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A REVIEW ON ADVERSE EFFECTS, DRUG INTERACTIONS AND CONTRAINDICATIONS OF ORAL KETOCONAZOLE FORMULATION.

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Abstract:

The imidazole topical ketoconazole has long been used to treat fungus diseases and seborrheic dermatitis. Ketoconazole inhibits fungus ergosterol production, a component of cell membranes, and has other antifungal properties. Ketoconazole is also available as a cream, solution, and shampoo to treat skin fungus diseases. common side effects include itching, nausea, rash, stomach pain, headache, vertigo, tiredness, impotence, menstruation irregularities, and gynecomastia. Ketoconazole foam and gel versions for the therapy of seborrheic dermatitis have recently been introduced to the market, and they are successful against superficial fungal and yeast diseases. In 1981, the FDA authorised ketoconazole as the first broad-spectrum dietary antifungal. Post-marketing complaints of hepatotoxicity, adrenocortical insufficiency, endocrine dysregulation, and medication interactions led in the medicine being withdrawn from the market in some countries and severe product relabelling in others.

Keywords: *Oral Ketoconazole, Adverse effect of oral ketoconazole (hepatotoxicity, Adrenocortical Insufficiency, endocrine dysregulation), Contraindications of oral ketoconazole,*

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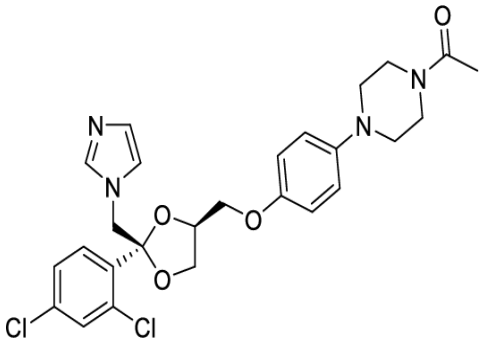
INTRODUCTION:

Oral ketoconazole was authorised by the FDA for the therapy of systemic mycoses in 1981[1]. The drug was a welcome addition to the therapeutic arsenal for systemic fungal infections, demonstrating efficacy comparable to that of amphotericin B against Para coccidioidomycosis [2]. and becoming the recommended therapy for chronic mucocutaneous candidiasis and an alternative treatment for oral candidiasis, vaginitis, histoplasmosis, and coccidioidomycosis [3]. Oral ketoconazole is only recommended for the treatment of blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and Para coccidioidomycosis in patients who have failed or are intolerant to previous medications. Ketoconazole should not be used to treat any dermatological problem. To guarantee patient safety, liver function tests must be conducted before to the start of treatment and during the course of treatment. Ketoconazole has also shown potential in the therapy of dermatophytosis, onychomycosis, and pityriasis versicolor when used off-label [4]. It was deemed a breakthrough in dermatology because it was the first broad-spectrum, orally active antimycotic, and it was considered the gold standard in cutaneous antifungal treatment for nearly a decade [5,6].

However, as the medication became more widely used, reports of oral ketoconazole- associated hepatotoxicity, including hepatic failure requiring transplantation or mortality, started to mount [7,8]. In addition to accounts of liver damage, instances of endocrine dysregulation,[9] and unexpected medication interactions [10,11] raised concerns about the safety of oral ketoconazole. Due to accumulating proof against oral ketoconazole, it was withdrawn from the European and Australian markets in 2013 [12,13]. ketoconazole was also subjected to stringent relabelling in Canada and the United States [14]. Based in part on the findings of the FDA Adverse Event Reporting System (FAERS), it was decided that oral ketoconazole would no longer be used as a first-line treatment for any superficial fungal infection and would only be used in cases of severe or life-threatening endemic mycoses, or when alternative treatments are ineffective or are not tolerated by the patient [15,16].

Drug overview.

Drug name	Ketoconazole
Phase	IV
Indication:	Systemic and deep mycoses (caused by sensitive fungus) where other antifungal treatments have failed or are prohibited. ketoconazole does not travel well into the Brain. As a result, fungus meningitis should not be managed with oral ketoconazole. Recalcitrant instances of superficial mycoses (caused by susceptible fungus) that do not react to topical therapy or other standard therapies
Pharmacology description/ mechanism of action	Lanosterol 14a-demethylase inhibitor
Route of administration	Oral
Chemical structure	$C_{26}H_{28}Cl_2N_4O_4$ 

Mechanism of action:
Ketoconazole (NIZORAL, chemical name: cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)- 1,3-dioxolan-4-yl] methoxy] phenyl] piperazine is an azole-based antifungal, which targets CYP450 enzymes vital to cell metabolism and detoxification. ketoconazole principally inhibits lanosterol 14a-demethylase the enzyme that regulates the synthesis of ergosterol. The disruption of ergosterol biosynthesis alters cell membrane structure, thus compromising membrane integrity and permeability, and consequently interfering with cellular growth and reproduction [17,18].

In humans, ketoconazole can cause AEs by interacting with the CYP450 class of enzymes in non-target cells. ketoconazole is hepatically metabolized and excreted and hepatotoxicity may result through the direct action of the drug and its primary metabolite, N-deacetyl ketoconazole on hepatic cells [19,20]. ketoconazole interacts with the human CYP3A isoforms impacting hepatic drug clearance and alters steroid synthesis [17]. Given that it is a potent inhibitor of CYP3A4, concomitant administration of oral ketoconazole with other drugs metabolized by this system can raise serum levels, consequently increasing the toxicity of these agents [21]. Furthermore, CYP450-dependent enzymes are responsible for the conversion of cholesterol to steroid hormones such as testosterone and cortisol, and thus are involved in regulating testicular and adrenal gland function [17].

Hepatotoxicity from Ketoconazole:
When compared to the other azoles, ketoconazole has the greatest rate of hepatotoxicity. It typically begins as an asymptomatic rise in liver enzymes.[22] Early investigations found hepatic deviations such as hepatitis, liver damage, and elevated liver enzymes (e.g., alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase [ALP]) in a limited number of cases.[23]The expected incidence of ketoconazole-induced hepatotoxicity is one in 1000 to 3000 individuals.[24] In a cohort analysis of 69,830 patients treated with oral antifungal drugs, ketoconazole was linked with the greatest proportional risk of acute liver damage when compared to the risk among nonusers, followed by itraconazole.[25] Chien et al. examined the liver damage caused by ketoconazole in 137 individuals with onychomycosis. 17.5% of the ketoconazole-treated individuals had silent transaminase elevation. Hepatotoxicity occurred in four individuals (2.9%), but it disappeared after the medication was stopped. Interestingly, despite ongoing ketoconazole treatment, the abnormal biochemical changes eventually reverted to normal condition in patients with asymptomatic liver damage.[26] In a trial of 160 patients treated with large dosages (400 -- 2000 mg) of oral ketoconazole for coccidioidomycosis, 5% developed elevated AST and ALP two and three times the ULN, respectively; however, the authors observed that liver function abnormalities did not appear to be dose-related.[27]

Endocrine dysfunction:
Endocrine disruption caused by oral ketoconazole has been documented in the literature. Gynecomastia developed in 7.5% of patients in clinical trials, with an additional seven instances described in a later publication. All gynecomastia instances happened while taking doses varying from 200 to 800 milligrams daily.[28] 21% of the 160 subjects who got daily ketoconazole doses ranging from 400 to 2000 mg experienced gynecomastia, which was dose-dependent, increased with higher doses, and resolved with therapy cessation. ketoconazole suppresses testosterone production by inhibiting CYP17A1, a CYP450- dependent enzyme.[29] Ketoconazole substantially reduced serum testosterone levels in vivo at doses ranging from 200 to 600 mg; however, this impact was reversed 12 hours later.[30] Ketoconazole caused a much longer, albeit transitory, testosterone synthesis blockade. At doses varying from 800 to 1200 mg/day.[31] Ketoconazole also preferentially displaces dihydrotestosterone and oestrogen from serum-binding globulins. As a result, ketoconazole may cause gynecomastia by inhibiting testosterone production and displacing oestrogens from sex hormone binding proteins, lowering the androgen/ oestrogen ratio in males. As a result, while instances of ketoconazole-associated gynecomastia are uncommon, the medication does have the potential to change endocrine function.[32]

Adrenocortical Insufficiency:
In-vitro investigations show that ketoconazole inhibits several enzymes linked with cytochrome P-450, including 11-beta hydroxylase, C-17-20 lyase (17,20-des-molase), and the Cholesterol side chain cleavage enzymes.[33] Pont et al. demonstrated that ketoconazole blunts the serum cortisol response to ACTH after a single oral dosage in healthy males, we examined a patient with a cortisol-producing adrenal adenoma and discovered a significant reproducible decline in serum cortisol levels after multiple oral doses of ketoconazole. Furthermore, in vitro, ketoconazole obviously reduced cortisol synthesis in tissue slices of the excised adrenal tumour.[34] ketoconazole suppresses P450-dependent mitochondrial enzymes in the adrenal gland. Both the cholesterol side chain cleavage stage and the 11-hydroxylation process were inhibited.[35]

Food Interaction:

Food usually improves ketoconazole uptake. In 30 individuals with onychomycosis, Gascoigne et al. (1981) discovered higher and more consistent plasma ketoconazole concentrations 1 and 2 hours after a 200mg dose given during a normal meal.[36] When ketoconazole was taken after breakfast, Brass et al. (1982) observed a non-significant reduction [37]and Mannisto et al. (1982) observed a substantial reduction in AVC.[38] Daneshmend et al. (1984) discovered a constant improvement in ketoconazole absorption when it was given with a normal breakfast; this impact was present at doses of 200mg, 400mg, 600mg, and 800mg.[39] (fig. 1).

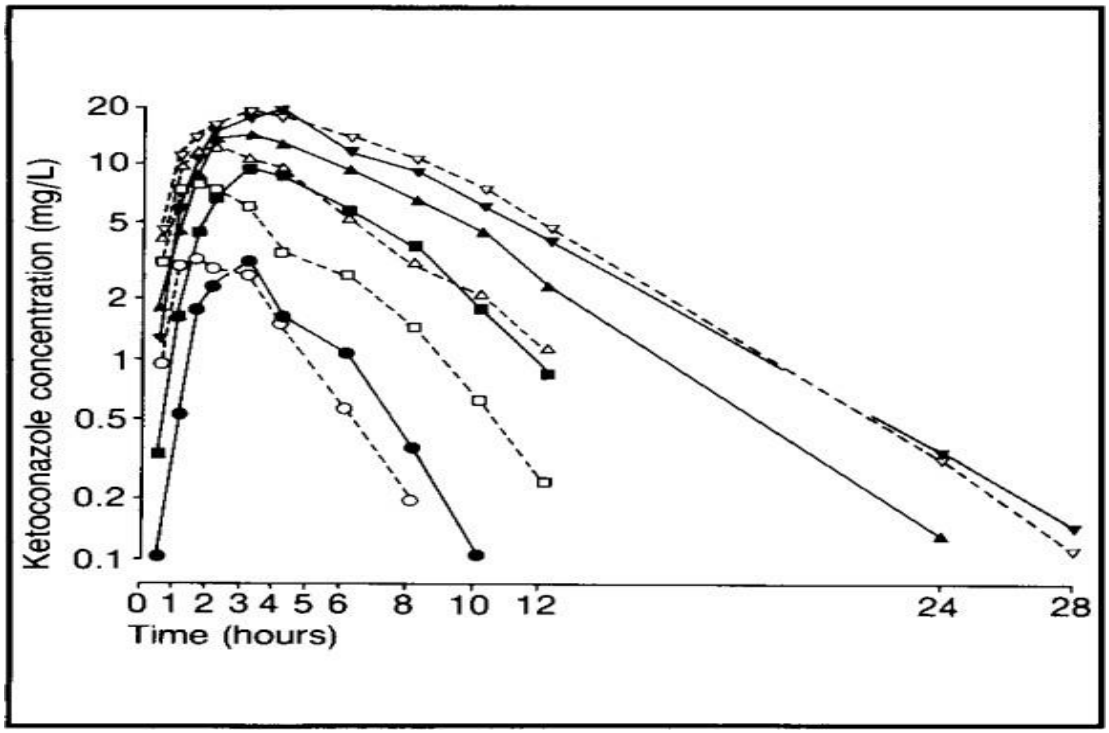


Fig. 1. Effect of food on ketoconazole administration. Open symbols represent administration while fasting, closed symbols represent administration with food A▼= 800mg; ▲∆ 600mg; ■□ = 400mg; ●o = 200mg (data from Daneshmend et al. 1984).

Drug Interactions:

1.Alcohol

A ketoconazole-treated Candida oesophagitis patient experienced sickness, vomiting, and facial redness, which appeared to be caused by alcohol consumption. Ketoconazole was administered in a weekly dosage of 200mg, but serum levels of the drug and alcohol were not tested. It was proposed that the association could be explained by a disulfiram-like impact.[40]

Another case was reported (Magnasco & Magnasco 1986), in which the patient experienced disulfiram-like acute alcohol intolerance on three separate occasions while taking ketoconazole 200mg per day.[41]

2.Anticoagulant

Ketoconazole has been shown to enhance the clotting impact of warfarin. A 75-year-old lady with steady anticoagulation on warfarin 19mg twice daily got spontaneous bruising after 3 weeks of ketoconazole 200mg twice daily. During this interaction, the anticoagulant impact was enhanced threefold. Three weeks after discontinuing ketoconazole, regular warfarin dosages were restarted. The author also noted another unpublished encounter in an 84-year- old guy.[42] According to the study, the process of this interaction is unknown.

3.Chlordiazepoxide

Brown et al. (1985) investigated the rates of chlordiazepoxide after a single dosage and after 5 days of ketoconazole 400mg. Ketoconazole decreased chlordiazepoxide clearance by 20% and volume of distribution by 26% in a single dosage. Because the AVC of metabolites (N-desmethylchlordiazepoxide and demoxepam) remained constant, the decrease in chlordiazepoxide clearance was not attributable to inhibition of chlordiazepoxide metabolism. The effects of a single 400mg dosage of ketoconazole on chlordiazepoxide excretion were discovered to last for 48 hours. Chlordiazepoxide clearance was decreased by 38% after 5 days of ketoconazole, and the AVC of its first oxidative metabolite, N-desmethylchlordiazepoxide, was reduced by 42 to

64%, but demoxepam AVC remained unaltered. (Brown et al. 1985).[43] The researchers found that ketoconazole inhibited at least one subgroup of the hepatic mixed immune system.

4. Cyclosporin

When cyclosporin and ketoconazole were administered, there were several case reports of elevated cyclosporin concentrations and associated nephrotoxicity. (Cunningham et al. 1982; Smith et al. 1983). Given the elevated cyclosporin concentrations, the findings were interpreted as ketoconazole-mediated inhibition of cyclosporin elimination, enhanced cyclosporin absorption caused by ketoconazole, or increased free cyclosporin due to ketoconazole-mediated displacement from cell and protein binding. [44,45]

Rat research found a connection between microsomal enzyme activity and cyclosporin-related nephrotoxicity.[46] In vitro research using rat hepatic microsomes discovered that cyclosporin decreased N-demethylation of aminopyrine by 20% and by 50% when combined with ketoconazole. At a ketoconazole concentration of 15 μ mol/L, the rate of aminopyrine N-demethylation by hepatic microsomes from untreated rats resulted in a reduction in V max and a rise in Km that was significant. These findings indicated that ketoconazole was a dual suppressor of liver N-Demethylation in rats.[47]

5. Phenytoin, Phenobarbitone, Rifampicin

Few formal studies have been conducted to investigate the possible interplay between ketoconazole and medications known to induce microsomal enzyme induction. Brass et al. (1982) found a 50% reduction in ketoconazole plasma AUC after a single 600mg dosage of rifampicin (rifampin). Ketoconazole AUC was decreased by 88% after 5 months of rifampicin 600mg daily (and isoniazid 300mg daily), from 17.33 to 2.02 mg/L' h. [37] (Brass et al. 1982). In healthy individuals, pre-treatment with rifampicin resulted in reduced ketoconazole concentrations.[48]

6. Methylprednisolone

Ketoconazole 200mg per day for 6 days raised the AUC of methylprednisolone by 135% and reduced its clearance by 60% in healthy subjects. Ketoconazole enhanced methylprednisolone's adrenal inhibitory impact. It is unknown whether ketoconazole affects cortisol excretion. This research indicates that when combined with ketoconazole, the dose of this corticosteroid may need to be reduced.[49]

Contraindications:

When the oral Ketoconazole is taken for a few weeks, Nausea and vomiting are the most common adverse effects, although others include loss of appetite, headache, paraesthesia, rashes, gynecomastia, loss of hair and libido, and oligozoospermia may develop. The main disadvantage of Ketoconazole is its hormonal effects. Some women experience menstrual abnormalities as a result of inhibition of oestradiol production.

It reduces androgen synthesis in the testes and removes testosterone from protein binding sites.[50]

Serum transaminase elevations are mild and asymptomatic in 5% of patients, although significant hepatotoxicity is infrequent.
It is not recommended for pregnant or breastfeeding women.

Ketoconazole suppresses the production of adrenal and gonadal hormones in humans, resulting in gynaecomastia, infertility, reduced libido, azoospermia, monthly abnormalities, and hypertension at high dosages.[51]
Problems with the gastrointestinal tract and pruritus are other common negative consequences.[52]

CONCLUSIONS:

In dermatology, the latest generation of azoles, triazoles, have shown similar or higher effectiveness than ketoconazole, as has terbinafine, an allylamine with an altogether different mechanism of action than previously available antifungals. The potency of antifungal agent ranges from triazole < echinocandin < azoles. The risk and benefit of oral ketoconazole usage over other oral antifungals is especially important in the treatment of superficial fungal infections. Terbinafine, for example, is considered the gold standard in oral antifungal therapy for many conditions, including onychomycosis; griseofulvin is still the treatment of choice for tinea capitis; and itraconazole and fluconazole are as effective as ketoconazole in treating pityriasis versicolor. As a result, the risk of hepatotoxicity, endocrine dysregulation, and medication interactions outweighs the benefit of taking oral ketoconazole.

Credit Author Statement

Shubham Veer: Investigation, Writing the initial draft, Reviewing and editing the manuscript, visualization with the figure. Prof. H. J. Pagar: Guidance, Rechecking the data and literature manuscript.

Declaration of competing interest

The authors state that they have no relevant financial relationship with any companies or organizations and have no conflict of interest.

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REFERENCES:

1. Ketoconazole approved for systemic fungal infections. FDA Drug Bull. U.S. Food and Drug Administration 1981; 11:18-19
2. Cuce LC, Wroclawski EL, Sampaio SA. Treatment of Para coccidioidomycosis, candidiasis, chromomycosis, lobomycosis, and mycetoma with ketoconazole. Int J Dermatol 1980; 19:405-8
3. Varkey B. Oral antifungal therapy. Current status of ketoconazole. Postgrad Med 1983; 73:52-3
4. Sohn CA. Evaluation of ketoconazole. Clin Pharm 1982; 1:217-24
5. Thienpont D, Van Cutsem J, Van Gerven F, et al. Ketoconazole -- a new broad spectrum orally active antimycotic. Experientia 1979; 35:606-7
6. Heel RC, Brogden RN, Carmine A, et al. Ketoconazole: a review of its therapeutic efficacy in superficial and systemic fungal infections. Drugs 1982; 23:1-36. Review of early clinical studies of efficacy and safety of oral ketoconazole in the treatment of systemic and superficial mycoses.
7. Lake-Bakaar G, Scheuer PJ, Sherlock S. Hepatic reactions associated with ketoconazole in the United Kingdom. Br Med J (Clin Res Ed) 1987; 294:419-22.
8. Stricker BH, Blok AP, Bronkhorst FB, et al. Ketoconazole-associated hepatic injury. A clinicopathological study of 55 cases. J Hepatol 1986; 3:399-406.
9. DeFelice R, Johnson DG, Galgiani JN. Gynecomastia with ketoconazole. Antimicrob Agents Chemother 1981; 19:1073-4.
10. Craven PC. Interaction of ketoconazole with rifampin and isoniazid. N Engl J Med 1985; 312:1061 12. D'Mello AP, D'Souza MJ, Bates TR. Pharmacokinetics of ketoconazole.
11. Murphy E, Hannon D, Callaghan B. Ketoconazole--theophylline interaction. Ir Med J 1987; 80:123-4.
12. European Medicines Agency. European Medicines Agency recommends suspension of marketing authorisations for oral ketoconazole [Internet] 2013.
13. Medicines and Healthcare products Regulatory Agency. Drug Safety Update: Oral ketoconazole: do not prescribe or use for fungal infections - risk of liver injury outweighs benefits [Internet] 2013.
14. European Medicines Agency. European Medicines Agency recommends suspension of marketing authorisations for oral ketoconazole. European Medicines Agency 2013;1-3.
15. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA limits usage of Nizoral (ketoconazole) oral tablets due to potentially fatal liver injury and risk of drug interactions and adrenal gland problems. 2013
16. Health Canada. Health Canada Endorsed Important Safety Information on Ketoconazole [Internet]. Ketoconazole - Risk of Potentially Fatal Liver Toxicity - For Health Professionals.
17. Bodey GP. Azole antifungal agents. Clin Infect Dis 1992;14(Suppl 1): S161-9.
18. Van den Bossche H, Willemsens G, Cools W, et al. In vitro and in vivo effects of the antimycotic drug ketoconazole on sterol synthesis. Antimicrob Agents Chemother 1980; 17:922-8
19. Rodriguez RJ, Acosta D. Comparison of ketoconazole- and fluconazole-induced hepatotoxicity in a primary culture system of rat hepatocytes. Toxicology 1995; 96:83-92.
20. Rodriguez RJ, Acosta D. N-deacetyl ketoconazole-induced hepatotoxicity in a primary culture system of rat hepatocytes. Toxicology 1997; 117:123-31
21. Administration AGD of HTG. Oral ketoconazole (Nizoral) 200 mg tablets [Internet]. Available from: http://www. tga.gov.au/safety/alerts-medicine-oral-ketoconazole- 131010.htm
22. Bercoff E, Bernuau J, Degott C, et al. Ketoconazole-induced fulmi-nant hepatitis. Gut. 1985;26(6):636–638
23. Petersen EA, Alling DW, Kirkpatrick CH. Treatment of chronic mucocutaneous candidiasis with ketoconazole: a controlled clinical trial. Ann Intern Med 1980; 93:791-5
24. Westphal JF, Brogard JM. Antibacterial and antifungal agents. In: Kaplowitz N, DeLeve LD, editors. Drug induced liver disease. New York (NY): Marcel Dekker Publishing; 2003. p. 471–504.
25. García Rodríguez LA, Duque A, Castellsague J, et al. A cohort study on the risk of acute liver injury among users of ketoconazole and other antifungal drugs. Br J Clin Pharmacol. 1999;48(6):847–852.
26. Chien RN, Yang LJ, Lin PY, et al. Hepatic injury during ketoconazole therapy in patients with onychomycosis: a controlled cohort study. Hepatology. 1997;25(1):103–107.
27. Sugar AM, Alsip SG, Galgiani JN, et al. Pharmacology and toxicity of high-dose ketoconazole. Antimicrob Agents Chemother 1987; 31:1874-8
28. Stevens DA, Stiller RL, Williams PL, Sugar

AM. Experience with ketoconazole in three major manifestations of progressive coccidioidomycosis. Am J Med 1983; 74:58-63
29. Santen RJ, Van den Bossche H, Symoens J, et al. Site of action of low dose ketoconazole on androgen biosynthesis in men. J Clin Endocrinol Metab 1983; 57:732-6
30. Pont A, Williams PL, Azhar S, et al. Ketoconazole blocks testosterone synthesis. Arch Intern Med 1982; 142:2137-40
31. Pont A, Graybill JR, Craven PC, et al. High-dose ketoconazole therapy and adrenal and testicular function in humans. Arch Intern Med 1984; 144:2150-3
32. Pont A, Goldman ES, Sugar AM, et al. Ketoconazole-induced increase in estradiol-testosterone ratio. Probable explanation for gynecomastia. Arch Intern Med 1985; 145:1429-31
33. Loose DS, Kan PB, Hirst MA, et.al: ketoconazole blocks adrenal steroidogenesis by inhibiting cytochrome P450-dependent enzymes. J clin Invest 71:1495-1499,1983
34. Engelhardt D, Mann K, H6rmann R, Braun S, Karl HJ (1983) Ketoconazole inhibits cortisol secretion of an adrenal adenoma in vivo and in vitro. Klin Wochenschr 61: 373- 375
35. D S Loose, R A Marcus, D Feldman, "Ketoconazole blocks adrenal steroidogenesis by inhibiting cytochrome P450-dependent enzymes", "The Journal of clinical Investigation", J Clin Invest. 1983;71(5):1495-1499
36. Gascoigne EW, Barton GJ, Michaels M, Meuldermans W, Hey-kants J. The kinetics of ketoconazole in animals and man. Clinical Research Reviews I: 177-187, 1981
37. Brass C, Galgiani IN, Blaschke TF, Defelice R, O'Reilly RA, et al. Disposition of ketoconazole, an oral antifungal, in humans. Antimicrobial Agents and Chemotherapy 27: 151-158, 1982
38. Mannisto PT, Mantyla R, Nykanen S, Lamminsivu U, Ottoila P. Impairing effect of food on ketoconazole absorption. Anti-microbial agents and Chemotherapy 21: 730-133, 1982
39. Daneshmend TK, Warnock DW, Ene MD, Johnson EM, Potten MR, et al. Influence of food on the pharmacokinetics of ketoconazole. Antimicrobial Agents and Chemotherapy 25: 1-3, 1984
40. Fazio RA, Wickremesinghe PC, Arsura EL. Ketoconazole treatment of Candida esophagitis: a prospective study of 12 cases. American Journal of Gastroenterology 78: 261-264, 1983
41. Magnasco AJ, Magnasco LD. Interaction of ketoconazole and ethanol. Clinical Pharmacy 5: 522-523, 1986
42. Smith EB, Henry Je. Ketoconazole: an orally effective antifungal agent. Pharmacotherapy 4: 199-204, 1984
43. Brown MW, Maldonado AL, Meredith CG, Speeg KV. Effect of ketoconazole on hepatic oxidative drug metabolism. Clinical Pharmacology and Therapeutics 37: 290-297, 1985
44. Cunningham C, Burke MD, Whiting PH, Simpson JG, Wheatley ON. Ketoconazole, cyclosporin and the kidney. Lancet 2: 1464. 1982
45. Smith JM, Hows JM, Gordon-Smith EC, Baughan A, Goldman JM. Interaction of cyclosporin A and ketoconazole. Clinical Science 64: 67P-68P, 1983
46. Cunningham C, Whiting PH, Burke MD, Wheatley DN, Simpson JG. Increasing the hepatic metabolism of cyclosporin abolishes nephrotoxicity. Transplantation Proceedings 15 (Suppl. I): 2712- 2715, 1983
47. Gumbleton M, Brown JE, Hawksworth G, Whiting PH. The possible relationship between hepatic drug metabolism and ketoconazole enhancement of cyclosporine nephrotoxicity. Transplantation 40: 454-455, 1985
48. Meunier-Carpentier F, Heymans C, Snoeck R. Interaction of rifampicin with ketoconazole and Bay n7133 in normal volunteers. Presented at the 23rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Las Vegas, October 24- 26, 1983
49. Glynn AM, Slaughter RL, Brass C, D'Ambrosio R, Jusko WJ. Effects of ketoconazole on methylprednisolone pharmacokinetics and cortisol secretion. Clinical Pharmacology and Therapeutics 39: 654-659, 198
50. KD Tripathi "Essential of Medical Pharmacology", "Jaypee Brothers Medical Publishers (P) Ltd", 8th Edition, 2019 Pg.no.844
51. KD Tripathi, "Essential of Medical Pharmacology", "Jaypee Brothers Medical Publishers (P) Ltd", 6th Edition, 2008, Chapter 57, Pg.no.763
52. James M. Ritter, "Rang and Dale's Pharmacology", "Elsevier Health Sciences", 8th Edition, 2020, Chapter 54, Pg.no.693