CHAPTER 1

INTRODUCTION

Liver fluke (*Opisthorchis viverrini*) is one of the most prevalent parasitic helminth in northeast Thailand. The infection induces hepatobiliary diseases, biliary obstruction, ascending cholangitis and cholangiocarcinoma which are important public health problems in country. In Thailand, the causative helminthes is *Opisthorchis viverrini* and the dominant species. The distribution of human infection is determined primarily by the distribution of the habit of eating raw freshwater fish; heterogeneity within endemic areas is probably due to environmental factors and control. Infection generally occurs during the first decade of life, often with a similar pattern in men and women, although men may be more frequently and heavily infected than women. Approximately 30 million people are infected by liver flukes, of whom 19 million are infected by *Clonorchis sinensis*, 9 million by *O. viverrini*, and 1.2 million by *O. felineus*. Liver fluke infection is endemic in China, Japan, Korea, Taiwan, and Vietnam (*C. sinensis*); Thailand and Laos (*O. viverrini*); and the Russian federation and Eastern Europe (*O. felineus*) (Parija and Marrie, 2002).

O. 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).

Praziquantel, an anthelminthic drug, exhibits broad activity against trematodes and cestodes. It is used in therapy as the racemate although the anthelminthic activity is mainly associated with the *R*-(-)-enantiomer (Lerch and Blaschke,1998). Praziquantel is

effective (> 95% cure rate) in a single dose 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*. Low dose of praziquantel can be used successfully to treat intestinal infections with adult cestodes, for example, a single oral dose of 25 mg/kg for *Hymenolepis nana* and 20 mg/kg for *Diphyllobothrium latum*, *Taenia saginata*, or *T. solium* (Tracy and Webster, 2001).

Praziquantel is rapidly absorbed after administration by mouth, even when taken with a meal, more than 80% of a dose is reported to be absorbed. Peak plasma concentrations are achieved 1 to 3 hours after a dose, but there is a pronounced first-pass effect and praziquantel undergoes rapid and extensive metabolism in the liver, being hydroxylated to metabolites that are thought to be inactive. It is distributed into the CSF. The plasma elimination half-life of praziquantel is 0.8 to 1.5 hours and that of the half-life of its inactive metabolites are 4 to 6 hours. It is excreted in the urine, mainly as metabolites, about 80% of the dose being eliminated within 4 days and more than 90% of this in the first 24 hours. Praziquantel is distributed into breast milk (Pearson and Hewlett, 1998; Prod Info Biltricide (R), 2000; Tracy and Webster, 2001).

The threshold plasma concentration of praziquantel in man is about 1.0 μM (approximately 0.3 μg/ml) and this has to prevail for about 6 hours in order to affect schistosomes lethally (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). Leopold *et al.* (1978) observed that doses of 5, 10, 20, and 50 mg/kg produced respective serum concentrations of 0.15, 0.25, 0.8 and 4.22 mg/L.

Azole antimycotics include two broad classes, imidazoles and triazoles. Both classes share the same antifungal spectrum and mechanism of action (Chambers, 2001). The important drugs in these groups are ketoconazole, itraconazole and fluconazole which have indication for the treatment for *Candida albicans*, *C. tropicalis*,

C. glabrata, *C. neoformans*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *C. immitis*, *Paracoccidioides brasiliensis*, and ringworm fungi (dermatophytes). *Aspergillus* spp. and *Sporotrichosis schenckii* are intermediate in susceptibility. *C. krusei* and the agents of mucormycosis appear to be resistant. These drugs do not appear to have any useful antibacterial or antiparasitic activity, with the possible exception of antiprotozoal effects against *Leishmania major* (Chambers, 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). Itraconazole is an oral antifungal agent of the triazoles class which contains three nitrogen atoms in the five-membered azole ring. The primary mechanism of action of azoles, in general, is the inhibition of sterol 14-α-dimethylase, a microsomal cytochrome P450-dependent enzyme system (Fabris *et al.*, 1993).

Oral absorption of ketoconazole varies among individuals. Since an acidic environment is required for dissolution of ketoconazole. Ingestion of food has no significant effect on the maximal concentration of the drug achieved in plasma. After oral dose of 200, 400, and 800 mg, peak plasma concentrations of ketoconazole are approximately 4, 8, and 20 μg/ml. The half-life of the drug increase with dose, and it may be as long as 7 to 8 hours when the dose is 800 mg. Ketoconazole is metabolized extensively, and the inactive products appear in the feces. Concentrations of active drug in urine are very low. In blood, 84% of ketoconazole is bound to plasma protein. Moderate hepatic dysfunction has no effect on the concentration of ketoconazole in blood. The concentration of ketoconazole in the CSF of patients with fungal meningitis is less than 1% of the total drug concentration in plasma (Chambers, 2001).

The absolute bioavailability of oral itraconazole is 55%. Itraconazole should be administered with food since the bioavailability is reduced by 40% when it is administered under fasting condition. The bioavailability of itraconazole is reduced by approximately 50% when administered together with H_2-antagonists. Itraconazole exhibits dose-dependent pharmacokinetic, leading to a more than dose-proportional

increase in the plasma level, especially after multiple dosing. The mean volume of distribution for itraconazole is 10.7 l/kg and the total clearance is 5.1 ml/kg (renal excretion negligible). Itraconazole is highly lipophilic and extensively distributed in tissues (99.8% protein bound). Body fluids such as CSF, eye fluid and siliva contain low to nondetectable amounts of itraconazole (Beule, 1996). Itraconazole is metabolized in the liver, primarily by the cytochrome CYP3A4 isoenzyme system, and it inhibits the metabolism of other drugs by CYP3A4. The half-life of itraconazole in the steady state is approximately 30 to 40 hours.

Pharmacokinetic drug interactions involving inhibition of cytochrome P450 activity have received considerable recent attention. Azole antifungals are important as inhibitors of human cytochrome P450-3A isoform. Coadministration of 3A substrate drugs with azole antifungals such as ketoconazole and itraconazole can result in impairment of clearance of such drugs which, in some case, can be quantitatively large and clinically important. This is particularly true for high-extraction compound given orally, since the azoles may inhibit both the gastrointestinal and hepatic of presystemic extraction (Greenblatt *et al.*, 1998).

In Thailand, fungal infections has been recognized as a major public health problem. Ketoconazole and itraconazole are 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 fungals and site of infection, whereas the liver fluke remains a major public health problem in northeast Thailand, where approximately one-third of the population is infected (Sithithaworn *et al.*,1994). Thus, the possibility of azole antifungals and praziquantel coadministration tends to have a chance to occur in clinical practice and may lead to azole antifungals-praziquantel drug interactions.

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 result in lowered maximum praziquantel serum levels and reduced bioavailability in rat. These results suggest that praziquantel is extensively metabolized by phenobarbital-inducible cytochrome P-450 isoforms (Masimirembwa *et al.*, 1993).

To our knowledge, there is no report studied in human on the possible interaction between azole antifungals and praziquantel. The purpose of this investigation is to study the effect of ketoconazole and itraconazole on the pharmacokinetics of a single 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 ketoconazole / itraconazole in clinical practice.