CHAPTER 1

INTRODUCTION

In Thailand, liver fluke infection has been recognized as a major local public health problem in northeastern region of the country for more than forty years (Jongsuksuntigul and Imsomboon, 1998). The causative helminthes are *Opisthorchis viverrini*, *O. felineus*, *O. sinensis* and the dominant species in Thailand is *O. viverrini*. The disease is found associated with jaundice, pancreatitis, cirrhosis and cholangiocarcinoma (Jadsri and Noojoy, 1999). The habit of eating raw fish is the source of infection. The infection is found in young people and increases with age. Immigration of infected people from northeast to the north impacts on prevalence. The northerners acquire the infection from eating raw-fish dishes called "lahb-pla" and "plasom" (Khamboonruang, 1991).

Opisthorchis viverrini trematode definitive hosts other than human are cat, dog, and other fish eating animals. The first intermediate hosts are snails *Bithynia*. The second intermediate hosts are numerous species of cyprinidae fishes. The egg hatches when ingested by a snail. The cercariae leave the snail in about 2 months encysted in the fresh of cyprinidae species fish, and become infective metacercariae. When ingested by a definitive host, they excyst in the duodenum and pass to the distal bile ducts, where they reach maturity in 3-4 weeks (Jongsuksuntigul and Imsomboon, 1998).

Jongsuksuntigul and Imsomboon (1998) reported that the latest data obtained from the liver fluke control evaluation in 1996 indicated the highest prevalence (32.6%) in the northern region. While the central region has its prevalence rate of 16.7%. The lowest prevalence is 15.3% in the northeastern region. After praziquantel was introduced in Thailand as a treatment for opisthorchiasis it was discovered that the drug is also effective against intestinal flukes. The adult worms can be stained and identified after being expelled in the feces (Radomyos *et al.*, 1998).

Praziquantel, a pyrazinoisoquinoline derivative, has a wide range of activity against trematodes and cestodes, and is widely used in schistosomiasis, as well as other fluke infections pathogenic to humans (Reynolds *et al.*, 1993). Praziquantel is effective (> 95% cure rate) in a single dose of 30 or 40 mg/kg for opisthorchiasis (de Silva *et al.*, 1997) or the three doses of 25 mg/kg taken 4 to 8 hours apart on the same day result in high rates of cure for infections with either the liver flukes, *O. sinensis* and *O. viverini*, or the intestinal flukes, *Fasciolopsis buski*, *Heterophyes heterophyes*, and *Metagonimus yokogawi* (Tracy and Webster, 2001). In man, the threshold plasma concentration of praziquantel is about 1.0 μM (approximately 0.3 μg/ml) and this has to prevail for about 6 hours in order to affect schistosomes lethallity (Andrew, 1988). Praziquantel is readily absorbed after oral administration, so that maximal levels in human plasma occur in 1 to 2 hours (Tracy and Webster, 2001). Mandour *et al.* (1990) showed that the values of C_{max}, AUC_{∞}, Vd and Cl of praziquantel in six healthy volunteers following a single oral dose of 40 mg/kg were about 820 ng/ml, 5410 ng/ml.hr, 7695 L and 11 L/kg/hr, respectively.

The pharmacokinetics of praziquantel are dose-related. Extensive first-pass metabolism to many inactive hydroxylated and conjugated products limits the bioavailability of this drug and results in plasma concentrations of metabolites at least 100-fold higher than that of praziquantel. The drug is about 80% bound to plasma proteins. Its plasma half-life is 0.8 to 3.0 hours, depending on the dose, compared with 4 to 6 hours for its metabolites, but this may be prolonged in patients with severe liver disease including those with hepatosplenic schistosomiasis. About 70% of an oral dose of praziquantel is recovered as metabolites in the urine within 24 hours; most of the remainder is metabolized in the liver and eliminated in the bile (Tracy and Webster, 2001).

Mycobacterium tuberculosis is a growing, worldwide public-health threat. About one third of the world' s population is infected; *M. tuberculosis* causes up to three million deaths annually (WHO, 1998). The burden of active tuberculosis is spread disproportionately between two key regions: Southeast Asia and sub-Saharan Africa. Of about 40 million episodes of active tuberculosis that was occurred in young adults worldwide between 1990 and 2000, more than 28 million was occurred in Southeast Asia, and 9 million in sub- Saharan Africa (McDonald *et al.*, 1999).

Rifampicin is a semisynthetic derivative of rifamycin B, a complex macrocyclic antibiotic. It is an antituberculosis drug, which is usually administered for 6 to 24 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. The induction is a highly selective process and not every drug

metabolized via oxidation is affected (Venkatesan, 1992). The enzyme induction caused by rifampicin affects the metabolism of many drugs, increasing their metabolism and reducing their effects. The drugs affected include HIV protease and nonnucleoside reverse transcriptase inhibitors, digitoxin, digoxin, quinidine, disopyramide, mexiletine, tocainide, ketoconazole, propranolol, metoprolol, clofibrate, verapamil, methadone, cyclosporine, corticosteroids, oral anticoagulants, theophylline, barbiturates, oral contraceptives, halothane, fluconazole and the sulfonylureas (William and Petri, 2001). Recently, Dilger *et al.* (2000) reported that rifampicin induced both phase 1 metabolism (*N*-dealkylation) and phase 2 metabolism (glucuronidation) of oral propafenone, resulting in a clinically relevant drug interaction.

The pharmacokinetic drug interactions of praziquantel have been investigated in a number of studies. Coadministration of dexamethasone with praziquantel resulted in lowered maximum serum praziquantel concentrations and reduced bioavailability in human (Vazquez *et al.*, 1987). In rat, cimetidine, ketoconazole and miconazole each increased the bioavailability of praziquantel *in vitro* (Diekmann *et al.*, 1989). Bittencourt *et al.* (1992) showed that carbamazepine and phenytoin significantly decreased concentrations of praziquantel, due to increased clearance secondary to induction of first pass-liver metabolism. Pretreatment with phenobarbital resulted in lowered maximum praziquantel serum levels and reduced bioavailability in rat (Masimirembwa *et al.*, 1993). It is likely that CPY2B1 and CYP3A, both inducible by phenobarbital, were predominantly responsible for the formation of 4-hydroxypraziquantel (Masimirembwa and Hasler, 1994).

The HIV pandemic has contributed to the increased spread of tuberculosis; HIV-infected patients are 30 times more likely to develop active tuberculosis and become infectious than are HIV-negative individual. Of the estimated 20 million individuals with HIV infection or AIDS in the world in 1997, more than five million were diagnosed in Southeast Asia, and 14 million in sub-Saharan Africa. In these regions, where both HIV and *M. tuberculosis* infections are prevalent, the hospital setting may have an important role in the spread of *M. tuberculosis* (McDonald *et al.*, 1999). Therefore, the chance of using rifampicin in tuberculosis treatment is increasing. Due to the increase in prescribing rifampicin, the possibility of rifampicin and praziquantel coadministration tends to have a chance to occur in clinical practice, and may lead to cause rifampicin-praziquantel drug interaction. To our knowledge, there are no reports studied on the possible interaction between rifampicin and praziquantel, and the possible role of cytochrome P450 enzymes in the metabolism of praziquantel. Therefore, the purpose of this investigation is to study the effect of rifampicin on the pharmacokinetics of a single and multiple oral dose of praziquantel in healthy volunteers, and the present study may be the guidance and useful data for decision making in case of coadministration of praziquantel and rifampicin in clinical practice.