CHAPTER II

REVIEW OF KETOCONAZOLE

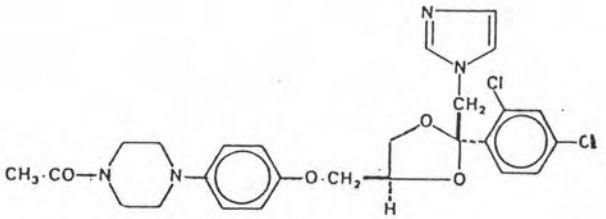

Figure 1 Chemical structure of ketoconazole

1. **Physicochemical properties** (Moffat, 1986; Carlson, Mann and Canafex, 1983; Mannisto et al, 1982)

Chemical name cis-1-Acetyl-4-{4-[2-(2,4-dichlorophenyl) -2-imidazole-1-ylmethyl-1,3-dioxalan-4-yl methoxy]phenyl} piperazine

Empirical formula $C_{26}H_{28}Cl_2N_4O_4$ (531.4)

Description White to slight beige powder

Solubility Practically insoluble in water, soluble 1 in 54 of ethanol, 1 in about 2 of chloroform, 1 in 9 of methanol, very slightly soluble in ether and soluble in aqueous pH lower than 3

pKa 2.94, 6.51

Partition coefficient 3.73 (octanol -water)

Melting point 146°c

2. Pharmacologic Effects

Like other imidazole derivertives, ketoconazole presumably exerts its antifungal activity by alterating cellular membranes, resulting in increased membrane permeability, secondary metabolic effects, and growth inhibition (American Society of Hospital Pharmacist, 1989; Heel et al., 1983; Hume and kerkering, 1983). Although the exact mechanism has not been fully determined, it has been suggested that the fungistatic action may result from interference with ergosterol synthesis, probably via inhibition of C-14 desmethylation of sterol intermediates (e.g.lanosterol) (American Society of Hospital Pharmacist, 1989; Heel et al., 1983). Besides antifungal activity, ketoconazole appears to inhibit steroid synthesis principally by blocking several P-450 enzyme systems (American Society of Hospital Pharmacist, 1989).

3. pharmacokinetics

3.1 Absorption

Ketoconazole is readily but not completely absorbed from GI tract. Concomitant administration with drugs which increase gastric pH (e.g. antacid, H_2-antagonist) may decrease its absorption and bioavailability (Carlson, Mann and Canafex, 1983; Heel et al., 1982; Mannisto et al., 1982). The effect of food on ketoconazole absorption has not been clearly determined because there have been conflicting reports indicating both enhancement

and reduction of absorption by food (American Society of Hospital Pharmacist, 1989; Brass et al., 1982; Daneshmend et al., 1982; Mannisto et al., 1982). More recent report suggested that coadministration of ketoconazole with food diminish the rate of drug absorption, and coadministration of the drug with a high carbohydate meal decrease the peak concentration of drug (Parichart et al., 1988).

In humans, a disproportionate increase in AUC has been noted following oral doses of 100, 200, 400, 600 and 800 mg of ketoconazole tablets (Daneshmend and Warnock, 1988). This has been interpreted as first-pass effect metabolism during absorption with transient saturation of hepatic metabolic capacity.

Oral bioavailability of the drug is similar when the drug is administrated in the forms of tablet or suspension. But when a drug solution is administered orally, its bioavailability is somewhat higher than the other two dosage forms (American Society of Hospital Pharmacist, 1989; Daneshmend and Warnock, 1983). In healthy fasting adults, peak plasma concentrations of approximately 4.2, 5 or 6.2 mcg/ml occurred 1-2 hr following oral administration a single 200-mg dose as tablets, a suspension, and a solution, respectively (Daneshmend and Warnock, 1988).

3.2 Distribution

Ketoconazole has been detected in urine, bile, saliva, sebum, cerumen, and synovial fluid following an administration of a 200-mg dose of the drug in adults. CNS penetration of the drug is unpredictable and has generally been considered to be minimal. It is not known if ketoconazole crosses the placenta in humans. Ketoconazole is distributed into the milk of dogs and is probably distributed into human milk (American Society of Hospital Pharmacist, 1989; Brass et al., 1982).

In human blood, only 1% of ketoconazole is presented as free drug in plasma, 83.7% is bound to plasma proteins, primarily albumin and 15.3% is in blood cell (Daneshmend and Warnock, 1988).

3.3 Elimination (Heel et al., 1982; Graybill and Craven, 1983; Hume and kerkering, 1988; Daneshmend and Warnock, 1988)

Plasma concentrations of ketoconazole appear to decline in a biphasic manner with half-lives of approximately 2 hr in the initial phase and approximately 8 hr in the terminal phase. Ketoconazole is partially metabolized in the liver to several inactive metabolites by oxidation and degradation of the imidazole and piperazine rings, by oxidative o-dealklylation, and by aromatic hydroxylation. The major route of elimination of ketoconazole and its metabolites appears to be excretion

into the feces via the bile.

4. Therapeutic Indication (Heel et al., 1982; Hay, 1985)

Systemic and Subcutaneous Mycoses

Ketoconazole is used orally in the treatment of pulmonary or disseminated coccidioidomycosis, paracoccidioidomycosis, histoplasmosis, chromomycosis, blastomycosis, candidiasis including oral infections and candiduria and chronic mucocutaneous candidiasis.

Dermatophytoses and Superficial Mycoses

Ketoconazole has been effective when used orally in the treatment of tineas caused by Trichophyton, microsporum, or epidermophytoses. Ketoconazole has been effective in the treatment of some dermatophytoses which are failed to respond to oral griseofulvin, however, controlled study are needed to compare the safety and efficacy of ketoconazole and griseofulvin in the treatment of chronic and extensive dermaphytoses when oral antifungal therapy is indicated.

Oral ketoconazole has been effective when used in the treatment of tinea versicolour caused by Malassezia furfur and vulvovaginal candidiasis in nonpregnant women.

Other Uses

Ketoconazole is also used in the prophylaxis of fungal infections in immunocompromised patients. More recently, it has been used as a treatment of advanced prostatic carcinoma as it blocks adrenal sex hormone synthesis.

5. **Adverse Effects** (Heel et al., 1982;Daneshmend and Warnock, 1988).

Nausea and vomiting occur in 3-10% of patients receiving the drug. Abdominal pain, pruritis, headache, fever, and chills, and photophobia develop in 1% or less than. Abdominal complaints were reported in up to 23% of patients during a 3-year study period. Gynecomastia occurs in 3-8% of patients receiving ketoconazole. Transient increase in SGOT, SGPT, alkaline phosphatase concentration has been reported. Ketoconazole has been associated with hepatotoxicity which rarely has resulted in death.

6. **Dosage** (American Society of Hospital Pharmacist, 1989)

The usual adult dosage of ketoconazole is 200 mg daily as single doses and may increase to 400 mg daily as single doses for severe infections or if the expected response is not achieved. The usual dosage for children who are older than 2 years of age is 3.3-6.6 mg/kg daily as single doses. The duration of ketoconazole therapy

depends on the infecting organism and the site of infection. Generally they should be continued until clinical and mycologic tests show that the fungal infection has subsided.