ABSTRACT

Falciparum malaria in Viet Nam is highly resistant to chloroquine and sulphadoxine/pyrimethamine and there is increasing resistance to alternative antimalarials such as quinine and mefloquine (MQ). The single oral dose of 500 mg MQ was effective in malaria treatment in 1988, but reduced to 68% in 1994. This problem results in the need to develop new antimalarials or to optimise the currently used drugs. Artemisinin (ARN) and derivatives are now promising antimalarials for treatment of multidrug resistant falciparum malaria. The main acting metabolite of ARN derivatives is dihydroartemisinin (DHA) which is more active against *P. falciparum* parasites than the parent drugs. DHA is relatively cheaper than other ARN derivatives because it is the intermediate compound in the semisynthesis of other derivatives. DHA is now produced in oral formulation in China and in some western countries. Like other ARN derivatives, DHA is promising to be used in monodrugtherapy or in combinations with other antimalarials, especially with MQ in falciparum malaria treatment. However, all of these regimens are based virtually on the clinical experiences. The use of MQ in Viet Nam has been based on the pharmacokinetic information which was published from the studies in other countries. The difference in ethnics could affect the kinetics of drug. The present study aimed to provide the basic pharmacokinetics of DHA and MQ in both Vietnamese healthy subjects and malaria patients. More specifically, the study consists of 6 parts; namely- (1) the investigation of pharmacokinetics of MQ in Vietnamese healthy subjects (2) the investigation of pharmacokinetics of a single oral dose of DHA in Vietnamese healthy subjects (3) the investigation of pharmacokinetics of a single oral dose of DHA in Vietnamese malaria patients (4) the investigation of pharmacokinetics of multi-oral doses of DHA in Vietnamese malaria patients (5) the investigation of pharmacokinetics of MQ when given alone or 24 h after DHA in Vietnamese malaria patients and, (6) the

clinical trial of DHA in a 5 day-monotherapy and in combination with MQ in treatment of falciparum malaria in Viet Nam.

The pharmacokinetics of MQ was investigated in 8 (5 males and 3 females) Vietnamese healthy subjects, following the administration of a single oral dose of 750 mg of Mephaquin® (250 mg per tablet; Mepha Pharmaceuticals, Switzerland). Pharmacokinetic parameters of MQ were similar between males and females except C_{max} and AUC which were significantly higher and V_{ss}/f which was lower in females than in males ($p = 0.025$). When normalising for dosage per kilogram of body weight, C_{max}/dosage and V_{ss}/f of both groups, but not AUC/dosage were still significantly different ($p = 0.025$). Difference in volume of distribution and sex-dependent kinetics could have contributed in part, to the observed higher whole blood concentrations of MQ in females. Therapeutic and prophylactic regimens of MQ based on doses for ranges of kilogram of body weight are suggested in Vietnameses.

Pharmacokinetics of a single oral dose of 240 mg DHA was investigated in 8 (5 males, 3 females) healthy Vietnamese subjects. The concentration-time profile of DHA was fitted with one-compartment model with a lag time. Pharmacokinetics of DHA is comparable between males and females even when adjusting with dosage. The median (range) values of pharmacokinetic parameters of oral DHA were: t_{lag} 0.41 (0.09-0.78) h, $t_{1/2a}$ 0.58 (0.17-1.43) h, t_{max} 1.6 (1.1-2.2) h, C_{max} 466 (128-787) ng/ml, C_{max}/dosage 97.7 (27.2-124.6) ng/ml/mg dose/kg body weight, $t_{1/2z}$ 2.0 (1.5-3.4) h, AUC 1867 (420-3535) ng.h/ml, AUC/dosage 364.3 (89.3-559.7) ng.h/ml/mg dose/kg body weight, CL/f 45.8 (30.0-190.0) ml/min/kg, V_z/f 8.0 (5.5-29.9) l/kg. Inter-individual variation was large, the coefficients of variation (CV) were 47.8% and 45.3% respectively, for AUC and C_{max}. The t_{max} of DHA formulation was comparable with that of DHA metabolite of artemisinin derivatives. The $t_{1/2z}$ was longer and shorter than

that of DHA metabolites of oral formulations of artesunate (ARS) and artemether (ARM) respectively.

The pharmacokinetics and pharmacodynamics of a single oral dose of 240 mg DHA was investigated in Vietnamese patients with uncomplicated falciparum malaria. Twenty-six patients were randomly received either a 5 day-DHA monotherapy (240 mg at 0 h, then 60 mg at 24, 48, 72, and 96 h) or DHA+MQ combination (240 mg DHA at 0 h, followed by 750 mg MQ at 24 h). There was no difference in DHA kinetics between male and female patients. Kinetic parameters in patients were significantly different from those corresponding in Vietnamese healthy subjects except the half-lives of absorption ($t_{1/2a}$) and elimination ($t_{1/2z}$). In patients, the median (range) of t_{lag} [0.82 (0-1.48) *vs.* 0.41 (0.09-0.78) h] and t_{max} [2.2 (1.1-3.84) *vs.* 1.6 (1.1-2.1) h] were prolonged, C_{max} [861 (345-2280) *vs.* 466 (128-787) ng/ml] and $C_{max/dosage}$ [179 (70.4-513) *vs.* 98 (27.2-124.6) ng/ml/mg dose/kg body weight] were higher, V_z/f [3.3 (1.4-11.07) *vs.* 8.0 (5.5-29.9) l/kg] and CL/f [24 (7.1-43.03) *vs.* 45.8 (29.9-190.1) ml/min/kg] were lower, compared with healthy subjects. The mean (SD) effective time for pharmacodynamic activity (EPAT) was 14.2 (3.6) h. There was a linear regression between EPAT and C_{max} ($p = 0.0004$). All patients had clinical recovery from malaria without adverse effect. The PCTs [mean (SD)] were 30.7 (11.4) and 30.3 (8.3) h, respectively to a 5 day-DHA and DHA+MQ. Six out of 9 patients in DHA alone and 11 out of 17 in DHA+MQ completed the 28 day follow-up and 2 patients in each group had RI response. Malaria changes the kinetics of DHA by the reduction in systemic clearance, contraction of volume of distribution and/or increase in bioavailability. Loading doses of DHA are suggested for at least 2 days in a 5 day-monotherapy for increasing the cure rate.

The pharmacokinetics of MQ at a single oral dose of 750 mg, when given alone (n = 13) or 24 h after a single oral dose of 240 mg DHA (n = 10) was investigated in

23 Vietnamese malaria patients in an open randomised study. Pharmacokinetics of MQ was different between female and male patients in the following parameters [median (range)]; in female patients, C_{max} [1,525 (1,120-2,080) *vs.* 1,060 (888-1,350) ng/ml], AUC [23.89 (16.87-32.17) *vs.* 14.31 (11.04-15.98) μg·day/ml], and AUC/dosage [1.44 (0.9-2.06) *vs.* 0.88 (0.59-1.13) μg·day/ml/mg dose/kg body weight] were significantly higher, while CL/f [0.49 (0.34-0.733) *vs.* 0.79 (0.62-1.18) ml/min/kg], Vss/f [14.0 (12.1-21.0) *vs.* 23.5 (16.0-26.6) l/kg] were significantly lower. In male patients, the pharmacokinetics of MQ in MQ monotherapy was different from that in MQ+DHA on 8 parameters [median (range)]: t_{lag} [0.27 (0.001-0.532) *vs.* 0.00001 (0.00001-0.0093) h] and $t_{1/2\alpha}$ [37.5 (31.8-48.1) *vs.* 22.9 (16.0-31.9) h] were longer, C_{max} [1480 (1280-2210) *vs.* 1060 (888-1350) ng/ml], C_{max}/dosage [102.4 (87.5-153.2) *vs.* 67.6 (45.9-95.4) ng/ml/mg dose/kg body weight], AUC [19.54 (16.67-30.43) *vs.* 14.31 (11.04-15.98) μg·day/ml], and total AUC/dosage [1.33 (1.14-2.11) *vs.* 0.88 (0.59-1.13) μg·day/ml/mg dose/kg body weight] were higher, CL/f [0.52 (0.33-0.61) *vs.* 0.79 (0.62-1.18) ml/min/kg] and V_{ss}/f [14.1 (10.9-15.5) *vs.* 23.5 (16.0-26.6) l/kg] were significantly lower. Discriminant analysis showed a significant discrimination between the two regimens by using the association of parasite clearance time (PCT) and $t_{1/2\alpha}$, (p = 0.018). The pharmacokinetics of MQ may have the sex-dependent characteristics. Both the reduction in severity of malaria when MQ was given 24 h after DHA and the drug interaction can allow the changes in kinetics of MQ in the combination regimen.

The pharmacokinetics of DHA following a 5 day-DHA monotherapy was investigated in 12 Vietnamese patients with uncomplicated falciparum malaria. The patients received 240 mg DHA as an initial dose, followed by 60 mg on the next 4 days. The kinetics of the initial dose of 240 mg showed a short $t_{1/2z}$ [median (range): 2.46 (1.20-2.97) h] and large inter-individual variability with the coefficients of variation (CVs) of 28, 55.2, 67.2 and 70.2% respectively, to $t_{1/2z}$, C_{max}, total AUC and

CL/f. Compare to the kinetics of 60 mg dose of DHA in the study of Benakis *et al.*, (1996), it could be only the $t_{1/2z}$ of DHA having the dose-dependent characteristics. Both C_{1h} and C_{6h} of 60 mg DHA on the following days were significantly lower than $C_{1h\ d0\ 60\ mg\ dose}$ and $C_{6h\ d0\ 60\ mg\ dose}$. On days 3 and 4, the means of C_{1h} and C_{6h} were into the 95% C.I. of $C_{1h\ d0\ 60\ mg\ dose}$ and $C_{6h\ d0\ 60\ mg\ dose}$ (58.4-123 ng/ml and 15.6-46.5 ng/ml, respectively) in healthy subjects (Chapter V) in previous study. No difference was seen for both C_{1h} and C_{6h} between the following doses (d1 to d4) ($p = 0.29$, $p = 0.10$, respectively). The early normalisation of physiological condition in patients due to the quick parasitaemia clearance of DHA can be the cause of the reduction of DHA concentrations in the following days of the 5 day-DHA monotherapy. EPATs were reduced in the following days compared to that of d0 (range: 12.5-14.2 *vs.* 11.0-22.9 h, $p < 0.03$). The initial dose of DHA is suggested to be consistent over at least 48 h for both regimens.

The clinical efficacy of a 5 day-DHA monotherapy (240 mg DHA as an initial dose, followed by 60 mg on the next 4 days, n = 129) was compared with that of DHA+MQ (240 mg DHA as an initial dose, followed by 750 mg MQ at 24 h, n = 124) in an open randomised study. Treament response was similar between these two regimens. Parasite clearance times (PCT_{100}) [mean (SD)] were 25.1 (10.6) and 25.1 (12.2) h respectively, for a 5 day-DHA and DHA+MQ. The cure rates by day 28 were 87.5 and 91.5% respectively, for a 5 day-DHA and DHA+MQ. In DHA+MQ, the cure rate was 88.3 and 85% by day 42 and 56, respectively. The lag times in dynamic action, $t_{dynamic\text{-}lag}$, of DHA were 0, 0.5-3, and 6 h respectively, for 55, 40 and 5% of the total number of patients. No adverse effect was found in both regimens. A simple non-compartmental kinetic model with log-transformation of the percentage of initial parasitaemia showed that $PCT_{99.99cal.}$ was around 30 h longer than the observed microscopic PCT_{100}. The presence of one RII case in DHA+MQ was also showed that the single loading dose of DHA was not strong enough to cover the MQ high resistance

of parasites. In conclusion, the 5 day-DHA monotherapy and DHA+MQ combination can be used alternately in malaria treatment. Further studies with a longer time for loading dose of DHA, *i.e.*, 2 days, for monotherapy, as well as for combination regimen, are suggested.