CHAPTER 1

INTRODUCTION

Filiariasis is a group of tropical diseases caused by various thread-like parasitic round worms (nematodes) including *Wuchereria bancrofti, Brugia malayi* and *Brugia timori*. The larvae transmits the disease to human through a mosquito bite. Lymphatic filariasis, known as Elephantiasis, puts more than a billion people in more than 80 countries at risk. Over 120 million have already been affected and over 40 million of them are seriously incapacitated and disfigured by the disease. One-third of the people infected with the disease live in India, one-third are in Africa and most of the remainder is in South Asia, the Pacific and the Americas (Bolla *et al*., 2002). In tropical and subtropical areas where lymphatic filariasis is well-established, the prevalence of infection is continuing to increase. A primary cause of this increase is the rapid and unplanned growth of cities, which creates numerous breeding sites for the mosquitoes that transmit the disease (WHO, 2000). In its most obvious manifestations, lymphatic filariasis causes enlargement of the entire leg or arm, the genitals, vulva and breasts. In endemic communities, 10-50% of men and up to 10% of women can be affected. The psychological and social stigma associated with these aspects of the disease is immense. In addition, even more common than the overt abnormalities is hidden, internal damage to the kidneys and lymphatic system caused by the filariae (WHO, 2000).

The two most common types of the disease are Bancroftian and Malayan filariasis, both forms of lymphatic filariasis. The Bancroftian variety is found throughout Africa, southern and southeastern Asia, the Pacific islands, and the tropical and subtropical regions of South America and the Caribbean. Malayan filariasis occurs only in southern and southeastern Asia. Filariasis is occasionally found in the United States, especially among immigrants from the Caribbean and the Pacific islands.

In Thailand, lymphatic filariasis is still a public health problem in someplaces. There are two types of filarial in Thailand namely; *W. bancrofti* and *B. malayi*. *W. bancrofti* was found at Mae Hong Sorn, Tak, and Karnjanaburi provinces. *B. malayi* was found in Surat-Thani, Phattani, Nakhon-Si-Thammarat, and Narathiwat. The highest prevalence rates were in Narathiwat province (21.79 per a hundred thousand) (Annual report of Filariasis Division, 2002).

Diethylcarbamazine (DEC) is the most important compound for the treatment of filarial infections (Gelband, 1994). It is the first-line agent which has been used for control and treatment of lymphatic filariasis and for therapy of tropical pulmonary eosinophilia caused by *W. bancrofti* and *B. malayi* (Ottensen and Ramachandran, 1995). Microfilarial forms and adult worms of susceptible filarial species are most affected by DEC, which elicits rapid disappearance of these development forms from host (Tracy and Webster, 2001). DEC is absorbed rapidly from the gastrointestinal tract after oral administration (Tracy and Webster, 2001), so that maximal levels in human plasma occur in 1-2 hours (Edward *et al*., 1981). Bolla *et al*. (2002) showed that the values of mean C_{max}, $AUC_{0\rightarrow\infty}$, t_{max}, and $t_{1/2}$ of DEC in twelve subjects following a single oral dose of 150 mg at two times (06.00 and 18.00) were 500 and 637 ng/ml, 5848 and 7220 ng.h/ml, 2.27 and 2.73 h, and 14.63 and 11.37 h, respectively. DEC is rapidly and extensively metabolized in liver (AMA, 1991; Gilman *et al*., 1990; Edwards *et al*., 1981; Hawking, 1979). A major metabolite is DEC-N-oxide. The plasma half-life varies, depending on the urinary pH (Tracy and Webster, 2001).

Mycobacterium tuberculosis is a widely spread infectious disease. 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 (CYP) 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 nonnucleotide 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.

Azole compounds are used extensively for the treatment of cutaneous and invasive fungal infections. 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, a potent CYP3A4 inhibitor, is an oral antifungal agent of the imidazole class, 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 [pK_a (1) = 6.51; pK_a (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 ± 1.70 mg/L occurred in 2.62 ± 0.52 h (Daneshmend, 1986). The mean half-life was reported to be 1.46 ± 0.39 h (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 ± 2.10 mg/L were achieved in 1.75 ± 0.94 h (Piscitelli *et al*., 1991). Daneshmend *et al*. (1984) performed 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 ± 1.65 mg/L occurred in about 2 h. The average half-life was 2.03 ± 0.42 h. For the 400 mg dose, peak concentrations of 6.5 ± 1.44 mg/L occurred in about 2.5 hours. The average half-life was 2.67 ± 0.48 h. 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_{0-24} (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 CYP3A4, the major CYP isoform of the liver (Suzuki, 2000). The inhibitions of CYP3A4 results in drug-drug interactions involving ketoconazole can a decrease in the rate of clearance of many drugs (Tsunoda, 1999).

DEC is both rapidly and extensively metabolized in the liver (Tracy and Webster, 2001; Micromedex Healthcare Series, 2004). Since CYP3A4 was most found in liver (about 25% of all CYP type) (Lin and Lu, 1998). Therefore, rifampicin and ketoconazole should theoretically alter the metabolism of DEC.

In Thailand, tuberculosis and fungal infections have been recognized as a major public health problem. Especially, in HIV patients, both diseases are opportunistic infections (OIs). Common OIs are tuberculosis both pulmonary and extra-pulmonary, oropharyngeal candidiasis, herpes zoster, herpes simplex, toxoplasmosis, cryptococcal meningitis, pneumocystis carinii pneumonia, cytomegalovirus retinitis and cryptosporidial diarrhea. Whereas lymphatic filariasis is also a major public health problem in Thailand. Thus, the possibility of rifampicin or ketoconazole and DEC co-administration tends to have a chance to occur in clinical practice and may lead to rifampicn-DEC or ketoconazole-DEC drug interaction. To our knowledge, there are no reports studied on the possible pharmacokinetic drug interaction between rifampicin or ketoconazole with DEC in humans. Therefore, the purpose of this investigation is to study the effects of rifampicin and ketoconazole on the pharmacokinetics of a single oral dose of DEC in healthy volunteers.