Artemisinin based combination therapy for malaria in Viet Nam
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General introduction

Malaria remains one of the most dangerous diseases with more than 300 million clinical cases worldwide and over 1 million deaths annually, 80 - 90% of these occurring in Africa. Apart from Africa, Asia is the region where malaria is a particular problem. Of the four species of human malaria, *Plasmodium falciparum* is the most dangerous one because of its potential to cause severe and complicated malaria leading to death. The battle against malaria is difficult for various reasons, in particular because of development of resistance to antimalarial drugs. Since the first reports of chloroquine resistance in the late 50's, early 60's of last century, *P. falciparum* has gradually developed resistance to almost all antimalarial agents such as amodiaquine, sulfadoxine-pyrimethamine, mefloquine, quinine (reduced sensitivity). So far the artemisinin drugs are an exception with universal sensitivity.

In several African countries chloroquine resistance led to a change in the first-line drug from chloroquine to sulfadoxine-pyrimethamine (SP). However, development of SP resistance threatens malaria control efforts of these countries. Meanwhile, in Asia, and particularly in Southeast Asian countries, multidrug resistant malaria has emerged and artemisinin and its derivatives have been used increasingly as the first-line drugs for falciparum malaria. With the spread of drug resistant malaria, especially after global eradication was considered not feasible, malarious countries needed new policies guided by WHO for malaria control, and as a result A Global Malaria Control Strategy was endorsed by the Ministerial Conference on Malaria Control in Amsterdam in 1992 and confirmed by the World Health Assembly in 1993. This strategy has four basic elements: early diagnosis and treatment; implementing selective and sustainable preventive measures, including vector control; to detect, contain, or prevent epidemics; and to strengthen local capacities in basic and applied research to permit and promote the regular assessment of a country’s malaria situation, in particular, the ecological, social and economic determinants of the disease. Applying this strategy resulted in documented success in malaria control of several countries, such as China, Viet Nam, Thailand, Brazil.

In Viet Nam, the malaria situation deteriorated during the 1980s and peaked in 1991 with a recorded incidence of 1.09 million clinical cases, 31.741 severe cases, 4646 deaths and 144 outbreaks. In 1992, with economic rehabilitation and increase in
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funding for malaria control, a new malaria control strategy based on the above four basic elements was implemented. Artemisinin and its derivatives were used as first-line drugs and offered free of charge by health services for malaria treatment, and insecticide treated bednets gradually became the main method for prevention. As a result, morbidity and mortality of malaria declined dramatically from year to year to a total recorded incidence of 293,000 clinical cases with 74,316 confirmed cases in 2000. Severe malaria decreased to 1,161 cases and mortality dropped to 148. The success of malaria control in Viet Nam was partly due to the use of artemisinin and its derivatives, drugs that play an important role in treating multidrug resistant malaria.

Artemisinin.

Artemisinin is a sesquiterpene lactone peroxide extracted from the herb Artemisia annua L., which had been used traditionally for treating fever since 2000 years in China. The actual antimalarial compound, artemisinin was isolated in 1971. Since then, artemisinin and its derivatives were further developed, tested, and marketed in China and in Viet Nam and they have proved to be very effective in the treatment of P. falciparum malaria. Artemisinin and its derivatives offer rapid clearance of parasite and fever, they can be used effectively in both uncomplicated and severe malaria with available forms for oral and parenteral use. They were first used as monotherapy in the treatment of uncomplicated P. falciparum malaria. But, because of their short half life (2.5h), duration of treatment usually takes 5 to 7 days to avoid recrudescences. Long treatment courses of uncomplicated malaria are generally supposed to lead to poor patient compliance because of the fact that patients will normally feel much better within a few days with disappearance of the fever. Thus there may be a tendency to keep the remaining drugs for another attack or for someone else in the household. So we studied the optimal duration of artemisinin monotherapy. In chapter 2, the result of a clinical trial comparing the efficacy of a 5-day course and a 7-days course of artemisinin monotherapy is presented.

Resistance to artemisinin derivatives has not been reported yet. Combination treatment of antimalarial drugs is nowadays advocated in order to reduce the emergence of drug resistance and its spread. Artemisinin, because of its short half life and quick and effective action, is an excellent candidate for combination treatment, in combination with drugs with longer half lifes. Along with other
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artemisinin derivatives, dihydroartemisinin has also been used in combination therapies, mainly with mefloquine, in the treatment of *Plasmodium falciparum* malaria and it was proved to be effective \(^{[14,16]}\). Recently, dihydroartemisinin has been used in a fixed combination with piperaquine, a bis-aminooquinoline that was first synthesised more than 30 years ago, and with trimethoprim and primaquine. This combination was developed by Chinese and Vietnamese scientists and was used in Viet Nam under the name CV8 and it was shown to be effective for treating *P. falciparum* infections in some preliminary trials \(^{[17,18]}\). After introduction in the malaria control programme in 2000 by The Vietnamese Ministry of Health (Decision 3952/QD-BYT of Minister of Health on 9 December 1999), CV8 has been used on a large scale as first line treatment of falciparum malaria in several regions in Viet Nam. Meanwhile, another fixed combination of atovaquone and proguanil (Malarone®) also proved to be very effective in treating *P.falciparum* malaria \(^{[19-21]}\). These two fixed combinations are relatively new and it seemed useful to evaluate their efficacy in treating malaria in Viet Nam. *The results of a randomised comparison between CV8® and Malarone® in the treatment of Plasmodium falciparum malaria in Viet Nam are presented in chapter 3.*

Malarone® has not been used to any extent in Asia because of the use of cheaper and effective combinations of artemisinin derivatives with mefloquine \(^{[15,22]}\). However, recrudescence after a low dose of mefloquine plus an artemisinin drug is common \(^{[16,23,24]}\). Treating recrudescent malaria cases with another drug, which is different from the initial drug to increase probability of success seems wise. Malarone®, as mentioned above, is an effective antimalarial drug for areas with multi-drug resistant malaria and it can also be an alternative for treatment of recrudescent multi-drug resistant *P. falciparum* malaria. *We studied Malarone® as an alternative for treating recrudescence of P. falciparum after primary treatment with a combination of artesunate and mefloquine, and the results are presented in chapter 4.*

Since the wide scale introduction of artemisinin drugs in malaria control in the 90's, morbidity attributable to *P. vivax* became more prominent because *P. falciparum*-infections gradually came under control in Southeast Asia \(^{[25,26]}\). Artemisinin derivatives were also effective in treating *P. vivax* malaria \(^{[27]}\), but they were never used widely for *P.vivax*-infection as *P. vivax* is considered sensitive to chloroquine and chloroquine is the first-line drug for treatment of *P. vivax* -infections
in most areas of the world \[^{28}\]. However, chloroquine-resistant *P. vivax* has recently been reported in Asia and South America \[^{29-31}\]. Thus alternatives for chloroquine will be needed. In Viet Nam, there has not been any report of chloroquine-resistant *P. vivax* so far and chloroquine is still the drug of choice for treating *P. vivax* malaria, but artemisinin derivatives were also used sometimes in practice despite no formal acceptance. Therefore, we carried out a study to compare efficacy of artemisinin to chloroquine in the treatment of *P. vivax* malaria, and by this to evaluate sensitivity to chloroquine of *P. vivax* in Viet Nam. The results are presented in chapter 5.

In the Global Malaria Control Strategy mentioned above and the programme of Roll Back Malaria launched later in 1998 (RBM), “early diagnosis and prompt treatment” (EDTM) was considered a key component in the control of malaria. But, despite playing such an important role, EDTM has no clear definition or standard on which evaluation of effectiveness for malaria control can be based. *In chapter 6, we present a study based on analysis of questionnaires from patients who presented at health units during the last decade to evaluate the influence of EDTM on malaria control in Viet Nam and by this to define the timing of “early”.*

*A review of pharmacokinetic interactions of antimalarial agents is presented in chapter 7. This discussion about interactions of antimalaria drugs in combinations is necessary because drugs used in combinations should not have adverse pharmacological interactions \[^{32}\]. Combination therapies are now increasingly used following recommendation of WHO to prevent the few remaining potent compounds from development of resistance while waiting for new antimalarial drugs \[^{3}\].*

**Study site**

The studies were conducted in Binh Thuan province, a 7992 sq. Km mountainous area located in the south of Viet Nam and 198 km north east of Ho Chi Minh City. The mountains lie from west to east and reach the beaches. The total population of Binh Thuan rose from 767,000 in 1989 to 1 096 700 in 2002 (population density 120 capita/km\(^2\)), of which approximately 75% lived in the rural areas. Binh Thuan is considered an endemic area of malaria. The annual rainfall ranges from 1000 to 1400 mm; the rainy season usually lasts from May to November. The annual average temperature is 27°C. Economic potentialities are: agriculture, marine resources, wood-processing industry. (data from Provincial Statistics Department and from http://encyclopedia.thefreedictionary.com)
Study objectives

1. To compare the efficacy of a 5-day course and a 7-day course of artemisinin monotherapy in the treatment of *P. falciparum* malaria.

2. To compare the efficacy of the combination dihydroartemisinin-piperquine-trimethoprim-primaquine (CV8®) to the combination atovaquone-proguanil (Malarone®) in the treatment of *P. falciparum* malaria in Viet Nam.

3. To evaluate atovaquone-proguanil (Malarone®) in the treatment of recrudescence of *P. falciparum* malaria after primary treatment with a combination of artesunate and mefloquine.

4. To compare the efficacy of artemisinin to chloroquine in the treatment of *P. vivax* malaria, and by this to evaluate sensitivity to chloroquine of *P. vivax* in Viet Nam.

5. To evaluate the contribution of early diagnosis and treatment in controlling malaria, and to define the timing of "early".

6. To review the pharmacokinetic interaction of antimalarial drugs in combination therapies.

References


Ref Type: Report


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