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Ketoconazole: A Review of It's Therapeutic Effectiveness in Superficial and Systemic Fungal Infections

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Abstract: ***In contrast with bacteria or viruses, fungi are more convoluted organisms. They have ribosomes, cellular membrane constituents, and a nuclear membrane. As a result, antibacterial antibiotics are, usually, worthless in case of pathogenic fungi[1]. Ketoconazole is an imidazole antifungal which is administered either locally or by mouth. It is taken orally for the cure of long - term mucocutaneous candidosis, for cure of fungal infections of the gastrointestinal tract, for cure of ringworm infections of the skin and fingernails that do not react to local administration, and for cure of systemic infections containing blastomycosis, candidosis, coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis[2]. This article gives an outline of the effectiveness of ketoconazole in superficial & systemic fungal infections.***

Keywords: Ketoconazole, Micro - emulsion, Antifungal, Treatment, Fungal Infection

1. Introduction

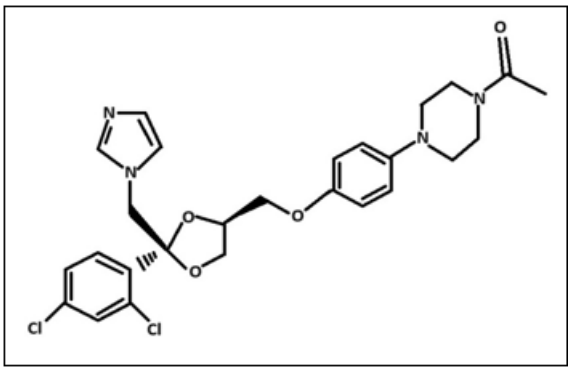
Fungal infections, both intrusive and exterior, have turned into progressively more usual during the last decades[3]. Fungi are progressively acknowledged as crucial pathogens in severely diseased patients. *Candida* spp. and *Cryptococcus* spp. are the yeasts most usual confined in clinical practice. The most usual filamentlike fungi (moulds) abstracted are *Aspergillus* spp., but *Fusarium* spp., *Scedosporium* spp., *Penicillium* spp. and Zygomycetes are rapidly seen ringworms of the genera Trichophyton, Microsporum, and Epidermophyton may begin disease by infecting the skin, hair, and nails[4]. A development in the number of immunosuppressed patients allied with AIDS and organ transplantation, and enlarged use of invasive appratus, such as urinary catheters, has increased the number of patients who are at high risk of invasive fungal infection. Patients with burns, neutropenia, HIV infection and pancreatitis are also affected to fungal infection. This growth is exactly connected to the increasing community of immunosuppressed respective, resulting from swaps in medical practice such as the use of all - out chemotherapy and immunosuppressive drugs[5].

Antifungal Activity of Ketoconazole

Ketoconazole is a strong, orally active, broad - spectrum antifungal agent[6]. The antifungal effects of ketoconazole were examined both in vitro and in vivo. Ketoconazole is supremely effective in vitro and possesses broadspectrum activity. It's in vitro action is largely depending on the medium used. Ketoconazole is very strong in the topical treatment of skin dermatophytosis, skin candidiasis, and in vaginal candidiasis of laboratory animals[7].

Description

Ketoconazole is cis - 1 - acetyl - 4 - [4 - [[2 - (2, 4 - dichlorophenyl) - 2 - (1H - imidazol - 1 - ylmethyl) - 1, 3 - dioxolan - 4 - yl]methoxyl]phenyl] piperazine and has molecular formula C26H28Cl2N4O4 with molecular weight 531.44 and has the following structural formula[8]:



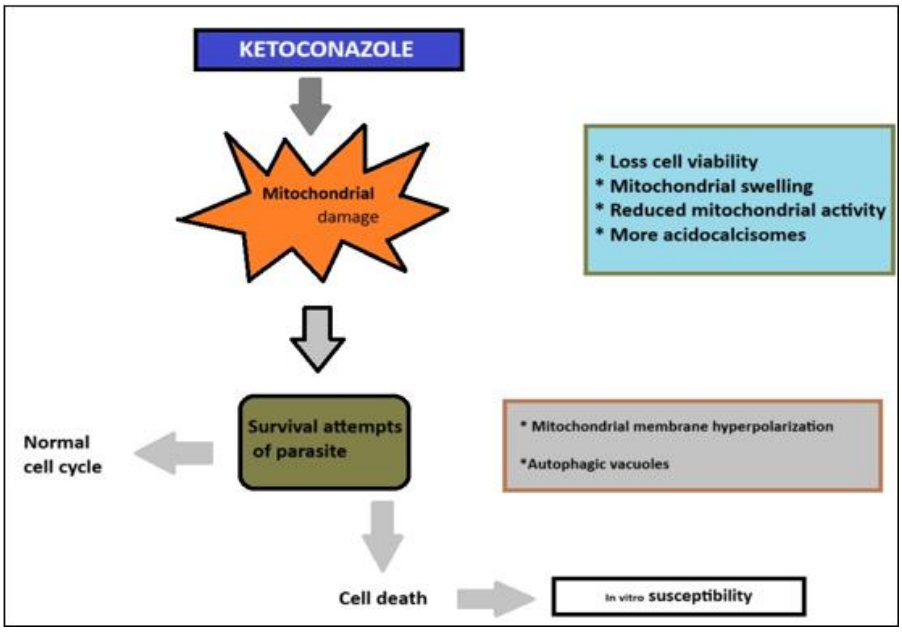
Chemical Structure of Ketoconazole

Ketoconazole is a white to light yellow odorless crystalline powder, having melting point 148 - 152 °C and boiling point 753.4±60.0 °C[9]. It is soluble in alcohols and acids & insoluble in water.

Pharmacodynamic Action of Ketoconazole: Ketoconazole, alike to other azole antifungals, is a fungistatic drug which causes inhibition of growth in fungal

cells through prohibiting growth and spread of the fungus throughout the body[10].

Mechanism of Action: Just like all azole antifungal agents, ketoconazole works basically by blockage of cytochrome P450 14a - demethylase (P45014DM). This enzyme is in the sterol biosynthesis pathway that conducts from lanosterol to ergosterol[11]. The affection of ketoconazole for fungal cell membranes is smaller as compared to that of fluconazole an itraconazole. Ketoconazole has thus more probable to results mammalian cell membranes and induce toxicity[12].



Mechanism of Ketoconazole

Storage Conditions: The medicines should be stored in a closed container at room temperature, away from heat, moisture, and direct light. Keep freezing. Keep out of the Children[13].

Indications & Uses: Ketoconazole is used to treat fungal and yeast infections on your skin, hair, nails, and in your blood. This drug is recommended only when other treatments haven't worked or caused excessive adverse effects[14].

Ketoconazole Tablets are indicated for the treatment of the following systemic fungal infections in patients who have failed or who are impatient to other therapies: blastomycosis, coccidi oidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis[15].

Ketoconazole Formulations: Ketoconazole is an imidazole antifungul drug. Just like other imidazoles, it has a five - membered ring structure including two nitrogen atoms. Ketoconazole has oral tablet, cream and dandruff shampoo preparations[16].

Contraindications: Ketoconazole is contraindicated in patients who have shown allergic rxn. with the drug or excipients of the formulation. Ketoconazole tablet is contraindicated in patients with severe or chronic liver disease[17].

Adverse Effects: Including its desired effects, a medicine may cause some undesired effects like: -

- vomiting,
- nausea,
- stomach pain,
- itching or skin rash,
- headache,
- dizziness,
- breast swelling,
- Loss of interest in sex.
- vision changes
- Mental/mood changes (such as depression, thoughts of suicide) [18].

Precautions: This medicine may cause severe allergic reactions, containing anaphylaxis[19]. Call your doctor immediately if you have skin rashes, itching, difficulty in breathing, difficulty in swallowing, or swelling of your hands, face, or mouth while you are using this medicine. Stay away from drinking alcohol while you are using this medicine. Do not take other medicines except that they have been induced with your doctor.

Research Work carried out in ketoconazole:

- A gel formulation containing niosomes loaded with Ketoconazole showed prolonged action than formulations containing Ketoconazole in non - niosomal form and it can be developed successfully to improve the antifungal activity[20].
- Ketoconazole is an effective drug with acceptable side effects. It should be used under close liver enzyme monitoring. Hepatotoxicity is usually mild and resolves after drug withdrawal[21].
- The efficiency of Micro - emulsion formulation in the topical delivery of ketoconazole was dependent upon the contents of water and Lauryl Alcohol as well as Lab/EtOH mixing ratio. The percutaneous absorption of ketoconazole from Micro - emulsion was enhanced with

increasing the Lauryl Alcohol and water contents, and with decreasing the Lab/EtOH ratio in the formulation[22].

- Ketoconazole shampoos significantly reduce the clinical manifestations of dandruff and seborrhoeic dermatitis. Ketoconazole 2% exhibits superior efficacy to Ketoconazole 1% in the treatment of severe dandruff and seborrhoeic dermatitis[23].
- Ketoconazole is very effective in inhibiting testosterone biosynthesis in vitro by blocking the 17a - hydroxylase and 17, 20 - desmolase reactions involved in the biosynthesis of testosterone from cholesterol within the testis. This inhibition of each of these two enzyme reactions was dose and time dependent[24].
- The novel drug loaded rose oil-based Micro - emulsion provides an enhanced antifungal activity against the fungal strain used in the study. Toxicity studies confirm that the formulated Micro - emulsion is safe for oral usage. Hence, it can be reasonably concluded that the rose oil-based Micro - emulsion for Ketoconazole can be a potential candidate for use as topical drug in treatment of fungal problems[25].
- Ketoconazole tablet has been reported to be effective in the treatment of some cases of: Cutaneous leishmaniasis, the low response rate in patients receiving ketoconazole cream indicates that it cannot be used as the single agent in the treatment of: Cutaneous leishmaniasis patients[26].

2. Conclusion

From above article it is concluded that the use of Ketoconazole has better antifungal effects against cutaneous and mucosal isolates of the *Candida* spp. and *Cryptococcus* spp.

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