CLINICAL PHARMACOLOGY OF ARTESUNATE AND DIHYDROARTEMISININ IN FALCIPARUM MALARIA IN VIETNAM

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ABSTRACT

Malaria continues to be a major endemic infectious disease in tropical countries including Vietnam, requiring research efforts aimed at its control and eradication. Some 40% of the population in Vietnam lives in malaria endemic areas. *Plasmodium falciparum* malaria in Vietnam was highly resistant to chloroquine and sulfadoxine/pyrimethamine and there was increasing resistance to alternative antimalarials quinine and mefloquine. In response to the increase in resistance of malaria parasites to conventional antimalarial drugs, Vietnam has deployed artemisinin and its derivatives with various formulations produced from locally grown *Artemisia annua* plant.

Dihydroartemisinin (DHA) is a semi-synthetic derivative of artemisinin (ARN) and has been used in clinical treatment of patients with falciparum malaria in many tropical countries in the world, especially those in the Asian region. Artemisinin derivatives have been used clinically in two approaches, *i.e.*, monotherapy and combination therapy with other antimalarials. The radical cure rates of monotherapy with artesunate (ARS), artemether, and DHA were reported as high as 90% in some

clinical trials, but were as low as 80% or lesser in other reports. To find out whether the efficacy of DHA could be enhanced by the increase of treatment dose, the clinical efficacy of the high dose monotherapy of DHA and the combination of high dose DHA with mefloquine (MQ) for the treatment of acute uncomplicated falciparum malaria was compared in an open randomized comparative study in 89 Vietnamese patients. The survival analysis of cure rate showed that the DHA-MQ combination had significantly higher cure rate compared to that of the 5-day DHA monotherapy (p = 0.003). High dose of DHA in the monotherapy regimen did not improve the clinical outcome. The DHA combination regimens are suggested to increase the treatment efficacy in patients with acute uncomplicated falciparum malaria.

MQ is considered a main counterpart to artemisinin derivatives in combination regimens. In these combination regimens, MQ has been used at different dosages, *i.e.*, 10, 15, and 25 mg/kg, given initially, or at 2, 6, 8, or 24 h or at 4 days after the first dose of artemisinin derivative. The treatment duration of the combination regimens also varies from a single combined dose to a 4 day-combination regimen. One of the reasons for having such different combination regimens is the limitation of information on drug interactions between artemisinin derivatives and MQ. More studies on pharmacokinetics of MQ in the combination regimens with artemisinin derivatives are needed to explore the possibility of drug interaction between the two drugs as well as to optimize therapy with these combination regimens. We have conducted a pharmacokinetic study of MQ given in two different regimens, *i.e.*, at 6 h after the first dose of DHA, and at 24 h concurrently with the second dose of DHA, in 12 Vietnamese patients with acute uncomplicated falciparum malaria. Both combination regimens were well tolerated. All patients responded well to treatment with no recrudescence during a 42 day follow-up period. The pharmacokinetics of MQ following both regimens was similar. It was concluded that since no pharmacokinetic drug interaction was observed, MQ dose given 24 h after an initial dose of DHA is a preferable combination treatment regimen with regard to patient compliance.

ARS is a water-soluble semi-synthetic derivative of ARN. Once absorbed, ARS is rapidly metabolized to DHA which then accounts for most of the antimalarial activity. ARS and DHA have been shown to be rapidly effective antimalarials implemented to combat multidrug-resistant *P. falciparum* malaria at concentrations of

only a few nanograms per milliliter. Sensitive techniques are therefore required to enable quantification of these substances in biological fluids. A simple, sensitive, and specific liquid chromatography-mass spectrometry (LC-MS) analytical method was developed and validated for the simultaneous quantification of ARS and its active metabolite, DHA, in human plasma. The sensitivity and accuracy attained with the current analytical method allow for the determination of ARS and DHA at very low concentrations. The limit of detection was 2 ng/ml. The limit of quantification was 10 ng/ml. The method was applied successfully for measuring DHA and ARS concentrations in plasma samples from patients and volunteers following the administration of DHA for uncomplicated falciparum malaria treatment and of ARS for time-dependent pharmacokinetic study, respectively.

The time-dependent pharmacokinetics of artemisinin has been reported in both healthy volunteers and in malaria patients. The auto-induction of artemisinin on its metabolism is thought to be the main cause for the reduction of drug bioavailability during treatment. The decline in concentrations of DHA in plasma during 5-day treatment with oral artesunate for falciparum malaria has also been reported. To verify whether or not this auto-induction phenomenon be a feature in case of oral DHA formulation, the pharmacokinetics of DHA in a 5-day oral monotherapy regimen was investigated in 10 adult Vietnamese patients with uncomplicated falciparum malaria. The pharmacokinetics of DHA in the acute phase was significantly different from that in the convalescent phase of malaria. Reduced half-life ($t_{1/2z}$) and lower area under concentration curve (AUC_{∞}) values were observed on the final day of treatment in comparison to those obtained on the first day. These decreases in $t_{1/2z}$ and AUC_{∞} were observed in concordance with increased drug clearance (Cl/f). Furthermore, the time required to reach maximum plasma DHA concentration (t_{max}) on day 4 was shorter than that on day 0. Together, these findings suggest that the change in pharmacokinetics of DHA is related to the physiological change in malaria patients between the acute and convalescent phases of the disease. An investigation on time dependency of DHA in healthy volunteers with either DHA or ARS would be necessary in order to clarify whether an increasing clearance with multiple dosing, and during the recovery from acute infection, is caused by disease effects, enzyme auto-induction or a combination of these two phenomena.

The pharmacokinetics of ARN and its derivatives has been investigated in many studies. It seemed that the auto-induction characteristic was usual to several endoperoxide sesquiterpen antimalarials. However, there was no evidence of time-dependent pharmacokinetics for oral DHA in patients with uncomplicated falciparum malaria in our previous study. The same result was reported in another study, in which it was mentioned that DHA did not alter the elimination of ARN, but DHA elimination was inhibited by ARN. The difference in drug metabolism between ARN and its derivatives was put forward as a hypothesis. To get the answer, the time dependency in pharmacokinetics of ARS was studied in 10 healthy male Vietnamese adults following the repeated doses of oral ARS. The concentrations of ARS and DHA were measured by the LC-MS method. There was no decline in ARS and DHA concentrations at timing points of 1, 2, and 4 h among days. There was no evidence for time-dependent pharmacokinetics of both parent drug ARS and its active metabolite DHA following repeated doses of oral ARS in healthy volunteers. This finding confirms that the enzyme auto-induction in drug metabolism may not be the general characteristic for the endoperoxide sesquiterpen antimalrial group.

In conclusion, the artemisinin-based combination therapies are recommended to prevent the emergence and spread of parasite resistance. In addition, the therapeutic drug monitoring is required for early detection of drug resistance as well as for better dosage regimens in the treatment of *P. falc*iparum malaria.

KEY WORDS: CLINICAL PHARMACOLOGY/ LIQUID CHROMATOGRAPHY-MASS SPECTROMETRY/ ARTESUNATE/ DIHYDROARTEMISININ/ MEFLOQUINE/ MALARIA/ VIETNAM