CONTINUING MEDICAL EDUCATION

KETOCONAZOLE IN DERMATOLOGY

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Ketoconazole (KZ) is an imidazole derivative, synthesized in 1976.[1] It is a broad spectrum imidazole and differs from earlier imidazoles by the presence of dioxolone ring. It has a molecular weight of 531.44 daltons. It is soluble in water as well as acids.[2]

Pharmacokinetics

Ketoconazole (KZ) is well absorbed after oral administration,[2-6] though there are contradictory reports about the effect of food on absorption, some workers found better absorption when given with a meal,[3-5] while some others found better absorption when given on an empty stomach.[6] The presence of gastric acid is essential for absorption, hence drugs like antacids, cimetidine and anticholinergics, that reduce gastric acid secretion should not be taken with KZ.[3,4] If treatment with any of these is indispensable, these should be taken not less than 2 hours after KZ.[3] The peak plasma concentrations ranging from 3 to 4 μg/ml are reached in 1 to 4 hours after a single oral dose of 200 mg KZ.[1] The half-life of KZ is 2 hours during the first 10 hours after administration, and 8 hours thereafter.[3] Most (99%) of the KZ in plasma is protein-bound mainly to albumin.[1,4] It is mainly metabolized in liver. The major route of excretion is enterohepatic, about 80-90% being excreted in the bile and faeces.[7] Ten to 15% of the drug is excreted in urine of which 2 to 4% is excreted unchanged.[7] In addition, KZ has also been found in saliva, sebum and cerumen.[1,7] As the renal excretion is minimal, there is no need to alter the dose in renal failure.[3] After a single oral dose of 200 mg, KZ was found in the stratum corneum within 3-8 hours and adequate concentrations were present even within 24 hours.[8] The CSF penetration of KZ is low,[9] though adequate concentrations may be achieved with higher doses.[10] The KZ crosses placenta and also diffuses into the breast milk.[3] Topically applied KZ does not diffuse into the blood and the penetration is limited to the superficial epidermal layers only.[11]

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Mechanism of action

KZ is active against most of the fungi and yeasts.[2-4,8] It interferes with the synthesis of ergosterol, a primary cellular sterol of fungi, by inhibiting the demethylation of lanosterol, which is a precursor of ergosterol.[1] In addition it interferes with the oxidative and peroxidative enzyme synthesis, leading to accumulation of toxic peroxides in the cell.[8] These alterations in the membrane sterols and peroxide accumulation change the cell permeability that leads to inhibition of the cell growth. KZ is primarily a fungistatic drug, though at higher concentrations, it may be fungicidal.[12] Fungicidal concentrations however, are not achieved at therapeutic dosage levels.[12] It has also been found to have in vitro inhibitory activity against *Staphylococcus aureus*,[13] *Plasmodium falciparum*,[14] *Trypanosoma cruzi*[15] and *Leishmania tropica*.[16] The mechanism of the inhibitory activity, is not known, but is thought to be due to alterations in lipid metabolism.[16]

Uses

Ketoconazole (KZ) has been tried and found effective in many diseases (Table I.)

Table I. Uses of ketoconazole

Dermatophytoses
Pityriasis versicolor
Candidiasis
Deep fungal infections
Seborrheic dermatitis
Acne vulgaris
Leishmaniasis
Miscellaneous

Dermatophytoses

KZ has been found effective in various dermatophytoses, though the cure rates are low in palmo-plantar and nail infections, especially the toe-nails.[17,18] The cure rates in glabrous skin infections vary from 63% to 85% after 4 to 11 weeks therapy with an oral daily dose of 200 or 400 mg.[1,2,4,17,19-23] In the case of tinea capitis, the cure rate was 75% for *Trichophyton* species and 29% for *Microsporon canis*.[4,8] Svejgaard however, reported 100% cure rate.[22] The improvement may start as early as 1 week but 4-11 months may be necessary for complete cure.[22] The response rates in palmo-plantar tinea varied from 24% to 62%,[17,22-24] while in tinea cruris, it was 100%.[17,21,23-25] In the case of nail infections, the cure rates ranged from 20% to 55%.[4,21,22] There was no correlation between the serum level of KZ and the initial clinical response.[19,26] Relapse of the dermatophytic infection following discontinuation of KZ is not uncommon[17-19,21,27] The relapse rates after 6 months follow-up were 67% in glabrous skin infections, 55 to 60% in palmo-plantar infections and 33 to 40% in the case of nail infections.[18,22,26] Long-term treatment with KZ for 12 to 18 months did not decrease relapse rates.[21,26] There was no difference in the relapse rates among patients who had cleared early or late in the course of treatment or among the patients, who had received 200 mg or 400 mg of KZ daily.[26] However, the relapses could be because of inadequate duration of treatment or due to reinfection. Several comparative studies between KZ and griseofulvin for the treatment of dermatophytic infections have been reported.[21-23,25-28] These studies have not shown any significant difference between KZ and griseofulvin.[8] But KZ is effective in griseofulvin resistant cases,[21,22,29] and it is also useful in patients with griseofulvin intolerance.[8,26] When long term systemic treatment of tinea infections is considered, griseofulvin should be the drug of choice in view of its reassuring risk-benefit ratio,[30] while KZ is an alternative, when replacement for griseofulvin is required.[26]

Topical KZ can be used as an adjunct to oral therapy or as the sole therapeutic agent.[11,31] Topical 2% KZ, used alone in tinea pedis gave about 60% cure rate.[31] There was no significant difference between once daily or twice daily applications.[11,31] KZ elicits some continuous therapeutic effect even after discontinuation of treatment.[31]

Pityriasis versicolor

KZ has also been found effective for the treatment of pityriasis versicolor,[32-35] with a cure rate of 92%. The duration of treatment in different studies has varied from 5 days[33] to a mean of 4 weeks.[32] Shafi and Khatri[34] have reported 88% cure rate after 2 weeks therapy, and the results were much better when combined with topical selenium sulphide shampoo. Treatment with a single dose of 400 mg has also been found to be effective.[35] The relapses however after discontinuation of treatment are not uncommon.[32,34] Some workers[36] have recommended continued use of 200 mg of KZ daily for 3 consecutive days in a month after the initial cure, to prevent relapses. A 2% ketoconazole topical cream has also been reported to be effective.[37] In a double-blind comparative

study in 101 patients with recurrent pityriasis versicolor, the topical 2% KZ gave 84% cure rates after 2 weeks of therapy compared to 10% with placebo. In a 2-year follow-up, 79% of patients treated with KZ remained in remission for 12 or more months.[37]

Candidiasis

KZ is found extremely useful for the treatment of chronic muco-cutaneous candidiasis.[2-4,38-42] In a study on 69 patients, 25% were cured and 52% showed marked improvement.[4] Similar results have been obtained by other workers as well.[38-42] KZ is an alternative to the polyenes for the prophylaxis of candidiasis in immuno-compromised hosts.[43,44] In vaginal candidiasis, cure rates of 86% have been reported after 4 weeks KZ therapy with 200 mg twice daily.[45] In oral candidiasis, occurring in cancer patients, clinical improvement has been reported in 80% (17 out of 21) of cases.[45] It has been used as a prophylactic agent in cancer patients against systemic mycoses especially against candida infections.[46]

Deep fungal infections

KZ has been found useful in coccidioidomycosis, paracoccidioidomycosis, histoplasmosis and systemic candidial infections.[2-4] It is generally highly effective in histoplasmosis[47,48] and meningeal cryptococcosis,[47] moderately effective in blastomycosis and coccidioidomycosis[47,49,50] and least effective in sporotrichosis (1 out of 7).[47] It is also effective in systemic candidiasis especially *C. albicans* septicemia in heroin addicts.[51,52] KZ has also been found useful for prophylaxis against aspergillosis complicating chronic granulomatous disease, but not in invasive aspergillosis.[53] It has also given good results in entomophthoromycosis.[53] The results in chromomycosis have been variable.[54,56] Cuce et al[54] used 200 to 400 mg of KZ in 7 patients with chromomycosis for upto 3 months and all the seven responded partially. Symoens et al[20] treated 12 patients using 200 and 400 mg daily for 1 to 4 months. Two of these patients were cured, 4 had moderate improvement and 3 had no response. Mcburney[55] and South et al[56] have treated 1 patient each with a good response. In mycetoma (eumycetoma as well as actinomycetoma) KZ has been found to be ineffective.[31,54] Experience with lobomycosis, cryptococcosis and phycomycosis is too small as yet to assess its effectiveness in these infections.[57]

Seborrhoeic dermatitis

The role of pityrosporum yeast in seborrhoeic dermatitis, is controversial. Some workers consider it of aetiologic significance,[58] while others regard the presence of increased number of these organisms as secondary colonisers.[59] KZ is active against these yeasts both in vitro[60] and in vivo,[32,61] it produces significant relief in seborrhoeic dermatitis both orally as well as topically. Given in a dose of 200 mg orally daily for 4 weeks, 14 of 19 patients improved remarkably, but erythema and scaling recurred within 3 to 4 weeks of discontinuation of the drug.[62] The chief limitation with oral KZ is the risk of hepatotoxicity on prolonged administration. Topical lotions and shampoos containing 2% KZ have been found effective in 80% of cases compared to relief in 29%, treated with a placebo.[11,63] Similar results have been reported by other workers as well.[64,65]

Acne

KZ is a potent inhibitor of testosterone synthesis.[66] It has been found useful in severe acne with raised testosterone levels. Given in a dose of 300 mg twice daily for 3 months to 3 patients with severe acne and raised testosterone levels, remarkable improvement with significant decrease in papules and pustules was observed.[67] In 2 of the 3 patients, testosterone levels also returned to normal in 3 months. All these 3 patients had hirsutism in addition and there was

a good response even in hirsutism.[66] The KZ has not been studied yet, for its topical effectivity in acne.

Leishmaniasis

Berman[16] provided the early evidence that KZ possessed antileishmanial activity in human macrophage cultures infected with parasites. Leishmania contain large amounts of ergosterol[68] and KZ probably acts against these protozoa by interfering with ergosterol synthesis. Urcuyo and Zaias[69] had treated 6 patients with cutaneous or muco-cutaneous leishmaniasis with 400 mg of KZ daily. All these 6 patients had improved after 2 weeks and were cured in 3 months. They observed that single ulcers healed faster than the muco-cutaneous disease. Weinrauch et al[70] treated 8 patients having cutaneous leishmaniasis with 400 mg KZ daily. Five of these were cured after 6 weeks. However, the duration of the disease prior to treatment was short (70 to 130 days) and since spontaneous remissions in cutaneous leishmaniasis are common it is not possible to attribute the remission in the 5 patients to KZ without an element of doubt. However, the same author[71] has further reported successful treatment of a case of cutaneous leishmaniasis of 8 months duration. Viallet et al[72] treated 2 patients with cutaneous leishmaniasis of 12 and 27 months duration with 400 mg of daily KZ. Both of them improved by 2 weeks and healed completely by 8 and 4 weeks respectively. Jolliffee[73] had treated 8 patients of cutaneous leishmaniasis with 800 mg daily oral KZ. Five of these had shown significant clinical improvement after 28 days. We have tried KZ in 2 patients with post kala-azar dermal leishmaniasis for 4 weeks but found it to be ineffective.

Miscellaneous

KZ has shown remarkable improvement in 3 patients with hirsutism, testosterone levels in 2 of these returning to normal after 3 months.[67] It has also been found effective in pityrosporum folliculitis,[61,74] psoriasis localised to seborrheic areas (sebo-psoriasis)[75] and in atopic dermatitis localised to head and neck.[76] It has also been reported to be effective in *Fusarium roseum* (opportunistic fungus) infection.[77] It has also been shown that KZ has antiviral activity against HSV-I and HSV-2 in an in vitro yield reduction assay.[78] The mechanism of this antiviral action is not known. Tkach and Rinaldi[79] had reported a patient with recurrent HSV-2 genital infection who had favourably responded to KZ. A female with recurrent genital HSV-2 infection for 4 years, recurring every 2 weeks and concomitant candidial vaginitis, had no further recurrence of genital HSV over a 5 month follow up period after KZ therapy. Though this may be a coincidental effect, a role of KZ in treatment of HSV infections cannot be excluded.

Drug interactions

KZ interacts with some other drugs. Rifampicin decreases the plasma levels of KZ.[80] KZ prolongs the half life of cyclosporin.[53] It does not induce any enzymes.[81] Combination of amphotericin B and KZ leads to antagonism and hence this combination is best avoided.[53] Concomitant administration of KZ and phenytoin may alter the metabolism of one or both the drugs.[7] Drugs like antacids, cimetidine and anticholinergics which reduce gastric acid secretion inhibit the absorption of KZ.[2,3,7]

Dose

The usually recommended dose of KZ is 200 mg once daily.[2,3] For candida infections and deep fungal infections, upto 600 mg per day have been tried.[47] In children, the usual dose is 5 to 10 mg per kg body weight per day,[53] but it should not exceed 100 mg daily.[2,3] In patients with immunodeficiency the recommended dose is 600 mg daily.[3] High dose of KZ upto 800 to 1200 mg daily have been used with success in treating CNS fungal infections.[7] KZ in doses of 400 mg 8 hourly has been used for the treatment

of advanced prostatic cancer.[7] Topically, it is being used as 2% creams, lotions or shampoos.[11]

Toxicity

The commonly reported side effects include nausea/vomiting (3%), pruritus (1.7%), abdominal pain (1.3%), headache (0.9%), dizziness (0.8%), somnolence (0.8%), diarrhoea (0.7%) and rash (0.7%). In a recent study,[47] gastrointestinal symptoms were recorded more frequently (21%). The gastro-intestinal symptoms can usually be avoided by taking KZ immediately before a meal.[57]

The most serious side effect of KZ is the hepatotoxicity. It can be silent or symptomatic.[81] The silent hepatic reactions include transient elevation of liver enzymes without clinical symptoms and signs of hepatic disease. The incidence of these reactions was 11 to 14%.[81,82] In most instances, the enzyme levels returned to normal without even stopping KZ. The symptomatic reactions could be icteric with dark urine and pale stools, or anicteric with fever, fatigue, weakness, malaise, anorexia, nausea or vomiting. The incidence of symptomatic reactions was reported to be 1 in 10,000.[81] The symptoms generally occur within the first few months of therapy and subside when the treatment is discontinued. Hepatotoxicity is not related to the daily dose, cumulative dose or the duration of the therapy. These are idiosyncratic reactions. Hepatic necrosis, leading to hepatic coma and death has been documented in 2 patients.[81]

The other notable side effects include gynaecomastia, impotence and decreased libido.[66,83] Oligospermia has been reported at doses higher than the normally recommended ones but not with the doses upto 400 mg daily.[7] These changes could be because of the fall in the testosterone levels with KZ therapy. Pont et al[66] showed that a single dose of 200 mg can decrease the testosterone levels by 30% in 4 hours but the levels returned to normal in 8 hours. The decrease in testosterone levels was dose dependent. In addition KZ inhibits the cortisol response to ACTH.[84] This may prove valuable in patients with Cushing's disease, breast carcinoma, hirsutism and prostatic carcinoma where blockage of the adrenal secretion is needed.[84] Neutropenia,[57] thrombocytopenia, urticaria, anaphylactic reactions[7] and lichenoid lesions[85] have been reported rarely. A slight rise in the serum triglyceride levels was reported with a high (600 mg) daily dose.[47] On the contrary, Kraemer and Pont reported 27% reduction in the total serum cholesterol levels without any change in the triglyceride levels in 6 of the 7 patients with prostatic cancer, treated with 1200 mg of KZ per day.[86] Mild teratogenic effects like syndactyly and oligodactyly have been reported in mice with KZ given in a dose of 80 mg/kg (this dose being nearly 25 times the human dose), though the relevance of this finding in humans is not known, it is better to avoid KZ in pregnancy.[7] As KZ is excreted in the breast milk, it should not be given to lactating mothers.[7] It is not safe to use KZ in children less than 2 years of age.[7] With topical ketoconazole, the side effects are few and seen in 5% of the cases.[11] These included irritation, pruritus and stinging.[11] It did not produce any allergic reaction in the 25 volunteers patch tested.[11]

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