Thesis Title Quinine and Mefloquine Interaction in Healthy Subjects and Its Antimalarial Activity

Name Suttirat Reangchainam

Degree Master of Science (Microbiology)

Thesis Supervisory Committee

Vithaya Meevootisom Ph.D.

Kesara Na-Bangchang Ph.D.

Peerapan Tan-ariya Ph.D.

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ABSTRACT

The pharmacokinetic and pharmacodynamic interaction between quinine (QN) and mefloquine (MQ) were investigated in seven healthy male Thais following the administration of three antimalarial drug regimens. The subjects were randomised to receive the drugs on three occasions i.e. a single oral dose of QN alone (600 mg QN sulfate; regimen-I), a single oral dose of MQ alone (750 mg MQ; regimen-II), and the combination (regimen-III) of MQ (750 mg) and QN (600 mg given 24 hr after MQ).

The pharmacokinetic interaction between QN and MQ was assessed through the analysis of serum or whole blood drug concentration-time profiles, using a model-independent method. We have demonstrated that, with the dosage used in the study, the pharmacokinetics of QN was uninfluenced by MQ, whereas the pharmacokinetics of MQ was affected by QN. In the presence of QN, CL/f of

MQ was significantly increased [0.52 (0.35-0.83) *vs.* 0.41(0.31-0.64] ml/min/kg, and $t_{1/2z}$ was significantly reduced [13.8 (9.5-20.4) *vs.* 22.6 (14.3-63)days].

Both MQ and QN were well-tolerated. Adverse experiences found after drug administration were mild and transient, consisting of nausea, vomiting, abdominal pain, dizziness, weakness, etc. No serious adverse experiences, or significant changes in vital signs, or drug-related toxicity in blood profiles (blood figures and serum biochemistry) were observed. Prolongation of QTc interval was the only signs of cardiotoxicity observed in these subjects. Significant prolongation (comparing to baseline) was noted in all of the seven subjects after all drug regimens, but the incidence seems most frequent after MQ+QN. The prolongation occurred at 2, and 6 hr after MQ alone, whereas it occurred at 2, 2.5, 3, 4, 6 and 2.5, 3, 4, 6, 8, 12, 18, 24 hr after QN alone and MQ+QN, respectively. QTc prolongation was dependent on serum QN but not blood MQ concentrations since only significant correlation between the percentage of changes in QTc interval and the serum QN concentration was observed.

The pharmacodynamic interaction between QN and MQ was evaluated by the assessment of blood schizontocidal activities against K_1 strain *P. falciparum*, of the serum samples, using the *in vitro* micro-technique of Rieckmann *et al.* (1978) with modifications. Superiority of activity was shown in the sera collected after the combination regimen. The pattern of MICs (minimum inhibitory concentrations) of QNEq of the sera from QN alone was constant throughout 24 hr period, with significantly higher concentrations than that after the combination regimen (118-150 vs 21.25-73.5 ng/ml). In the sera colletced after given the combination regimen, however, the MICs was gradually increased from 0.5 hr until 4 hr, and thereafter gradually returned to the same levels again during the period of 6-24 hr. The MICs of MQEq when given as MQ alone or as the combination appeared constant, with significantly higher value in the former regimen (30.6-32.5 *vs* 16.9-19.1 ng/ml).

On the pharmacodynamic point of view, the superiority of antimalarial activity exploited from the combination (regarding potency and duration of activity) would benefit the therapy of malaria. Reduced terminal elimination half-life of MQ resulted from the interaction is unlikely to have major contribution to therapy as MQ has a relatively long half-life. Although the number of patients was limited, the study propably points out the precaution when a loading dose of QN is to be applied in patients with severe malaria who have previously been treated with MQ within 72 hr. Close monitoring of ECG (QTc) is necessary in this group of patients who require rapid and prompt therapeutic drug action.