 mg/kg/day artesunate given once a day for 3 days and 25 mg/kg of mefloquine either split over 2 days as 15 mg/kg or 10 mg/kg over 3 days, equivalent to 8.3 mg/kg/day once a day for 3 days.

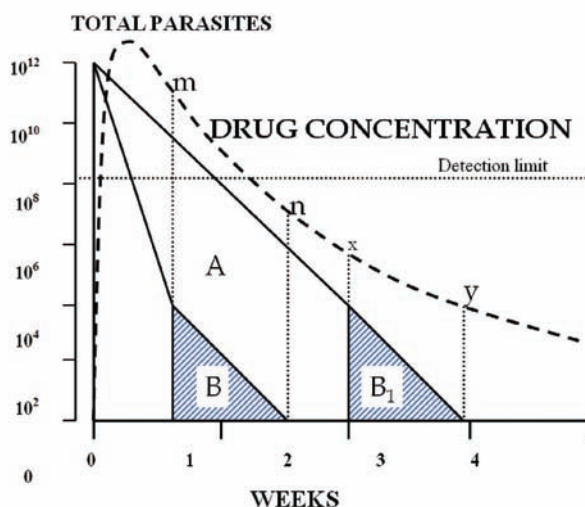


Figure 3 Combining an artemisinin derivative (in this case artesunate given for 3 days: shaded box at the top left of the panel) with mefloquine improves cure rates. This is because the parasites that remain after artesunate has been stopped are exposed to much higher concentrations of mefloquine (a to b on the mefloquine blood concentration profile) than the corresponding residium of viable parasites (shown as equivalent shaded areas under the parasite-time graphs) when mefloquine is used alone (c to d). Blood mefloquine levels are shown as a broken line. (adapted from Pukrittayakamee & White, 2002)



Artesunate plus amodiaquine

This is currently available as a fixed-dose formulation and blister packs of separate scored tablets containing 50 mg of artesunate and 153 mg base of amodiaquine, respectively. A target dose of 4 mg/kg/day artesunate and 10 mg/kg/day amodiaquine once a day for 3 days. This combination was sufficiently efficacious only where 28-day cure rates with amodiaquine monotherapy exceeded 80%.

Artemether plus lumefantrine

This is currently available as a fixed-dose formulation with dispersible or standard tablets containing 20 mg of artemether and 120 mg of lumefantrine. An advantage of this combination is that lumefantrine is not available as a monotherapy, and it has never been used by itself for the treatment of malaria. Lumefantrine absorption is enhanced by co-administration with fat. It is essential that patients or caregivers are informed of the need to take this ACT immediately after a meal or drink containing at least 1.2 g fat—particularly on the second and third days of treatment. The recommended treatment is a 6-dose regimen over a 3-day period. The adult dose is 4 tablets given twice a day for 3 days. This extrapolates to 1.7/12 mg/kg body weight of artemether and lumefantrine, respectively, per dose.

Dihydroartemisinin plus piperazine

Dihydroartemisinin plus piperazine is currently available as a fixed-dose combination with tablets containing 40 mg of dihydroartemisinin and 320 mg of piperazine. A target dose of 4 mg/kg/day dihydroartemisinin and 18 mg/kg/day piperazine once a day for 3 days, with a therapeutic dose range between 2–10 mg/kg/day dihydroartemisinin and 16–26 mg/kg/dose piperazine .

Artesunate plus tetracycline or doxycycline or clindamycin

Artesunate plus tetracycline or doxycycline or clindamycin are reserved for the very rare occasions of treatment failure with the recommended ACTs and in some special groups, e.g. pregnant women failing ACT treatment. The very recommended doses are artesunate (2 mg/kg once a day) plus tetracycline (4 mg/kg four times a day or doxycycline (3.5 mg/kg once a day) or clindamycin (10 mg/kg twice a day). Any of these combinations should be given for 7 days.

Quinine-tetracycline/Quinine-clindamycin

Quinine in combination with tetracycline has been widely used for nearly 20 years in multi-drug resistant areas. In Thailand, the cure rate of monotherapy with quinine given for 7 days was 100% in 1963. Since the 1970s there has been a decline in the susceptibility to quinine but this has been relatively slow (Figure 2). The addition of a tetracycline, most commonly, doxycycline, to quinine consistently improves the cure rates for falciparum malaria to over 90%. A limitation of this combination is that tetracycline cannot be used in children less than 8 years old or during pregnancy. Quinine-clindamycin has proved effective in adults and children with acute malaria in South America, Africa and in Thailand where the most drug-resistant *P. falciparum* strains are found (Pukrittayakamee et al, 2000, Figure 4). The regimen was well tolerated, and there were no adverse effects attributable to clindamycin.

WHO Recommendations on malaria treatment (WHO, 2010)

WHO Guidelines Development Group recommends that all countries experiencing resistance to conventional monotherapies, such as chloroquine, amodiaquine or sulfadoxine–pyrimethamine, should use combination therapies, preferably those containing artemisinin derivatives for falciparum malaria. The ACT

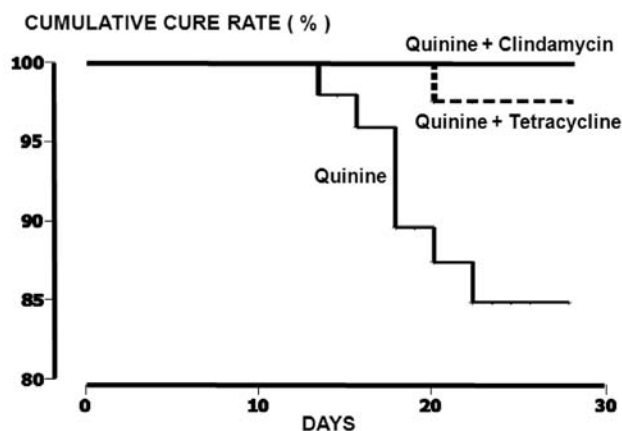


Figure 4 Cumulative cure rates for quinine and quinine in combination with tetracycline or clindamycin in patients with uncomplicated *P.falciparum* malaria. (adapted from Pukrittayakamee et al, 2000).



has the advantages of simplicity, and where available, a fixed-dose combination formulation improves compliance. Antimalarial treatments on the basis of the evidence from current practice and the consensus opinion regarding preference may use an alternative ACT known to be effective in the region e.g. artesunate plus tetracycline or doxycycline or clindamycin, quinine plus tetracycline or doxycycline or clindamycin .

References

- Dondorp AM, Nosten F, Yi P, Das D, Phyo AP, Tarning J, Lwin KM, Arieu F, Hanpithakpong W, Lee SJ, Ringwald P, Silamut K, Imwong M, Chotivanich K, Lim P, Herdman T, An SS, Yeung S, Singhasivanon P, Day NP, Lindegardh N, Socheat D, White NJ, 2009. Artemisinin resistance in *Plasmodium falciparum* malaria. *N Engl J Med*, 361: 455-467.
- Pukrittayakamee S, Chantra A, Vanijanonta S, Clemens R, Looareesuwan S, White NJ, 2000. Therapeutic responses to quinine and clindamycin in multidrug resistant *falciparum* malaria. *Antimicrob Agents Chemother*, 44: 2395-2398.
- Pukrittayakamee S, White NJ, 2002. Combination therapy: making the best use of existing drugs. *Pharmaceutical News*, 8: 21-25.
- WHO. Guidelines for the treatment of malaria, second edition. *WHO*, 2010