Artemisinin based combination therapy for malaria in Viet Nam
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SUMMARY

Drug resistant malaria is of great concern in malaria control worldwide. The history of antimalarial resistance shows that it was difficult indeed to control malaria because of the spread of multidrug resistant malaria. However, with tremendous efforts of man, encouraging success has been obtained in treating multidrug resistant malaria, especially since 1990s after introduction of artemisinin drugs and combination therapies. At the same time, the Global Malaria Control Strategy launched in 1992, contributed to the control of malaria via other components like bednets.

This thesis is based on studies on uncomplicated malaria in south Vietnam and reviews discussing about it.

The objectives of study were:

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

3. To evaluate atovaquone-proguanil (Malarone®) in the treatment of recrudescence of *Plasmodium 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 *Plasmodium vivax* malaria, and by this to evaluate sensitivity to chloroquine of *Plasmodium 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.

Chapter 1 is a general introduction of this thesis.

Chapter 2 presents results of a clinical trial of artemisinin monotherapy of different duration--5 days (A5) versus 7 days (A7)--in the treatment of uncomplicated falciparum malaria.

After being rediscovered, artemisinin and its derivatives have become mainstay in the treatment of *Plasmodium falciparum* infection in Southeast Asia because they can lead to
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rapid clinical recovery and clearance of parasites. However, because of short half-life, artemisinin monotherapy course usually lasts from 5 to 7 days. But, the longer the therapy course is, the more difficult the patient’s compliance is. Therefore, we conducted a clinical trial comparing 2 oral regimens of artemisinin monotherapy of different duration---5 days (A5) versus 7 days (A7)---in the treatment of uncomplicated falciparum malaria. Two hundred and twenty seven patients were randomly allocated in 2 groups of treatment, which were artemisinin monotherapy in 5 days and 7 days. It was found that there was no significant difference in terms of parasite clearance and cure rate between the two groups. The conclusion is that the 7-day course of artemisinin is not superior to the 5-day course in the treatment of uncomplicated falciparum malaria.

Drug pressure by the use of a drug alone monotherapy, especially of a drug with a long elimination half-life, will lead to development of drug resistance. Therefore, combination of available antimalaria drugs in treating malaria is now recommended by WHO to prevent further development of drug resistance. Recently, Chinese and Vietnamese scientists have developed a fixed combination of dihydroartemisinin, an artemisinin derivative, with three other drugs including piperaquine, primaquine, and trimethoprim. The combination of these four agents is produced and marketed under the name CV8\textsuperscript{K} in Viet Nam and it was proved to be very effective in some preliminary trials. However, formal comparative trials with CV8\textsuperscript{*} were not yet published. Therefore we performed a randomized clinical trial comparing CV8\textsuperscript{*} to Malarone\textsuperscript{*}, another active antimalarial drug combination of atovaquone and proguanil. The study was conducted with 165 uncomplicated falciparum malaria patients (chapter 3). Tolerance to both study drugs was good; no significant side effects were recorded. All patients recovered rapidly. The mean (95% CI) parasite clearance time of regimens CV8\textsuperscript{*} and Malarone were 35 (31-39) h and 34 (31-38) h respectively (p= 0.9). The radical cure rate was 94% and 95% respectively (odds ratio 0.84, 95% CI 0.18-3.81). In conclusions, CV8\textsuperscript{*} and Malarone\textsuperscript{*}, both offer equally rapid recovery and high rates of radical cure from falciparum malaria in an area with multi-drug resistant malaria. Antimalarial combinations with dihydroartemisinin and piperaquine are expected to be cheap and effective and merit further studies.

Malarone\textsuperscript{*} was shown to be very effective for multi-drug resistant falciparum malaria, but it has not been used yet in Viet Nam. In chapter 4, we conducted a study to assess the efficacy of Malarone\textsuperscript{*} when used for recrudescence of P. falciparum after primary treatment with artesunate and mefloquine. Thirty-nine patients were included of which 37 completed follow up. Parasite clearance time (PCT) and fever clearance time (FCT) were 36 (30 – 42) h
and 21 (18 - 24) h [mean (95% CI)], respectively. Thirty two patients were definitely cured, five recrudesced [cure rate 86% - (95% CI 76% – 98%)]. All patients tolerated the drug well. The conclusion is that Malarone® is a safe and promising alternative for treatment of *P. falciparum* infections in Southeast Asia, but recrudescence of multi-drug resistant *P.falciparum* malaria may occur.

Chloroquine-resistant *P.vivax* has been recently reported in Asia and South America. In Viet Nam *P.vivax* was still considered sensitive to chloroquine but this was not confirmed. Chloroquine is still the drug of choice for vivax malaria, but sometimes artemisinin was also used for vivax malaria. In chapter 5, results of a clinical trial comparing efficacy of artemisinin and chloroquine in treating vivax malaria in Viet Nam are presented. Two hundred and forty vivax malaria patients were recruited and randomly allocated to artemisinin or chloroquine. The median (range) parasite clearance time of regimens artemisinin and chloroquine were 24 (8-72) h and 24 (8-64) h respectively (p= 0.3). Recrudescence of parasites was observed in 23% and 16% of patients in the artemisinin group and chloroquine group respectively (p= 0.3). This study proved that R-I resistance (recrudescence) to chloroquine of *P.vivax* is prevalent in Viet Nam and that three days of artemisinin monotherapy is not an adequate therapy to prevent recrudescence.

In Chapter 6, a discussion is presented on one of the components of the Global Malaria Control Strategy, notably “early diagnosis and prompt treatment”. This 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. Many factors may cause delay of diagnosis and treatment. We analysed questionnaires from patients who presented with fever at the health care units during the last decade and were able to analyse patient delay and delay caused by the health care system. Based on this analysis we propose a definition for the timing of "early" in the term “early diagnosis and prompt treatment”.

Chapter 7 gives a review of combination therapiies and of studies on their pharmacokinetic interactions. We focused on the special properties of the respective agents that could turn them into potential precipitators or objects of drug interactions. The role of the cytochrome P450 (CYP) enzyme complex is discussed. Two distinct features have emerged. The first is that relatively little is known about pharmacokinetic interactions between antimalarial agents in humans. The magnitude of malaria as a global problem certainly merits more research into drug interactions, not only between antimalarial agents but also between several other groups of drugs, at least the agents on the essential drugs list. The second is that the limited information available suggests that interactions between antimalarial agents are
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rare. This experience is, for example, much different from that with the antiretroviral agents: pharmacotherapy of patients with HIV infection has become a labyrinth of inter-actions. Clearly, the short duration of antimalarial treatment courses is important here, but also the drugs themselves allow for many combinations without losing efficacy or increasing toxicity.