INTRODUCTION

Half of the World 's population lives in malaria-endemic areas and about 20-30 million people, mainly Europeans and North Americans, either travel or stay in malarious areas. Morbidity and mortality from this disease is considerably high with approximately 200 million incident cases and two million deaths annually (Foster, 1994). In such an environment, prophylaxis and treatment of the disease are of prime public health importance.

Malaria is a deadly disease which constitutes one of the most serious public health problems in Thailand. Approximately 60% of malaria cases are caused by *Plasmodium falciparum*, almost all are chroroquine resistant, over 80% and 30% are sulfadoxine-pyrimethamine and quinine resistant, respectively. The use of mefloquine has been shown to be effective against multi-drug resistant *falciparum malaria* (Harinasuta et al., 1983 ; Karbwang and White, 1990). This drug seems to be the only available drug for prophylaxis in Thailand (Karbwang et al., 1991).

Mefloquine is a 4-quinolinemethanol, structurally related to quinine and selected for development by the Walter Reed Army Institute of Research in the US from over 30,000 screened compounds. Although it was only marketed in 1985, mefloquine is effective single dose therapy for all species of malaria infecting humans, including multi-drug-resistant *Plasmodium falciparum*. It is used both in prophylaxis and treatment of the disease (Karbwang and White, 1990). Mefloquine is relatively well tolerated and has the advantage of a single daily dose regimen. It has ideal properties for prophylactic use (Nosten and Price, 1995). Mefloquine is a reasonably well

tolerated drug for both curative therapy and prophylaxis of malaria, with minor side effects (Crevoisier et al., 1997). Because it produces fewer adverse effects than quinine, the drug has an important advance in the treatment of *falciparum malaria* (Goldsmith, 1992).

Rifampicin is a semisynthetic derivative of *rifamicin B*, a complex macrocyclic antibiotics. It is an antituberculosis drug which is usually administered for 4 to 12 months with other antituberculosis drugs. A potential for drug interactions often exists because 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 (Venkatesan, 1992). The induction is a highly selective process and not every drug metabolised via oxidation is affected (Venkatesan, 1992). The enzyme induction caused by rifampicin affects the metabolism of many other drugs, increasing their metabolism and reducing their effects. The drugs affected include anticonvulsants, oral antidiabetic drugs, digoxin, anticoagulants, sex hormones including the contraceptive pills, steroids, vitamin D, ketoconazole, theophylline, protease inhibitors, zidovudine, delavirdine, itraconazole, nifedipine, midazolam, triazolam, nortriptyline, doxycycline and quinine (Strayhorn et al., 1997).

Wanwimolruk, et al. (1995) reported rifampicin pretreatment caused a marked increase in the clearance of quinine, possibly due to enzyme induction.

Mefloquine has a structure chemically related to quinine. Since quinine is extensively metabolized by CYP450 3A4 (Mirghani, et al., 1999); therefore, rifampicin would theoretically altered the metabolism of mefloquine

similar to its effect on quinine pharmacokinetics. Very low plasma concentrations of mefloquine are associated with an increased risk of prophylaxis, treatment failure and spreading drug resistance.

The purposes of this investigation is to study the effect of rifampicin on an oral single-dose mefloquine pharmacokinetics in healthy volunteers. Due to the lack of interaction data between rifampicin and mefloquine, the present study may be the guidance and useful data for decision making in case of coadministration of mefloquine and rifampicin.