

CHAPTER 1

INTRODUCTION

1.1. Introduction

Ketoconazole, an imidazole piperazine antifungal agent, is used for the treatment of *Candida* infection, where oropharyngeal and esophagus candidiasis are the two most common fungal infections in AIDS patients (McEvoy ed., 2001a). Ketoconazole is also used in the relapsed prophylaxis of *Penicillium marneffeii* infection which rapidly spreads among AIDS patients in Thailand (Hospenthal and Bennett, 2000). However, failure of ketoconazole in treatment of esophageal candidiasis in AIDS patients was reported due to resistance (Tavitian *et al.*, 1985) and incomplete drug absorption (Lake-Bakaar *et al.*, 1988a).

Ketoconazole is a weak dibasic compound with pK_a of 2.94 and 6.51 (McEvoy ed., 2001a; Daneshmend and Warnock, 1988; Carlson, Mann and Canafex, 1983). The dissolution of ketoconazole is pH dependent. The *in vitro* study showed that it is almost insoluble in neutral solution except buffer solution at pH lower than 3 (Carlson, Mann and Canafex, 1983). The gastric pH of AIDS patients was reported to be less acidic than that in healthy volunteers (5.9 ± 3.2 , mean \pm SD, compared with 2.9 ± 0.1) (Lake-Bakaar *et al.*, 1988b). Significantly reduced maximum acid output (MAO) and intrinsic factor secretion were reported as a result of increased gastric pH (Lake-Bakaar *et al.*, 1988b, 1996; Shaffer *et al.*, 1992; Belistsos *et al.*, 1992; Welage *et al.*, 1995). The incomplete absorption of ketoconazole was observed in AIDS patients (Lake-Bakaar, *et al.*, 1988a). Decreased ketoconazole absorption was also reported in healthy volunteers who received drugs inducing gastric hypoacidity, such as antacids (van der Meer *et al.*, 1980), cimetidine (van

der Meer *et al.*, 1980; Blum *et al.*, 1991), ranitidine (Piscitelli *et al.*, 1991), sucralfate (Piscitelli *et al.* 1991; Carver *et al.*, 1994) and omeprazole (Chin, Loeb and Fong, 1995).

Enhanced absorption of ketoconazole was observed when the drug was co-administered with acidic agents. Lake-Bakaar *et al.* (1988) found that AIDS patients whose MAO was less than 15 mEq/L had significantly increased ketoconazole absorption when 200-mg of the drug was administered with 200 mL of 0.1 N hydrochloric acid. The mean \pm SD of area under the serum ketoconazole concentration-time curve over 24 hours (AUC_{0-24h}) increased from 1.4 ± 0.9 mg.h/L without acid to 9.9 ± 1.9 mg.h/L in the presence of acid ($p < 0.005$). However, the use of dilute hydrochloric acid solution is associated with several drawbacks including difficulty to obtain this non-commercial preparation, unpalatability, damage of dental enamel and irritation of the oropharangeal mucous membranes (Chin, Loeb and Fong, 1995). Moreover, significant increase in ketoconazole absorption was observed in healthy volunteers receiving drug-induced gastric hypoacidity when co-administered the drug with 680 mg or more of glutamic acid capsule (Lelawong *et al.* 1988) or acidic beverage, such as 240-ml of classic Coca-Cola (pH = 2.5) (Chin, Loeb and Fong, 1995). The manufacturer canceled glutamic acid capsule from the market. Also, administration of Coca-Cola to AIDS patients should not be recommended in caffeine intolerance, active peptic ulcer, or in some patients who feels difficult to take it.

Vitamin C is an acidic compound with pK_a s of 4.2 and 11.6. The 50 mg/ml and 5 mg/ml of vitamin C solution produce the pH of 2 and 3, respectively (Budavari, ed., 1996). Vitamin C functions as a cofactor and effective antioxidant. Recommended dietary allowance (RDA) of vitamin C in adult by the National Academic Sciences (NAS) is 75 - 90 mg/day. The dose of 1-3 g or greater per day is recommended to prevent and/or to treat the common cold, while the dose of 4-12 g/day is used as urinary acidifying agent. Vitamin C is apparently nontoxic. Excess of vitamin C is excreted in the urine as an unchanged form. High doses (more than 1 g/day) may cause diarrhea and gastrointestinal disturbances (McEvoy ed., 2001b).

It is proposed that concomitant administration of vitamin C and ketoconazole in AIDS patients might enhance the absorption and consequently therapeutic efficiency of ketoconazole.

1.2. Objective of the Study

This study was conducted to determine the influence of vitamin C on ketoconazole absorption in AIDS patients.