DISCUSSION

Mefloquine, a quinoline methanol derivative of quinine, is an antimalarial drug which is effective for all species of malarial parasites infecting humans, including multidrug-resistant *Plasmodium falciparum,* and was first introduced for clinical use in Thailand in late 1984. It is given both as a prophylactic and as a therapeutic agent (Crevoisier, et al., 1997). Mefloquine is relatively well tolerated and has the advantage of a single day regimen. It has ideal properties for prophylactic use (Nosten and Price, 1995). During the past years, there have been several failures of mefloquine treatment, it is not clear whether this represents genuine resistance (Karbwang, et al., 1991) Rifampicin is a potent enzyme inducer of hepatic drug metabolism in humans by CYP 2C8-10 and CYP 3A, mainly CYP 3A4 (Venkatesan, 1992) and is known to interact with a number of drugs such as warfarin, digitoxin, dapsone, chlorpropamide, metoprolol, theophylline, antipyrine, hexobarbitone and cyclosporine (Venkatesan, 1992). It has been shown that rifampicin decreases the elimination half-life of quinine and quinidine, a diastereoisomer of quinine (Wanwimolruk, et al., 1995). Mefloquine is structurally related to quinine (Nosten and Price, 1995) and cytochrome P450 3A4 is important for the 3-hydroxylation of quinine in humans *in vivo* (Mirghani, et al., 1999). In addition, CYP3A4 is the principle isozyme induced by rifampicin (Venkatesan, 1992). In the pharmacokinetic point of view, there is the possibility of a pharmacokinetic

interaction between mefloquine and rifampicin in humans *in vivo*. Therefore, we investigated the effect of rifampicin on the pharmacokinetics of mefloquine in healthy Thai male volunteers.

In the present study, the profile of plasma mefloquine concentrations and the derived pharmacokinetic parameters in healthy subjects receiving a single oral dose of 500 mg mefloquine were similar to those previously reported. (Table 13) (Karbwang, et al., 1991 ; Karbwang, et al., 1992 ; Crevoisier, et al., 1997 ; Mansor, et al., 1989 and Sunbhanich, et al., 1997). The mean peak plasma mefloquine concentrations in each study were depended on the oral doses of mefloquine. Nevertheless, the variations of these pharmacokinetic parameters may be influenced by inter-individual variation and environmental factors (e.g., sex, races, diet, smoking, coffee and alcoholic drinking). In this study, there were considerable inter-individual variability in plasma concentration-time profiles, and as a consequence there were large variations in the derived pharmacokinetic parameters as previously reported by Crevoisier et al. (1997) and Karbwang et al. (1988).

The semi-logarithmic plots of the plasma mefloquine concentration-time curve (Figure 7) shows that the data are well described by one compartment model with first-order kinetics for both absorption and elimination. The pharmacokinetic parameters such as the area under the concentration-time curve (AUC), the elimination rate constant (Ke), the elimination half-life ($t_{1/2}$), the maximum plasma concentration (C_{max}) and the

apparent oral clearance (Cl/f) of the subjects receiving rifampicin treatment were significantly different from those receiving mefloquine alone. These findings suggest that rifampicin alters the pharmacokinetics of mefloquine if the two drugs are concomitantly administered.

In a long term rifampicin coadministration (~56 days), oral clearance (Clo) of mefloquine increased by about 4-fold (273.83%), the C_{max} decreased from 855.63 ng/ml to 695.67 ng/ml (18.46%), the $t_{1/2}$ was shorter about 2.5-fold (62.85%) and the AUC decreased about 3-fold (67.95%) from control. In addition, the $t_{1/2}$ of mefloquine metabolite decreased about 1.5-fold (39.31%) and T_{max} decreased about 4-fold (76.21%) when rifampicin and mefloquine were coadministered. The efffect of rifampicin on the pharmacokinetics of mefloquine may be mediated by induction of the hepatic mixed function oxidase system by rifampicin which were similar to those occuring with quinine (Wanwimolruk, et al., 1995) since mefloquine has a chemical structure related to quinine and quinidine. Significant quantities of CYP 3A4 are found in small bowel enterocytes and liver (Villikka, et al., 1997). CYP 3A4 is the most abundantly expressed CYP and accounts for approximately 30 to 40% of the total CYP content in human adult liver and small intestine (Wildt, et al., 1999). Since rifampicin is a potent inducer of CYP 3A4 in both liver and small bowel enterocytes, therefore the obvious explanation of the strong significant interaction observed between rifampicin and mefloquine in this study was based on CYP 3A4 activity induced by rifampicin. The decrease in mefloquine concentrations after a rifampicin

coadministration was due to induction of metabolic transformation of mefloquine in the liver rather than in the gut wall, as T_{max} of mefloquine was not significantly affected by rifampicin coadministration. Moreover, $t_{1/2}$ of mefloquine was significantly decreased by rifampicin coadministration. Accordingly, the decrease in bioavailability of mefloquine after rifampicin coadministration is the result of an increase in metabolism in the liver rather than in the small bowel enterocytes.

Rifampicin is a potent inducer of hepatic drug metabolism, as evidenced by a proliferation of smooth endoplasmic reticulum and an increase in the cytochrome P450 content in the liver. The induction is a highly selective process and not every drug metabolised via oxidation is affected (Venkatesan, 1992).

The hepatic microsomal enzyme cytochrome P450 3A4 is responsible for metabolizing both quinine and quinidine (Krishna and White, 1996). Quinidine (dextrorotatory stereoisomer of quinine) elimination is enhanced by phenobarbitone, phenytoin and rifampicin and reduced by the hepatic CYP inhibitors including cimetidine, amiodarone, verapamil and possibly erythromycin (Gonzalez and Idle, 1994 and Spinler, et al., 1995). Cimetidine reduces the clearance and prolonged the elimination $t_{1/2}$ of mefloquine in a manner similar to quinine (Sunbhanich, 1997).

Many clinical studies and case reports have shown that rifampicin can enhance metabolism of several drugs, and most of these interactions are of clinical importance. The pharmacokinetics of warfarin, quinidine,

propranolol, verapamil, norethindrone, ethinylestradiol, prednisolone, tolbutamide, cyclosporin, and ketoconazole were all significantly altered by rifampicin, thus dosages of these drugs will be increased or use of alternative compounds to maintain adequate clinical responses when these medications are coadministered with rifampicin (Venkatesan, 1992).

In vitro minimum inhibitory concentrations of mefloquine have been reported as 10^{-7} M (41.48 ng/ml) to 1.7×10^{-7} M (70.51 ng/ml) (Suebsang, et al., 1986) and plasma levels of 200-300 ng/ml may be necessary to achieve chemosuppression in *Plasmodium falciparum* infections (Goldsmith, 1998). In this study, maximum plasma concentration of mefloquine after mefloquine administration alone and coadministration with rifampicin were 855.63 ± 168 ng/ml and 695.67 ± 56.63 ng/ml, respectively which are adequate for a schizontocidal activity for *Plasmodium falciparum* malaria.

It has been reported that mefloquine concentrations in blood samples from volunteers who experienced prophylaxis failure were all below 400 ng/ml, suggesting that higher mefloquine concentrations are necessary to suppress *P.falciparum* parasitaemia (Crevoisier, 1997). Recently, it has been estimated that 99% and 95% prophylactic efficacy can be achieved at mefloquine blood concentration of 915 ng/ml and 620 ng/ml, respectively (Lobel, et el., 1993). In the present results, plasma concentrations of mefloquine in subjects administered mefloquine alone and rifampicin treatment were 855.63 ± 168 ng/ml and 695.67 ± 56.63 ng/ml, respectively which is higher than the 95% prophylactic efficacy, but there was an increase

in clearance of mefloquine from 0.0214 ± 0.0038 l/hr/kg to 0.08 ± 0.03 l/hr/kg and a decrease in $t_{1/2}$ from 305.31 ± 47.15 hr to 113.43 ± 49.71 hr when coadministration with rifampicin. These results may lead to a prophylaxis failure, increase risk of treatment failure and spread of drug resistance because mefloquine is given as a single dose regimen. However, concentrations in plasma associated with succesful response and treatment failure must vary considerably depending on the intrinsic susceptibility of the parasites (Karbwang and White, 1990).

Food increases the rate and the extent of mefloquine absorption, administration of mefloquine after a high-fat meal resulted in a 4% higher prophylactic efficacy compared with administration during a complete fasting. Differences in absorption may contribute to explain some of the failures which can occasionally occur during prophylaxis, although failures are due not only to inadequate drug blood concentration (variation in kinetics, non compliance) but also to drug resistance of the parasites (Crevoisier, et al., 1997). The pharmacokinetic parameters of mefloquine after administration of a generic tablet of mefloquine and the reference tablet showed significant differences ($P < 0.05$). The C_{max} and AUC values of the test formulation were significantly lower and the t_{max} value was considerably longer than the respective values of the reference formulation (Weidekamm, et al., 1998). Therefore, if mefloquine and rifampicin were coadministered, mefloquine should be administered with high fat diet and qualified drug should be used to maximise therapeutic outcome.

In conclusion, in a long term rifampicin treatment it has shown that rifampicin markedly decreased the plasma concentration of mefloquine and significantly increased the clearance and decreased the elimination half-life of mefloquine. These effects may be mainly due to the induction of CYP3A4 isozyme by rifampicin. Therefore, mefloquine and rifampicin should not be coadministered in order to maximise therapeutic efficacy and prevent a risk of resistant of *P. falciparum*. Moreover, in the present results it also indicates that CYP 3A4 is important for the metabolism of mefloquine in humans *in vivo*.