CHAPTER 1

INTRODUCTION

Malarial infection is caused by unicellular animals, class *Sporozoa* genus *Plasmodium.* More than 120 species of *Plasmodium* have been found but only 4 species are the cause of malarial disease in humans i.e. *Plasmodium falciparum* (*P. falciparum*), *P. vivax, P. ovale* and *P. malariae. P. falciparum* is the most dangerous form of human malaria results in severe or complicated malaria such as malaria with renal failure or cerebral malaria. (Looareesuwan and Chongsuphajaisiddhi, 1994)

Malaria is the important health problem in the world including Thailand. Half of the world populations settle down at the outbreak of malarial infection. The person at risk is estimated to be around 2.4 billion, and estimated death due to the disease is 1.1-2.7 million yearly; mostly (90%) in children under 5 years of age in Africa and South of the Sahara (WHO, 2000). Ten years ago in Thailand it was found patients with malaria more than 300,000 cases each year with the mortality rate of 2,000-3,000 cases per year. In 1994, it was found that patients with malaria about 100,000 cases. However, the data may less than the actual one because some malarial infections may treat the infection by themselves (Looareesuwan, 1995).

Chloroquine and primaquine are used to treat uncomplicated malarial infections in patients infected with *P. vivax, P. malariae* and *P. ovale,* whereas patients infected with *P. falciparum* are treated with chloroquine and

sulfadoxine-pyrimethamine. Quinidine, quinine, mefloquine and artesunate can be used when *P. falciparum* is resistant to chloroquine and sulfadoxine-pyrimethamine (White, 1988). Quinine is the cinchona alkaloid widely used for blood schizontocide in patients infected with *P. falciparum* and resistant to chloroquine both complicated and severe malaria. (Hall, 1976 ; Krishna and White, 1996). The severity of infection is criteria for making decision of route of quinine administration. For the chloroquine resistant falciparum malaria, quinine is used in a dose of 10 mg/kg (600 mg) orally 3 times a day for 7 days in combination with Fansidar® (25 mg pyrimethamine and 500 mg sulfadoxine per tablet) or 250 mg tetracycline or doxycycline, whereas in severe cases 10 mg/kg quinine dihydrochloride (highest dose not more than 600 mg) mixed with 300 ml normal saline is intravenously infused in 1-2 hours as loading dose and followed by 10 mg/kg every 8 hours for 7 days, the drug should be changed to oral administration as soon as the patient can take medication orally. However, in areas of quinine resistant falciparum malaria, 20 mg/kg of quinine infusion in 2 hours as loading dose is required (Karbwang and Cross, 1997). Quinine is also prescribed as the treatment of choice for the nocturnal leg cramps (Mackie and Davidson, 1995).

In healthy volunteers after oral administration, quinine was rapidly and completely absorbed, and the time to peak plasma concentration was between 1-4 hours. Quinine was 69-92% bound in human plasma (Wanwimolruk and Denton, 1992), and α_1-acid glycoprotein is the important binding protein (Van Henbroek *et al.*, 1996). Volume of distribution was about 2 l/kg. Quinine was mainly metabolized in the liver by oxidative biotransformation catalyzed by

CYP3A4 (Barrow *et al.,* 1980 ; White, 1985). The major metabolite is 3-hydroxyquinine, and the unchanged drug is excreted in urine by 20% of the dose (Krishna and White, 1996). Elimination half-life ($t_{1/2}$) of quinine and the effective concentration in plasma are 10-18 hours and 5-10 mg/l, respectively (Franc *et al.*, 1987). The pharmacokinetics of quinine is altered by many factors such as genetics, disease status and drug coadministration. Toxicity occurred when prolonged treatment and plasma concentrations are equal or more than 10 mg/l (Powell and McNamara, 1972). Side effect of quinine such as cinchonism was found in patients with plasma concentration higher than 5-12 mg/l (Painisko and Keystone, 1990 ; White, 1996). The symptoms of cinchonism include tinnitus, vertigo, transient loss of hearing, nausea, vomiting, abdominal pain, dysphoria, headache and blurred vision (Painisko and Keystone, 1990). The QRS interval may be prolonged when total plasma quinine exceeds 10 mg/l (Dollery, 1999). The symptoms of severe toxicities are decrease in blood pressure and irregular heart rate (Boland *et al.,* 1985 ; Dyson *et al.*, 1985). However, electrocardiogram changes can be seen in healthy volunteers with quinine concentrations around 5 mg/l (Karbwang *et al.,* 1993b).

Azole antimycotics (ketoconazole and itraconazole) are broad spectrum of antifungal activity. The important drugs in this group are ketoconazole, itraconazole and fluconazole which have indication for the treatment of *Candida albicans, Candida tropicalis, Candida globata Cyptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum, Coccidiodes immitis* and *dermatophytes* (Bennett, 1996). The side effects

depend on dosage such as 400 mg/day result in nausea and vomiting, increase in triglyceride, reduce in potassium, rash and asymtomatic elevation of hepatic enzymes i.e. alanine aminotransferase, aspatate aminotransferase and gamma-glutamyltransferase (Janssen and Symoens, 1983). Azole antimycotics inhibit enzyme cytochrome P450s that metabolize many drugs in humans. Ketoconazole and itraconazole are potent inhibitors of isozyme CYP3A4 (Jalava, Olkkola and Neuvonen., 1997 ; Olkkola *et al.*, 1994 ; Varhe, Olkkola and Neuvonen., 1994). The results of CYP3A4 inhibition produce an increase in plasma concentration of drug coadministered such as triazolam, terfinadine and felodipine (Varhe *et al.*, 1994 ; Crane and Shih, 1993 ; Jalava *et al.*, 1997), which may be life threatening.

Ketoconazole and itraconazole inhibited metabolism of quinidine *in vitro* by inhibition of CYP3A4 and 2C9 (Zhao *et al.*, 1997). Recently, Mirghani *et al.* (1999) showed that CYP3A4 is important for the 3-hydroxylation of quinine in humans. However, the effect of itraconazole on quinine pharmacokinetics in healthy volunteers has not been reported. Since quinine has a narrow therapeutic index, therefore coadministration of some azole antimycotics (ketoconazole or itraconazole) with quinine may cause a significant increase in plasma concentrations of quinine, and leads to side effects. Normally, azole antifungal agents require long term in the treatment of fungal infection. The more increase in number of patients with HIV infection, the more increase in using antifungal agents. Moreover, evidence of malaria is increased not only transmission by infective female mosquito bites but also by coinfection with malaria and HIV injecting drug users (Bastos *et*

al., 1999). Therefore, quinine is possibly coadministered with ketoconazole or itraconazole in clinical practice. The purposes of this study were to observe and compare the effects of azole antimycotics (ketoconazole and itraconazole) on the pharmacokinetics and pharmacodynamics of a 300 mg single oral dose of quinine in healthy volunteers. The present study may be the guidance and useful data for making decision in case of coadministration of quinine with ketoconazole or itraconazole.