

CHAPTER 2

REVIEW OF LITURATURE

2.1. Ketoconazole

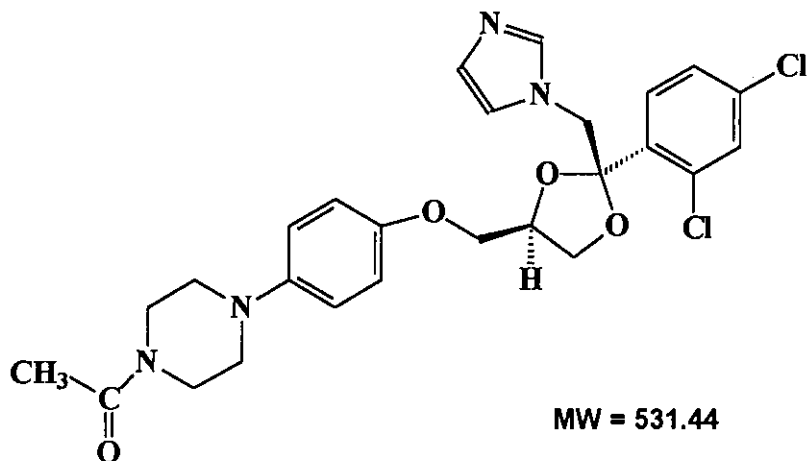


Figure 1: The chemical structure of ketoconazole (Budavari ed, 1996)

Ketoconazole is a weak dibasic antifungal agent with a pK_{a_1} of 2.94 and 6.51. It is almost insoluble in neutral water. The solubility of ketoconazole is completed in buffer solution pH lower than 3. (Carlson, Mann and Canafex, 1983; Daneshmend and Warnock, 1988; McEvoy ed., 2001a) A slightly decrease in the solubility of ketoconazole at pH of 4 and a rapid decline in solubility as the pH exceeded 5.5. Approximately 8 % of the drug are remained in solution even at the alkaline pH values. (Carlson, Mann and Canafex, 1983)

Mechanism of Action

Ketoconazole has usually fungistatic action. The exact mechanism of action of the drug has not been fully determined. However, it has been suggested that ketoconazole may interfere with ergosterol synthesis, probably via inhibition of C-14

demethylation of ergosterol synthesis. Ketoconazole at high concentrations may be fungicidal as a result of direct physicochemical effect of the drug on the fungal cell membrane (McEvoy ed., 2001a).

Pharmacokinetics

(1) Absorption

Ketoconazole is lipophilic drug and it should be absorbed across the gastrointestinal mucosa when it is in the solution (Carlson, Mann and Canafex, 1983). The mean maximum plasma concentration (C_{max}) of the single 200-mg ketoconazole in healthy volunteers has been reported to be 4.2 $\mu\text{g/ml}$ at 1.7 hours after oral administration (Huang *et al.*, 1986). The bioavailability of oral ketoconazole depends on the pH of the gastric contents in the stomach. An increase in the pH results in decreased absorption of the drug (McEvoy ed., 2001a).

(2) Distribution

Ketoconazole has been detected in urine, bile, saliva, sebum, cerumen, synovial fluid and cerebrospinal fluid following oral administration of a single 200-mg dose of the drug in adult (McEvoy ed., 2001a). In blood, 84% of ketoconazole is bound to plasma proteins, primarily albumin; 15% is bound to erythrocytes, and 1% is free (Hardman and Limbird, eds, 1996a).

The mean (\pm SD) of apparent oral clearance and the volume of distribution after 200-mg ketoconazole solution were 209.9 (\pm 82.9) ml/min and 88.31 (\pm 68.72) L, respectively (Huang *et al.*, 1986).

(3) Metabolism and excretion

Ketoconazole is partially metabolized in the liver to several inactive metabolites by oxidation and hydroxylation (McEvoy ed., 2001a). Plasma concentration of the drug was appeared to decline in a biphasic manner, with a mean (\pm SD) half-life ($t_{1/2}$) of 1.7 (\pm 0.6) h during the first 8 to 12 h and a mean $t_{1/2}$ of 7.9 (\pm 3.8) thereafter after the administration of the 200-mg of ketoconazole tablet (Huang *et al*, 1986). The major route of elimination of ketoconazole and its metabolites appears to be excretion into the feces via the bile (McEvoy ed., 2001a).

Indications (McEvoy ed., 2001a)

Oral ketoconazole is used to treat susceptible fungal infections, including blastomycosis, candidal infections (i.e. oropharyngeal candidiasis and/or esophageal candidiasis, vulvovaginal candidiasis, candiduria, chronic mucocutaneous candidiasis), histoplasmosis, paracoccidioidomycosis, coccidioidomycosis, and certain recalcitrant dermatophytoses.

Contraindication (McEvoy ed., 2001a; Micromedex, 2002)

Ketoconazole is contraindicated in patients with known hypersensitivity to the drug. Concomitant administration of ketoconazole and terfenadine, astemizole, or cisapride is contraindicated due to the risk of potentially fatal cardiac arrest.

Adverse Drug Reaction (McEvoy ed., 2001a; Micromedex, 2002)

(1) Gastrointestinal (GI) Effects

The most common adverse reactions of ketoconazole are nausea and/or vomiting (3 -10 %). Other GI effects include abdominal pain, constipation,

flatulence, GI bleeding, and diarrhea ($\leq 1\%$). Adverse GI effects appear to be dose related. Administration of ketoconazole with food minimized adverse GI effects, which usually subside with continued therapy.

(2) Hepatic Effects

Several cases of hepatotoxicity, hepatitis, and transient elevations in liver enzymes (SGOT, SGPT, and alkaline phosphatase) have been reported with ketoconazole therapy. Onset of the symptom has ranged from short-term (1 to 3 weeks) to long-term (12 to 15 months after initiation of therapy). Accompanying symptoms include nausea, backache, fever and weakness. Hepatotoxicity has been observed in patients receiving 200 to 800 milligrams daily. Symptoms may progress to jaundice, anorexia, and malaise and potentially death. Withdrawal of ketoconazole or reduction in therapy can result in resolution of jaundice and hepatic function tests within 7 weeks. Ketoconazole should be discontinued, when signs or symptoms of hepatotoxicity occur.

(3) Endocrine Effects

Bilateral gynecomastia with breast tenderness has occurred in some men during the therapy. A possible mechanism of ketoconazole-induced gynecomastia is inhibition of sterol synthesis through its direct inhibitory effect on adrenal steroidogenesis with a blunting of the cortisol response to adrenocorticotropin hormone. These would indicate that in some patients receiving ketoconazole there may be decreased adrenal reserve. The steroid blockade usually persists for 4 to 16 hours following a daily dose and should not be of major significance. Although available data indicate that ketoconazole must be given in higher dose for certain resistant fungal diseases and more frequently (two to three times daily), the patients may be at higher risk of developing a state of hypoadrenalism. The incidence of

gynecomastia was 21%. Endocrinologic toxicity was dose related and increased at doses greater than 800 mg.

(4) Other Adverse Effects

About 2% of patients receiving ketoconazole have experienced pruritus and less than 1 % experienced rash, dermatitis, and urticaria. Anaphylactic reactions occurring after the first dose of ketoconazole has rarely been reported.

Headache, dizziness, somnolence, lethargy, asthenia, nervousness, insomnia, abnormal dreams, photophobia, and paresthesia occurred in less than 1 % of patients receiving ketoconazole.

Dosage and administration (McEvoy ed., 2001a; Micromedex, 2002)

(1) Dosage

The recommended dose for ketoconazole is 200-400 mg daily for the treatment of chromomycosis, paracoccidioidomycosis, or oropharyngeal and esopharyngeal candidiasis. The 400-mg dose given once or twice daily is recommended for the treatment of blastomycosis, coccidioidomycosis, or histoplasmosis. The duration of ketoconazole therapy depends on the infecting organisms, the site and severity of the infection.

(2) Administration

To ensure absorption of oral ketoconazole in patients with achlorhydria, it has been recommended that each 200 mg of ketoconazole be dissolved in 4 ml of 0.2 N hydrochloric acid solution or taken with 200 ml of 0.1 N hydrochloric acid.

Alternatively ketoconazole may be administered with an acidic beverage (Coca-Cola™, Pepsi™) or dissolved in 60 ml of citric juice prior administration.

Drug Interactions (McEvoy ed., 2001a; Micromedex, 2002)

Since gastric acidity is necessary for the dissolution and absorption of ketoconazole, concomitant administration of ketoconazole and drugs which decrease gastric acid output or increase gastric pH, such as, antacids, cimetidine, ranitidine, omeprazole, antimuscarinics, may decrease absorption of ketoconazole.

Concomitant administration of ketoconazole and isoniazid and/or rifampicin has resulted in decreased serum ketoconazole levels.

Concomitant administration of ketoconazole and phenytoin reportedly may alter metabolism of one or both of the drugs, and serum concentrations of both drugs should be monitored.

Concomitant administration of ketoconazole and theophylline has resulted in decreased theophylline concentrations in a limited number of patients; however, serum theophylline concentrations and the patient should be closely monitored.

Prolongation of the QT interval and QT interval corrected for rate, and rarely, serious cardiovascular effects, including, arrhythmias (torsades de pointes, ventricular fibrillation, ventricular tachycardia), cardiac arrest, palpitations, hypotension, dizziness, syncope, and death, have been reported in patients receiving ketoconazole concomitantly with therapeutic doses of terfenadine, cisapride or astemizole.

Concomitant administration of ketoconazole and cyclosporine or tacrolimus has been reported to increase plasma concentration of both immunosuppressant drugs and

serum creatinine concentrations. Renal function and plasma concentrations of cyclosporine or tacrolimus should be monitored, and dose adjustment may be necessary.

Ketoconazole may inhibit warfarin metabolism resulting in increased anticoagulant effect when ketoconazole is used concomitantly with warfarin.

Elevated plasma concentrations of digoxin have been reported in patients receiving ketoconazole. Although the mechanism is unclear, digoxin concentrations should be monitored closely in patients receiving the antifungal agent.

Concomitant administration of ketoconazole and prednisolone or methylprednisolone may result in increased plasma concentrations of the corticosteroids, possibly due to decreased clearance of prednisolone or methylprednisolone. Ketoconazole may enhance the adrenal suppressive effect of corticosteroids. Adjustment in corticosteroids dose may be needed when ketoconazole is administered concomitantly with these drugs.

Disulfiram reactions, including flushing, rash, peripheral edema, nausea, and headache, have rarely occurred in patients who ingested alcohol while receiving ketoconazole therapy but usually resolved within a few hours. Some clinicians recommend that alcohol be avoided during and for 48 hours after discontinuance of ketoconazole therapy.

2.2. Vitamin C

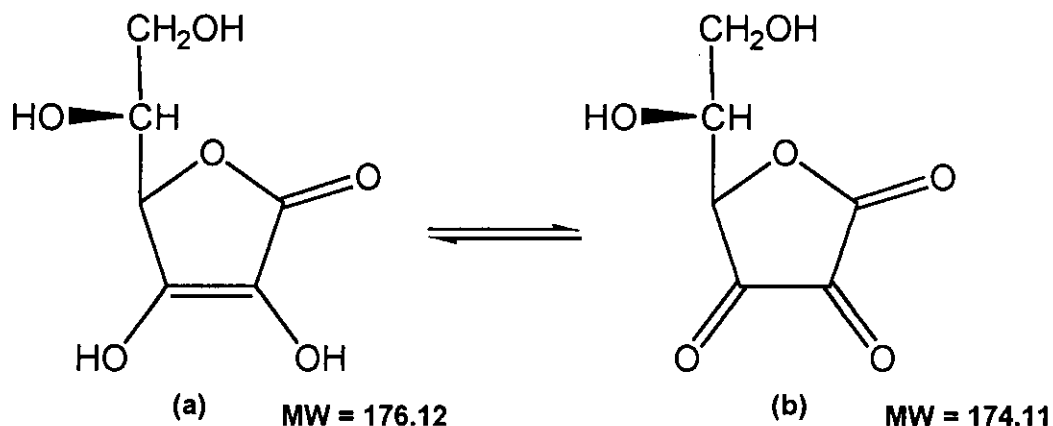


Figure 2: The chemical structure of ascorbic acid (a), and dehydroascorbic acid (b)
(Budavari ed, 1996)

Vitamin C is an essential water-soluble vitamin, which is present in fresh fruits and vegetables. The term of vitamin C refers to both ascorbic acid and dehydroascorbic acid (DHA), reversibly oxidized form of ascorbic acid. Both compounds exhibit antiscorbutic activity. Vitamin C is a weak acid with pKa values of 4.2 and 11.6 for ascorbic acid and 3.90 for DHA. It is freely soluble in water and has acidic taste (McEvoy ed., 2001b). Vitamin C solution at the concentration of 5 mg/ml and 50 mg/ml has the pH of 3 and 2, respectively (Budavari ed., 1996). Furthermore, 500-mg vitamin C tablet also decreased the pH of 10-ml synthetic saliva from 5.62 to 3.02 ($p < 0.05$) (Bailey *et al.*, 1990).

Mechanism of Action

Vitamin C works as an essential cofactor for the hydroxylation and oxygenase metalloenzymes, and effective antioxidant secondary to its ability of donate electrons (McEvoy ed., 2001b).

In this study, vitamin C was used as an acidifying agent to facilitate ketoconazole dissolution and absorption. Each mole of ascorbic acid (176 g/mole) yields approximately 1 equivalent of hydrogen ion. *In vitro* preliminary study showed that pH of phosphate buffer dropped from 4 and 6 to 3.4 and 3.3, respectively in the presence of 1.5-g of ascorbic acid. The dissolution of ketoconazole increased by more than 80% in buffer solution pH 6, with the presence of vitamin C. (unpublished data)

Pharmacokinetics

(1) Absorption

Ascorbic acid is readily absorbed from the intestine via an energy-dependent process that is saturable and dose-dependent (Hardman and Limbird, eds, 1996b). The 70-90 % of the usual dietary vitamin C (30-180 mg daily) ingested is absorbed (McEvoy ed., 2001b). When vitamin C is given in a single oral dose, absorption decreases from 75% at 1-g to 20% at 5-g (Hardman and Limbird, eds, 1996b).

(2) Distribution

Vitamin C is widely distributed in body tissues. Large concentrations of the vitamin are found in the liver, leukocytes, platelets, glandular tissues, and eye lens. About 25% of ascorbic acid in the plasma are bound to protein (McEvoy ed., 2001b).

(3) Metabolism and Excretion

Ascorbic acid is reversibly oxidized to DHA. Some ascorbic acid is metabolized to inactive compounds including ascorbic-acid-2-sulfate and oxalic acid,

which are excreted in the urine. When the body is saturated with ascorbic acid, unchanged ascorbic acid is excreted in the urine (McEvoy ed., 2001b).

Dosage and Indications

The RDA dose of vitamin C in adult is 75 – 90 mg daily. The oral administration of 100 – 250 mg vitamin C once or twice daily is used to prevent and treat scurvy. The dosage of 1 – 3 g per day or greater of vitamin C is recommended to prevent and treat the common cold. Dosage of 4 -12 g per day of vitamin C has been used as a urinary acidifying agent (McEvoy ed., 2001b).

Precautions

Vitamin C should be used cautiously in patients with preexisting kidney stone disease, erythrocyte G6PD deficiency, hemochromatosis, thalassemia, or sideroblastic anemia (Micromedex, 2002).

Adverse of Reactions (McEvoy ed., 2001b; Micromedex, 2002)

Vitamin C is usually nontoxic, however GI disturbances are the most common effects associated with high vitamin C intake (3 g or more daily). Diarrhea may occur after oral dosage of 1 g daily or greater, probably due to the osmotic effect of high doses of ascorbic acid. Other GI disturbances include nausea, abdominal pain, transient colic, and flatulence distention. Esophagitis and gastrointestinal obstruction are rarely reported after ingestion of ascorbic acid.

The observation that megadose vitamin C ingestion may increase urinary oxalate excretion and thereby increase the risk of nephrolithiasis was repudiated by a study demonstrating that oxalates measured in urine is formed during analysis and not *in vivo*. When the conversion of vitamin C to oxalate was prevented during analysis of urine

samples, no elevation of oxalate was found in urine of subjects who consumed 1 to 10 grams of ascorbic acid per day for 5 days. In a prospective study in which nearly 50,000 men were followed for 6 years, the level of vitamin C consumption (ranging from less than 250 mg/day to more than 1500 mg/day) was not correlated with the occurrence of the kidney stones.

Megadoses of vitamin C can cause harmful calcium oxalate crystalluria in some individuals who have a predisposition for increased crystal aggregation. Acute renal failure as a result of calcium oxalate crystals has occurred in several patients receiving a single intravenous dose of ascorbic acid, ranging from 2.5 to 60 grams.

Drug Interactions (McEvoy ed., 2001b; Micromedex, 2002)

Concurrent administration of more than 200 mg of ascorbic acid per 30 mg of elemental iron increases absorption of iron from the GI tract. However, this effect appears to be variable and in some cases either insignificant or significant only when the ferric iron is involved.

Increased urinary excretion of ascorbic acid and decreased excretion of aspirin occur when the drugs are administered concurrently.

High dose of ascorbic acid has interfered with the prothrombin time of patient receiving warfarin. However, the effect was a shortened prothrombin time rather than a potentiation.

Concomitant ascorbic acid and ethinyl estradiol therapy may increase the plasma concentration of ethinyl estradiol (when high doses of 1 g per day of ascorbic acid are administered). When ascorbic acid is discontinued, plasma levels of ethinyl estradiol drop and breakthrough bleeding has occurred. The effect may increase the risk for contraceptive failure.

2.3. The Studies of Ketoconazole Dissolution and Absorption

Ketoconazole is a weak dibasic compound. Dissolution of ketoconazole is pH-dependent. The *in vitro* study of Carlson and colleague (1983) demonstrated that 85 % of ketoconazole rapidly dissolved within 5 minutes and completely dissolved in 30 minutes using buffer solution having pH lower than 3 as dissolution medium. Only a slight decrease in drug solubility occurred at pH 4 and it precipitated rapidly in solution with pH exceeding 5.5. The pH solubility profile is shown in Figure 3. Eight percent of ketoconazole was estimated to dissolve in basic solution. Thus, the incomplete absorption of ketoconazole has been reported in healthy subjects who took the drug elevating gastric pH, for instance, cimetidine (van der Meer *et al.*, 1980; Blum *et al.*, 1991), ranitidine (Piscitelli *et al.*, 1991), omeprazole (Chin, Loeb and Fong, 1995), and sucralfate (Piscitelli *et al.* 1991; Carver *et al.*, 1994). Interestingly malabsorption of ketoconazole was observed in the AIDS patients due to reduced gastric acid secretion (Lake-Bakaar *et al.*, 1988a).

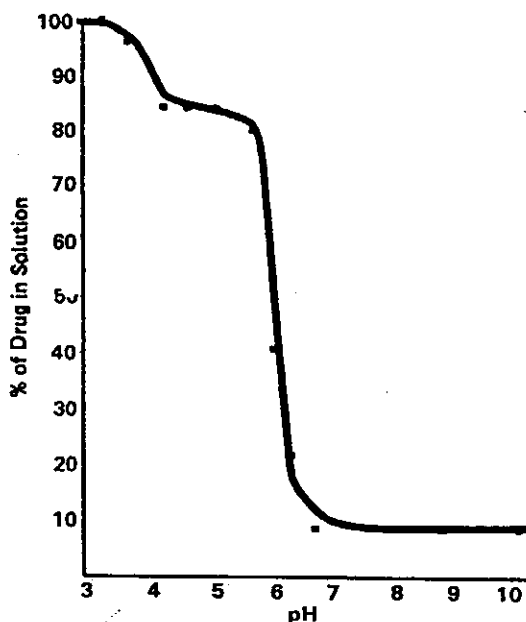


Figure 3. Precipitation of ketoconazole 200 mg in 900 ml of unbuffered dissolution medium as pH increased from 3 to 10. (Carlson, Mann, Canafex, 1983)

Cimetidine, the H₂-receptor antagonist, elevated gastric pH. Oral cimetidine dramatically reduced ketoconazole absorption in healthy volunteers when 400-mg dose of cimetidine was administered 2 hours before 200-mg dose of ketoconazole. The mean maximum concentration (C_{max}) of ketoconazole also reduced from 4.5 $\mu\text{g/ml}$ to 1.3 $\mu\text{g/ml}$ (van der Meer *et al.*, 1980). Blum *et al.* (1980) demonstrated that the significant reduction of ketoconazole was observed in healthy volunteers whose gastric pH raised over than 6.0 by intravenous cimetidine. AUC_{0-24h} (mean \pm SD) values were reduced from 34.1 ± 12.0 $\mu\text{g. h/ml}$ (without cimetidine) to 1.7 ± 1.5 $\mu\text{g.h/ml}$ (with cimetidine) ($p < 0.01$). C_{max} values were also significantly reduced from 7.01 ± 2.21 $\mu\text{g/ml}$ to 0.48 ± 0.37 $\mu\text{g/ml}$. Moreover, administration of cimetidine 300-mg tablet and 2-g of sodium bicarbonate were given 2 h and 1 h respectively prior to 200 mg ketoconazole statistically reduced ketoconazole absorption in 12 healthy volunteers. The mean AUC_{0-24h} was 15.25 $\mu\text{g.h/ml}$ without achlorhydria reduced to 1.29 $\mu\text{g. h/ml}$ (Lelawong *et al.*, 1988).

Similarly in healthy volunteers, ketoconazole absorption decreased when 150-mg dose of ranitidine given orally every 12 hours for 2 days prior to the study and 2 hours before the 400-mg oral dose of ketoconazole. Continuous monitoring of gastric pH with an ingestible Heidelberg pH transmitting radiotelemetry capsule showed values above 6.0 for 4 hours after ketoconazole administration. AUC_{0-12h} (mean \pm SD) was significantly reduced from 37.05 ± 9.54 $\mu\text{g.h/ml}$ (without ranitidine) to 1.64 ± 2.07 $\mu\text{g.h/ml}$ (with ranitidine). C_{max} values were significantly reduced from 8.20 ± 2.10 $\mu\text{g/ml}$ to 0.64 ± 0.52 $\mu\text{g/ml}$ ($P < 0.01$) (Piscitelli *et al.*, 1991).

Omeprazole, the proton pump inhibitor, is more potent than H₂-receptor antagonists in inhibiting gastric acid secretion. A 60-mg dose of oral omeprazole was given to nine healthy volunteer for at least 6 hours and gastric pH was monitored at pH greater than 6.0 (achlorhydria) by gastric aspiration via nasogastric (NG) tube prior to 200-mg ketoconazole dose. The results showed that ketoconazole absorption was reduced by more than 80 % after the administration of omeprazole. AUC_{0-12h} (mean \pm SD) was decreased from 17.89 ± 13.11 $\mu\text{g.h/ml}$ in normal group (without omeprazole) to 3.46 ± 5.08 $\mu\text{g.h/ml}$ in achlorhydria

group (with omeprazole). C_{max} (mean \pm SD) was significantly reduced from 4.13 ± 1.95 $\mu\text{g/ml}$ to 0.80 ± 1.09 $\mu\text{g/ml}$ and the time to reach maximum concentration (T_{max}) was extended from 1.5 ± 0.5 h to 2.9 ± 1.5 h (Chin, Loeb and Fong, 1995).

Sucralfate, a basic aluminum salt of sucrose octasulfate, is used in the treatment and prophylaxis of acid-peptic disorder. Although sucralfate does not disturb gastric secretion, there were reported that it interfered with both the dissolution and absorption of ketoconazole. The *in-vitro* study demonstrated that the pH of simulated gastric fluid (SGF) solutions at the initial pH of 1, 2, and 3 were markedly increased by the addition of sucralfate to 2.7, 4.35, and 4.35, respectively. Nevertheless, the pH levels of SGF were dropped from the initial pH of 6 to 5 because sucralfate effectively buffered solution to approximate pH of 4.5. Fourteen percent decrease in ketoconazole solubility was induced by sucralfate in the mixture of ketoconazole in SGF, though the final pH of the mixed solution was acidic (pH = 2.72). In fact, 96 % ketoconazole was soluble at the pH 2.72 in the absence of sucralfate (Hoeschele *et al.*, 1994). Furthermore, *in vivo* study showed that concomitant administration of 400-mg of ketoconazole and 1.0-g of sucralfate to healthy volunteers decreased $AUC_{0-\infty}$ from 78.12 ± 12.20 $\mu\text{g. h/ml}$ (without sucralfate) to 59.32 ± 13.61 $\mu\text{g. h/ml}$ (with sucralfate). C_{max} was also significantly decreased. Administration of sucralfate 2 hours prior to ketoconazole minimally affected $AUC_{0-\infty}$ (80.78 ± 15.56 $\mu\text{g. h/ml}$) and C_{max} (Carver *et al.*, 1994). Unlike the single dose of sucralfate, administration of 1.0-g of sucralfate orally four time daily for 2 days and 1.0 g of sucralfate suspension 5 minutes before the 400-mg oral ketoconazole dose (study group) minimally affected AUC_{0-12h} (a 20.2 % decrease noted) in six healthy volunteers compared with control (a single dose of ketoconazole) (Piscitelli *et al.* 1991).

Therefore gastric acid is an essential factor for adequate dissolution and absorption of oral ketoconazole. The drug is commonly used for the treatment and prophylaxis of *candida* esophagitis and *Penicillium marneffeii* infection in HIV-infected and AIDS patients (Hospenthal and Bennett, 2000). However, failure of ketoconazole treatment in AIDS patients has been reported due to ketoconazole-resistant organisms (Tavitian *et al.*, 1985)

or malabsorption of the drug (Lake-Bakaar *et al.*, 1988a). Focusing on the malabsorption, AUC_{0-24h} (mean \pm SE) of all ten AIDS patients taking 200-mg of ketoconazole tablet was significantly increased from 5.5 ± 2.8 mg. h/L to 12.4 ± 2.8 mg.h/L after the drug was taken with 200 ml of 0.1 N hydrochloric acid ($p < 0.05$). More importantly, ketoconazole absorption in patients, whose MAO was less than 15 mEq/h, was significantly increased. The AUC_{0-24h} was increased from 1.4 ± 0.9 mg.h/L to 9.9 ± 1.9 mg.h/L as presence of acid ($p < 0.005$) (Lake-Bakaar *et al.*, 1988a). However, the usage of dilute hydrochloric acid solution is associated with several drawbacks, for instance, inconvenience due to its availability, unpalatability, damage of dental enamel and irritation of the oropharyngeal mucous membranes (Chin, Loeb and Fong, 1995).

An acidic beverage, 240-ml of Coca-Cola classic (pH 2.5), enhanced 200-mg ketoconazole absorption in healthy volunteers with induced achlorhydria. The AUC_{0-12h} increased from 3.46 ± 5.08 μ g.h/ml (without Coca-Cola) to 11.22 ± 10.57 μ g.h/ml (with Coca-Cola). The C_{max} value significantly increased from 0.80 ± 1.09 μ g/ml to 2.44 ± 1.72 μ g/ml whereas T_{max} was decreased from 2.9 ± 1.5 h to 2.2 ± 1.1 h (Chin, Loeb and Fong, 1995). However, acidic beverage recommended for AIDS patients should be questioned in caffeine tolerance and symptoms of AIDS gastropathy such as gastric distension, dyspepsia. Besides diluted hydrochloric acid and acidic beverage, 680-mg of glutamic acid capsule was also found to significantly increase ketoconazole absorption in 12 healthy volunteers inducing achlorhydria with cimetidine and sodium bicarbonate. The mean AUC_{0-24h} raised from 1.29 to 3.30 μ g.h/ml and C_{max} value also significantly increased from 0.32 to 1.46 μ g/ml (Lelawong *et al.*, 1988). However, the manufacturer now cancels glutamic acid capsule from the market. Moreover, ketoconazole solution prepared by dissolving the drug in 10 ml of 0.1 M HCl and mixing the sequentially solution in 240 ml of orange juice resulted in significant increase of AUC_{0-12h} as compared with the whole tablet taken with orange juice (Baxter *et al.*, 1986).

Another study was done by encapsulated ketoconazole on citric acid carrier compared with the normal tablet aimed to decrease inter-subject variation of ketoconazole

absorption in healthy volunteers. The results showed not significantly increase ketoconazole absorption (11% increased absorption) (Daneshmend et al., 1986). Due to studying in healthy volunteers who never induced gastric hypoacidity, they might not found the different results. So there is still the suggestion of dissolving ketoconazole in 60 ml of citrus juice which is the source of citric acid before administered to ensure absorption (McEvoy ed., 2001a). All data improved ketoconazole absorption studies are summarized in **Table 1**.

Table 1 Summary studies on improving ketoconazole absorption

study	sample size	Subjects and study design	Pharmacokinetic parameters (mean \pm SD)			
			AUC (mg/L h)	Cmax (mg/L)	Tmax (h)	t _{1/2} (h)
Huang <i>et al.</i> , 1986	23	Healthy volunteers : ketoconazole 200 mg	14.74 \pm 8.48	4.22 \pm 2.47	1.7 \pm 0.9	7.9 \pm 3.8
Daneshmend <i>et al.</i> , 1986	8	Healthy volunteers Control : ketoconazole 200 mg (conventional tablet)	14.41 \pm 7.83	3.63 \pm 1.70	2.62 \pm 0.52	1.46 \pm 0.39
		Study : encapsulated ketoconazole on citric acid carrier	16.03 \pm 7.22	3.90 \pm 1.19	2.75 \pm 0.70	1.64 \pm 0.50
Baxter <i>et al.</i> , 1986	5	Healthy volunteers Control : ketoconazole 400 mg + 240 ml of orange juice	50 \pm 15.2	9.3 \pm 2.5	2.6 \pm 1.2	
		Study : ketoconazole solution (400 mg of the drug dissolved in 10 ml of 0.1 M HCl and mixed in 240 ml of orange juice)	62.2 \pm 21.2 *	10.5 \pm 2.0	1.5 \pm 0.32	
Lake-Bakaar <i>et al.</i> , 1988	10	AIDS patients Control : ketoconazole 200 mg	5.5 \pm 2.8 ^(a)	1.4 \pm 0.6 ^(a)	2.2 \pm 0.3 ^(a)	2.0 \pm 0.1 ^(a)
		Study : ketoconazole 200 mg + 200 ml of 0.1-N HCl	12.4 \pm 2.8* ^(a)	3.3 \pm 0.3* ^(a)	1.6 \pm 0.3 ^(a)	2.6 \pm 0.5 ^(a)

Table 1 (continued)

study	Sample size	Method	Pharmacokinetic parameters (mean \pm SD)			
			AUC (mg/L h)	Cmax (mg/L)	Tmax (h)	t1/2 (h)
Lelawong <i>et al.</i> , 1988	12	Healthy volunteers : ketoconazole 200 mg	15.25	4.37	1.21	
		Healthy volunteers induced achlorhydria with cimetidine and sodium bicarbonate				
		- Control : ketoconazole 200 mg - Study : ketoconazole 200 mg + 680-mg of glutamic acid capsule	1.29 3.30*	0.32 1.46*	2.04 1.79	
Chin, Loeb and Fong, 1995	10	Healthy volunteers : ketoconazole 200 mg	17.89 \pm 13.11	4.13 \pm 1.95	1.5 \pm 0.5	
		Healthy volunteers induced achlorhydria with omeprazole				
		Control : ketoconazole 200 mg Study : ketoconazole 200 mg + 200 ml of classic Coca-Cola	3.46 \pm 5.08 11.22 \pm 10.57*	0.80 \pm 1.09 2.44 \pm 1.72*	2.9 \pm 1.5 2.2 \pm 1.1	

* statistically significant different between study and control ($p < 0.05$)

^(a) mean \pm SE

2.4. The Incidence of Gastric Hyposecretion in HIV and AIDS Patients

There are conflicted reported on gastric hypoacidity (minimum gastric pH of ≥ 3) in HIV-infected and AIDS patients. Lake-Bakaar *et al.* (1988b) found that 93 % of AIDS patients (n = 29) had reduced MAO and the mean gastric pH \pm SD of fasting gastric juice was statistically increased in AIDS compared with the normal subjects, from 5.9 ± 3.2 to 2.9 ± 0.1 . In addition they also reported pH of fasting gastric juice in AIDS patients, HIV-infected subjects, and normal subjects to be 5.8 ± 2.6 , 5.3 ± 2.4 , and 1.8 ± 0.2 , respectively (Lake-Bakaar, *et al.*, 1996). Subsequent studies have not found gastric hypoacidity common, for example, Welage *et al.* (1995) found that only 22 % of AIDS patients (n = 9) had gastric hypoacidity and Shelton *et al.* (1998) found 17 % of HIV-infected patients (n = 146) had gastric hypoacidity. Whereas Shaffer *et al.* (1992) did not find gastric hypoacidity in HIV-1 infected patients. Belistos *et al.* (1992) found that 57% of AIDS patients (n= 14) with chronic, more than 1 month, diarrhea had high fasting gastric pH more than 3 (mean pH of 6.1 ± 1.0) and all of them had gastric bacterial overgrowth, more than 10^4 bacteria/ml. The mean gastric pH was generally higher in AIDS patients with chronic diarrhea (4.3 ± 2.3) than those without diarrhea (2.9 ± 1.5).

Several mechanisms for reduce gastric acidity in HIV or AIDS patients have been postulated. Only one study found a high prevalence of antiparietal cell antibodies (Lake-Bakaar *et al.*, 1988b). The other mechanisms were evaluated by gastric mucosal biopsies. The result was showed those varying degrees of vacuolar degeneration of parietal cells on light microscopy. On electron microscope, tuberculo-vesicles were reduced and intracellular canaliculi were dilated with striking loss of microvilli (Lake-Bakaar *et al.*, 1996).