INTRODUCTION

Malaria is the most common killer of all the parasitic diseases that affect human. About 2000 million live in endemic areas. 300 million people are infected every year and most of them are children. In sub-Saharan Africa, over a million children die annually from the disease. Malaria is a complex multi-system disease affecting erythrocytes, the brain, lungs, kidneys, placenta and other tissues. Plasmodium, a unicellular eukaryotic cell of the protozoa group is the fatal parasite responsible for malaria. There are four species of this parasite, *Plasmodium falciparum* (malignant tertian), *vivax* (benign tertian malaria), *malariae* (quartan malaria) and *ovale*. (Ovale tertian). *Plasmodium falciparum* is the most important of the malaria plasmodium species.

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

Mefloquine is 4-quinolinemethanol, structurally related to quinine and selected for development by the Water 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 human, including multi-drug-resistant *Plasmodium falciparum*. It is use both in prophylaxis and treatment of the disease (Karbwang and White, 1990).

Mefloquine is relatively well tolerated and has 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 faciparum malaria (Goldsmith, 1992). Mefloquine was first used to treat chloroquine-resistant faciparum malalia in Thailand, where it was formulated with pyrimethamine-sulfadoxine (FANSIMEF) to delay development of drug-resistant parasite. This strategy failed, largely because slow elimination of mefloquine fostered the selection of resistant parasite at subtherapeutic drug concentration (White, 1999). Mefloquine now is recommended for oral use exclusively for the prophylaxis and chemotherapy of chloroquine-resistant or multidrug resistant falciparum malaria. This quinoline is most effective for treating uncomplicated drug-resistant falciparum malaria when given 48 hours after the parasite burden has been substantially reduced by prior administration of an artemisinin antimalarial (White, 1999). Following the oral administration of a single 25 mg/kg dose of mefloquine to population patients with acute falciparum, the mean values of Cl/f, V_d/f, Ke, $t_{1/2}$ and AUC $_{0-\alpha}$ of mefloquine were 0.733 L/kg/day, 20.37 L/kg, 0.036 day^{-1}, 19.3 days and 34,106 ng/ml.day, respectively (Simpson et al., 1999). After 1000 mg (divided into three doses over 12 h) mefloquine administration orally in healthy Caucasian male, the mean ± SD values of C_{max}, t_{max}, AUC_{0-846h}, $AUC_{0-\alpha}$ and $t_{1/2}$ were 1000 ± 266 ng/ml, 23 ± 10 h, 280 ± 107 µg/ml.h, 375± 125 µg/ml.h and 427 ± 198 h, respectively (Lef ever, et al., 2000).

Two metabolites of mefloquine have been identified in humans are hydroxy metabolite and carboxylic acid metabolite. The main metabolite, 2,8-bis - trifluoromethyl-4-quinoline carboxylic acid, is inactive in *P. falciparum.* In a study in healthy volunteers, the carboxylic acid metabolite appeared in plasma 2 to 4 hours after a single oral dose. Maximum plasma concentrations, which were about 50% higher than those of mefloquine, were reached after 2 weeks. Thereafter, plasma levels of the main metabolite and mefloquine declined at a similar rate. The area under the plasma concentration-time curve (AUC) of the main metabolite was 3 to 5 times larger than that of the parent drug. The other metabolite, an alcohol, was present in minute quantities only.

Azole compounds are used extensively for the treatment of cutaneous and invasive fungal infections, and ketoconazole is the current drug of choice for treating systemic fungal infections such as candidiasis, blastomycosis, histoplasmosis as well as candida vulvovaginitis. This drug does not appear to have any useful antibacterial or antiparasitic activity, with the possible exception of antiprotozoal effects against Leishmania major (Chamber, 2001).

Ketoconazole is an oral antifungal agent of the imidazole class (Piscitelli, et al., 1991), which contains two nitrogen atoms in the five-membered azole ring (Cleary, et al., 1992) The primary mechanism of action of ketoconazole and azoles, in general, is the inhibition of sterol 14-α-dimethylase, a microsomal cytochrome P450-dependent enzyme system (Fabris, et al., 1993) Ketoconazole is a dibasic compound (pKa (1) = 6.51; pKa (2) = 2.94) and almost insoluble in water except at a pH lower than 3 (Daneshmend ,1990). Therefore any conditions that lower the acidity or increase the pH of stomach will decrease the absorption and hence reduce the bioavailability of ketoconazole.

Following the oral administration of a single 200 mg dose of ketoconazole to eight healthy volunteers after a standard breakfast, peak serum concentrations of 3.63 (SD =1.70) mg/L occurred in 2.62 (SD = 0.52) hours (Daneshmend, 1986). The mean half-life was reported to be 1.46 (SD =0.39) hours (Daneshmend, 1986). In a similar study involving the administration of a single 400 mg dose of ketoconazole to six healthy males under fasting conditions, peak concentrations of 8.20 (SD =2.10) mg/L were achieved in 1.75 (SD =0.94) hours (Piscitelli, et al., 1991). Daneshmend et al. (1981) did a study where six healthy males were given single 200-mg and 400-mg doses of ketoconazole after a standard breakfast. For the 200 mg dose, mean peak concentrations of 3.60 (SD =1.65) mg/L occurred in about 2 hours. The average half-life was 2.03 (SD =0.42) hours. For the 400 mg dose, peak concentrations of 6.5 (SD =1.44) mg/L in about 2.5 hours. The average half-life was 2.67 (SD =0.48) hours. Daneshmend et al. (1984) completed an extensive study on ketoconazole at four different doses under fasting and fed conditions. Lelawongs et al, (1988) studied the effects of food on the bioavailability of ketoconazole tablet. This study found a significant difference in C_{max} (3.01 vs 4.37 µg/ml) and $AUC_{0\text{-}24h}$ (15.25 vs 20.47 µg.h/ml) between the fasting group and high carbohydrate meal.

As ketoconazole is one of azole compounds, a number of side effects are associated with ketoconazole as a result of inhibition of these mammalian enzymes (Venkatakrishnan, 2000). Ketoconazole leads to liver damage due to its ability to inhibit P4503A4, the major P450 isoform of the liver (Suzuki, 2000). The inhibition of P4503A4 results in drug-drug interactions involving ketoconazole and a decrease in the rate of clearance of many drugs (Tsunoda, 1999). Steroid biosynthesis by P450 enzymes is also inhibited by ketoconazole, presumably due

to the binding of ketoconazole to the mitochondria P450 enzymes, and the administration of low doses of ketoconazole leads to a significant reduction in serum androgen levels (Sikka, 1985).

Mefloquine has a structure chemical relate to quinine. Since quinine is extensively metabolized by CYP450 3A4 (Mirghani, et al., 1999), therefore, ketoconazole would theoretically alter the metabolism of mefloquine.

In Thailand, fungal infections has been recognized as a major public health problem, ketoconazole and azole antifungals with a broad spectrum of activity against a number of fungal pathogens and the duration of antifungal agents therapy is 5 days to 1 year depending on type of fungal and site of infection, whereas malaria a major public health problem in Thailand. Thus, the possibility of ketoconazole and mefloquine co-administration tends to have a chance to occur in clinical practice and may lead to azole antifungals-mefloquine drug interaction.