CHAPTER 5

DISCUSSION

Gastrointestinal drug absorption may be affected by any diseases that cause changes in (1) intestinal blood flow, (2) GI motility, (3) stomach emptying time, (4) gastric pH, (5) intestinal pH, (6) permeability of gut wall, (7) bile secretion, (8) digestive enzyme secretion, and (9) alteration of normal gut flora. Gastric pH plays an important role in drug dissolution. Stomach hydrochloric acid is essential for solubilizing insoluble free base drugs. Without the acid, many weak base drugs will not form soluble salts and remain undissolved in the stomach resulting in diminished absorption of the drugs (Shargel ed., 2000).

Ketoconazole, an imidazole antifungal agent, is a dibasic compound. The dissolution requires pH lower than 3 (Carlson, Mann and Canafex, 1983). Many reports have shown that ketoconazole absorption was significantly decreased when concomitantly administered with drugs inducing gastric hypoacidity, such as cimetidine, ranitidine, antacids, omeprazole, and sucralfate (van der Meer *et al.*, 1980; Blum *et al.*, 1991; Piscitelli *et al.*, 1991; Carver *et al.*, 1994; Chin, Loeb and Fong, 1995). AIDS patients were also found to have impaired ketoconazole absorption, 5 of 10 patients failed to absorb, due to gastric hypoacidity (Lake-Bakaar *et al.*, 1988a).

Similarly, this study found that one patient failed to absorb ketoconazole but with greater amount compared with the former report (the mean $AUC_{0-\alpha}$ of 10.22 and 5.5, respectively). One explanation of the dissimilar absorption might be varied incidence of gastric hypoacidity in AIDS patient, ranging from 22 to 93% (Lake-Bakaar *et al.*, 1988b; Belistos *et al.*, 1992; Welage *et al.*, 1995; Lake-Bakaar *et al.*, 1996). The acid assessment of gastric can be done by gastric acid analysis quantities basal and maximum acid secretion, and intragastric pH monitoring allows only the determination of pH. The correlation of these two technique remains controversial.

By using intragastric pH monitoring with aspiration technique in the present study found that 72.7% of patients had gastric pH greater than 3.1, the mean ± SD of gastric pH was 6.14 ± 1.19 (ranging from 4.25 to 7.7), whereas the others was 2.37 ± 0.73. The potential problem from the choosing method was day-to-day variations of basal acid output. Neutralization of acid with swallowed saliva after harvested mucous aspirated content and improper gastric contents since the exact position of the tip of the tube did not monitor by fluoroscopy were also concerned. However, the results were similar to those reported by Lake-Bakaar *et al.* (1988b and 1996). By using the same technique they reported that 93% and 80% of AIDS patients had hypoacidity (gastric pH > 3.0). On the contrary, other techniques with longer gastric pH monitoring, such as radiotelemetric pH-monitoring device (Heidelberg pH capsule), and nasogastric sump tube containing pH probe, found hypoacidity 22% to 57% of AIDS patients (Belistos *et al.*, 1992; Welage *et al.*, 1995; Shelton *et al.*, 1997).

Enhancing ketoconazole absorption in drug-induced gastric hypoacidity subjects by concomitant administration of the drug with acidic agents, such as diluted hydrochloric acid, glutamic acid capsule, and acidic beverage (Classic Coca-Cola) was found to significantly increase its absorption (Lake-Bakaar *et al.*, 1988a; Lelawong *et al.*, 1988; Chin, Loeb and Fong, 1995). However, use of these agents in AIDS patients may be associated with several drawbacks, such as difficulty to obtain commercially diluted hydrochloric acid, unpalatability, damage of dental enamel and irritation of the oropharyngeal mucous membranes. Nowadays, glutamic acid capsules were withdrawn from the market. Also, use of acidic beverage in AIDS patients should be carefully concerned in caffeine tolerance and active peptic ulcer, and some patients may find that it is hard to take. Therefore, new acidic agents enhancing ketoconazole absorption are needed.

Vitamin C is an essential vitamin with acidic property. Then, this present work evaluates the potential of vitamin C to improve ketoconazole absorption in AIDS patients. Although the result of all patients did not show significant difference of $AUC_{0-\alpha}$, T_{max}, and $t_{1/2}$, a patient who initially failed to absorb showed dramatic improvement of absorption with vitamin C, as indicated by 5-fold increase in $AUC_{0-\alpha}$. In addition, C_{max} was shown significantly increased in the presence of vitamin C (p =

0.016). Regarding to the variation of inter-patient absorption (high value of SD), to diminish the variation by using the absorption ratio, $AUC_{0-\alpha}$ with vitamin C / $AUC_{0-\alpha}$ without vitamin C (**Table 7**). The result was shown the increment approximately 2-fold ketoconazole absorption after concomitant administration of the drug and vitamin C.

According to the variation of gastric pH, patients could be partition into two groups: the group of gastric pH greater than 3.1 and gastric pH less than or equal to 3.1. The results still showed the same in the group of gastric pH greater than 3.1 with significant increased C_{max} (p = 0.007) (**Table 8**). Ketoconazole is lipophilic, so it should be absorbed across the gastrointestinal mucosa when it is in solution (Carlson, Mann, and Canafex, 1983). That is the rate of ketoconazole absorption depends on the rate of drug dissolution. Therefore, increased C_{max} of ketoconazole can be attributed to vitamin C-induced improvement in ketoconazole dissolution.

Furthermore, patients could be partition into two groups according to disease state: the group of stable illness, and the group of progressive illness. Concomitant administration of ketoconazole and vitamin C significant increased of $AUC_{0-\alpha}$ and C_{max} in the stable illness group (**Table 9**). It inferred that vitamin C improved the extent of ketoconazole absorption in stable illness patient. Stable illness patients were on cotrimoxazole or none medication. Previous studies have not shown any significant effect of cotrimoxazole on intestinal function (absorption, permeability, and inflammation) (Shrapstone *et al.*, 1999), hence it might be less effected on ketoconazole absorption. The progressive illness group did not show the difference. On the contrary, $AUC_{0-\alpha}$ in the presence of vitamin C showed lesser values than without vitamin C (p = 0.08) in these group. The pathogenesis of gastrointestinal abnormalities in AIDS is complex and multifactorial. The significant reduced absorptive capacity, increased intestinal permeability, and accelerated small intestinal transit were reported in AIDS patients (Sharpstone *et al*, 1999). Moreover, the concomitant medication may be responsible for alteration of ketoconazole absorption.

Focusing in the progressive illness group, patient No.4 diagnosed and treated for PCP infection during the study period with high dose of cotrimoxazole and

prednisolone tapering dose. The dose of 40 mg/day and 10 mg/day of prednisolone was given to the patient prior to treatment A and B, respectively. Although concomitant ketoconazole and prednisolone has not reported the effect of prednisolone on ketoconazole absorption, there was reported only ketoconazole unaffected blood level of prednisolone (Yamashita *et al.*, 1991). The competition for protein binding might be occurred because both ketoconazole and prednisolone have high protein binding, 93 to 96 % (McEvoy ed., 2001a), and 65 to 91 % (Lacy ed., 2001), respectively.

Patient No. 6 and 10 received ciprofloxacin and norfloxacin, fluoroquinolone antibiotics. Previous report showed that ciprofloxacin and norfloxacin depressed the activity of cytochrome P450, CYP3A4, in human liver microsomes by 64 % and 65 %, respectively (Mclellan *et al.*, 1996). CYP3A4 is also the essential enzyme for ketoconazole metabolism; therefore concomitant ketoconazole and ciprofloxacin or norfloxacin should be concerned in competitive inhibition CYP3A4. However, further investigation is needed to evaluate if strongly evidence of this interaction is existed.

Optimal dose of vitamin C is another factor that plays an important role in influencing drug absorption. Each mole of vitamin C (176 g/mole) yields approximately 1 equivalent of hydrogen ion (Budavari ed., 1996). According to our preliminary *in vitro* study, it was shown that addition of 1.5 g of vitamin C resulted in more than 80% increase of ketoconazole dissolution in phosphate buffer pH 6. Furthermore, adverse reactions of vitamin C, especially nausea, vomiting, and diarrhea, are reported when the dose of vitamin C is higher than 1.0 g. Therefore, in the present study, fixed dose 1.5-g of vitamin C was selected. However, the dose of vitamin C may not work adequately for improved ketoconazole absorption in every patient. Since none patients in this study had adverse drug reaction, the individual dose adjustment of vitamin C depending on patients' tolerance is suggested for enhanced ketoconazole absorption. Even though vitamin C solution is not commercially available due to instability of the solution dosage form. Development of new preparation of vitamin C used concomitantly with ketoconazole will be beneficial for further investigation.

Vitamin C offers advantages for AIDS patients. High dose of vitamin C ingestion is used for common cold prophylaxis and it also plays role as an antioxidant.

Antioxidant deficiency has been reported in HIV-positive populations. This probably due to increased utilization of antioxidant micronutritions because of increased oxidative stress (Allard *et al.*, 1998, Batterham *et al*, 2001).

Nevertheless, there are inadequate data on the relationship between minimum inhibitory concentration of ketoconazole on *Candida* species, 0.25 mg/L (Cartledge *et al.*, 1997), and the clinical response in treatment of mucocutaneous candidiasis. Also gastric hypoacidity in AIDS patient is controversial in varied incidences ranging from 22 to 93% (Lake-Bakaar *et al.*, 1988b; Belistos *et al.*, 1992; Shaffer *et al.*, 1992; Welage *et al.*, 1995; Shelton *et al.*, 1998; Lake-Bakaar *et al.*, 1996). Therefore, current medication used for fungal infection treatment in AIDS patients is fluconazole because its absorption is unaffected by lack of gastric acidity. However, significant limitation to the routine and widespread use of fluconazole is emerging of *in vitro* and clinical resistance of *C. albicans* in HIV infected patients (Cartledge *et al.*, 1997). Fluconazole should be reserved for deep fugal infection. Superficial Candida infections in AIDS patients having stable illness may be treated with the regimen of ketoconazole and vitamin C. However, they must be closely monitored for therapeutic failure since this regimen may not work adequately for every patient, or fungal resistance to ketoconazole may occurred.