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ITRACONAZOLE: THE INHIBITOR OF LANOSTEROL 14-ALPHA-DEMETHYLASE IN MUCORMYCOSIS

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ABSTRACT

Mucormycosis previously called zygomycosis, also known as black fungus, is a serious fungal infection, usually in people with reduce ability to fight infection.it is caused by the group of molds called mucoromycetes these molds live through the environment. In this review, based on the current understanding of the disease. It has been observed that itraconazole, as an antifungal medicine used in the treatment of mucormycosis, its work by slowing the growth of fungi that causes infection, or by killing yeast or fungi. It's also having some role as anti-viral activity, and as an anti-cancer medicine because of the anti-viral activity, it can used in the treatment of covid-19 and also used in the cancer treatment.

KEYWORDS: Mucormycosis; zygomycosis; itraconazole.

INTRODUCTION

Itraconazole [CAS: 84625-61-6] is an antifungal medication that is used in adults to treat infection caused by fungus. It includes infection in any part of the body including the lungs, mouth, throat, toenail, or fingernails. Itraconazole belongs to a class of drug known as azole antifungal. It is approved for medical use in the 1992 in united states.

Chemistry

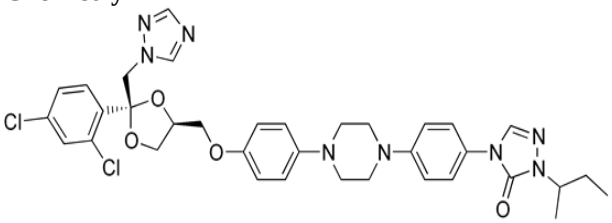

Figure-1: Structure of itraconazole.

IUPAC NAME: 1-(butan-2-yl)-4-{4-[4-(4-{[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy}phenyl)piperazin-1-yl]phenyl}-4,5-dihydro-1H-1,2,4-triazol-5-one.

Chemical Formula: $C_{35}H_{38}Cl_2N_8O_4$

Average Molecular Weight: 704.239 g/mol

Description: Belongs to the class of organic compounds known as phenylpiperazines. Phenylpiperazines are compounds containing a phenylpiperazine skeleton, which consist of piperazine bound to a phenyl group.

Melting Point: 166.2°C.

USES: Itraconazole capsule are indicated for the treatment of following fungal infection in immunocompromised and non –immunocompromised patient: Blast mycosis, pulmonary and extra pulmonary, histoplasmosis, including chronic cavity pulmonary disease and disseminated, non-meningeal histoplasmosis and Aspergillosis. Itraconazole is also indicated for the treatment of: Onychomycosis of the toenail, with or without finger nail involvement, due to *Tinea ungium* and Onychomycosis of finger nail due to dermatophytes.

Mechanism of Action: Itraconazole acts by inhibiting the fungal cytochrome P-450 dependent enzyme lanosterol 14-α-demethylase. When this enzyme is inhibited, it blocks the conversion of lanosterol to ergosterol, which disrupts fungal cell membrane synthesis, Itraconazole exhibits fungistatic activity against yeast-like fungi and fungicidal activity against aspergillus spp.

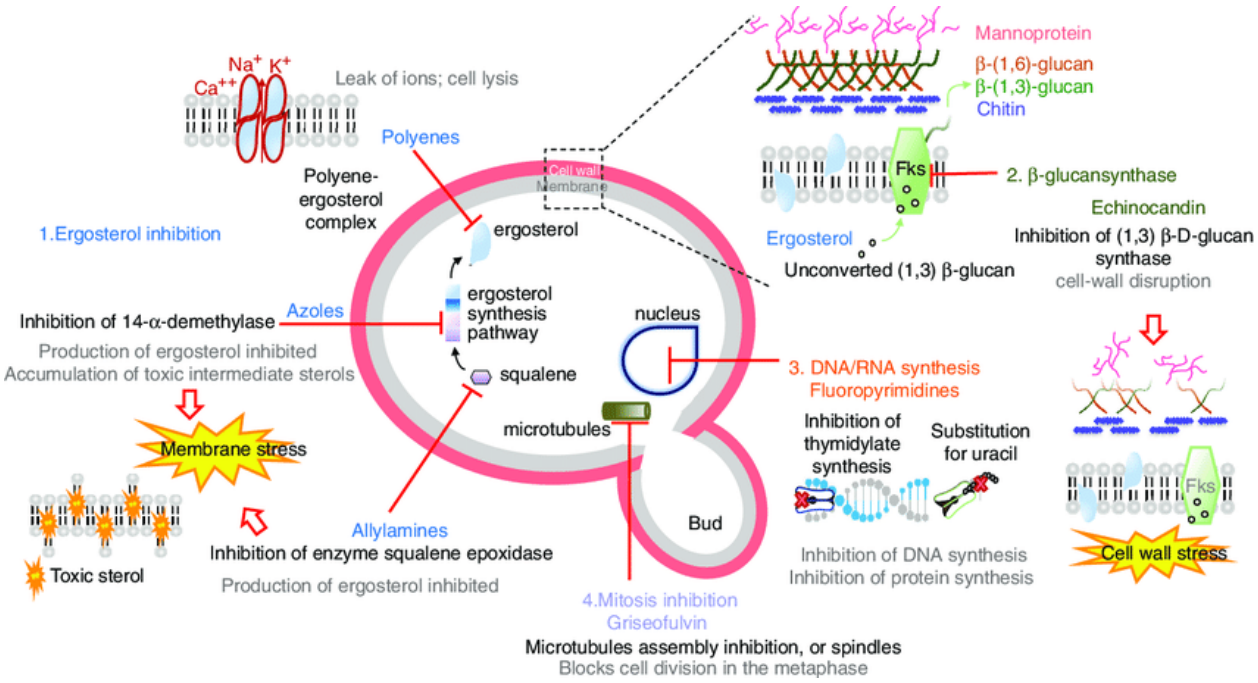

Figure-3: Mechanism action of antifungal drug [Itraconazole].

Side Effects: Itraconazole can causes minor side effects and rarely serious side effects. Side effects such as constipation, upset stomach, headache, sore or bleeding gums, depression, nervousness, muscle pain have been noted. More serious side effects such as nausea, yellowing of skin or eyes, pale stools, fever, dark urine, rash, hives etc. This side effect may be caused by an allergy to the medication, hypokalaemia or rarely hepatotoxicity.

Indication: Prophylaxis of IFA, treatment of IPA, treatment of CPA, treatment of ABPA etc.

WHAT IS MUCORMYCOSIS? Mucormycosis is a fungal infection. It is spread by spores of molds of the order mucorales, most often through inhalation, contaminated food, or contamination of open wounds. These fungi are common in soils, decomposing organic matters etc. This disease is close link to diabetes, and condition that compromise the immune system. This disease is not contagious, which means it cannot spread from contact between humans and animals. it is spread from fungal spores which are present in the air or in the environment.

Types Of Fungi Which Cause Mucormycosis: The most common types that cause mucormycosis are Rhizopus species and Mucor species. Other examples include *Rhizomucor* species, *Syncephalastrum* species, *Cunninghamella bertholletiae*, *Apophysomyces*, *Lichtheimia* (formerly Absidia), *Saksenaea*, and *Rhizomucor*.[17]

Signs & Symptoms: There are several key signs which point towards mucormycosis. One such sign is fungal invasion into the blood vessels which result in the formation of blood clots and surroundings tissue death due to a loss of blood supply. If the disease involves the brain, then symptoms may include a one-sided headache behind the eyes, Facial pain fevers, nasal congestion that progresses to black discharge, and acute sinusitis along with eye swelling. Affected skin may appear normal during the earliest stages of infection. This skin quickly becomes reddened and may be swollen before eventually turning black due to tissue death. Other forms of mucormycosis may involve the lungs, skin, or be widespread through the body; symptoms may include difficulty breathing and persistent cough. In case of tissue death, there may be nausea and vomiting, coughing in blood, and abdominal pain.[18]

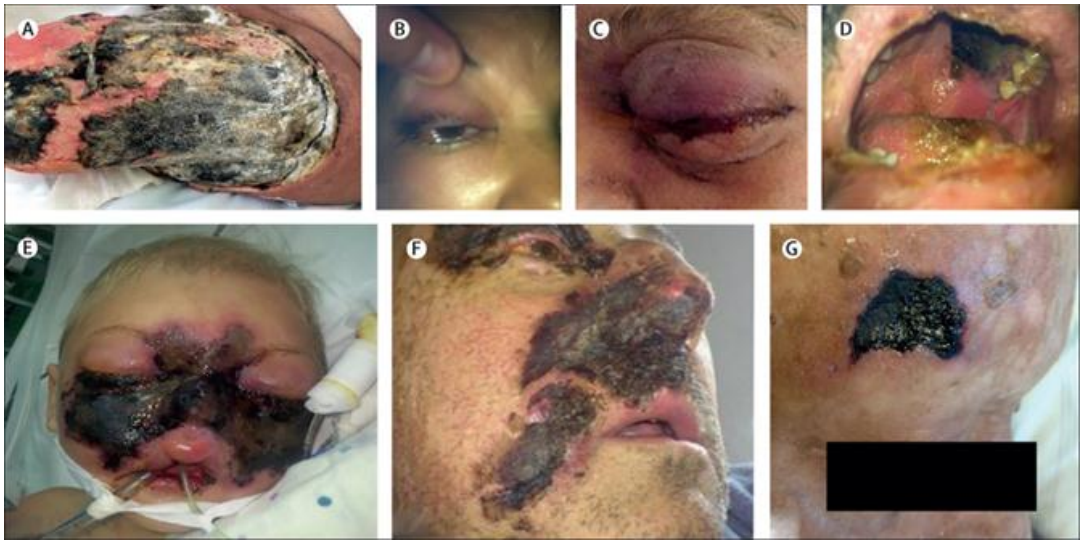

Figure-4: Mucormycosis.

Working Of Itraconazole In The Treatment Of Mucormycosis: Itraconazole is an imidazole / triazole type fungal agent. Itraconazole is highly selective inhibitor of fungal cytochrome p-450 sterol C-14 Alpha-demethylation via the inhibition of the enzyme cytochrome p450 14 alpha-demethylase. This enzyme converts lanosterol to ergosterol, and is required in fungal cell wall synthesis. Itraconazole exibits *in-vitro* activity against *Cryptococcus neoformans* and candida spp. Fungistatic activity has also been demonstrated in normal and immunocompromised animal models for systemic and intracranial fungal infection due to cryptococcus neoformans and for systemic infection due to *candida albicans*.[19]

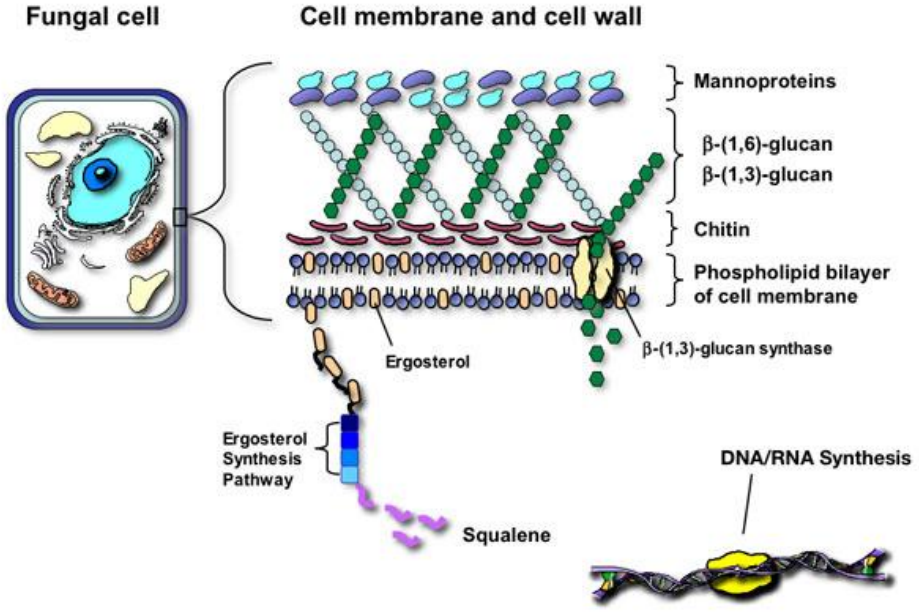

Figure-5: Pharmacology of anti-fungal drugs [itraconazole],

What is ergosterol? Ergosterol (ergosta-5,7,22-trien-3 beta-ol) is sterol found in cell membranes of fungi and protozoa, serving many of the same functions that cholesterol serves in animal cells. Because many fungi and protozoa cannot survive without ergosterol. The enzymes that synthesize it have become important target for drug discovery.

Target for antifungal drug: **ITRACONAZOLE** (**azole** class drug) work in different way, inhibiting synthesis of ergosterol from lanosterol by interfering with 14 alpha-

demethylase. Molecules of farnesyl pyrophosphate, a 15-carbon-long terpenoid, into lanosterol, which has 30 carbons. Then, two methyl groups are removed, making ergosterol. The "azole" class of antifungal agents inhibits the enzyme that performs these demethylase steps in the biosynthetic pathway between lanosterol and ergosterol.[20]

Toxicity of ergosterol: Ergosterol powder is an irritant to skin, eyes, and the respiratory tract. Ingestion of large amount can cause hypercalcemia, which can lead to calcium salt deposits in the soft tissue and kidneys.

CONCLUSION

Mucormycosis, also known as black fungus, is rare but dangerous infection. It's caused by group of molds called mucormycosis and often affects the sinuses, lungs, and brain, you can inhale the mold spores or come into contact with them in things like soil, rotting produce or bread, or compost piles. Most people will come into contact with the fungus at some point in their everyday lives but you're more likely to get sick if you have a weak immune system or because you have health condition like: Diabetes, HIV, AIDS etc. Mucormycosis isn't contagious. The symptoms of mucormycosis are fever, cough, headache, stomach upset, vomiting. etc.

Preferred medicine for mucormycosis: Itraconazole, Isavuconazole, Posaconazole, Amphotericin B, Fluconazole

Itraconazole medication is in capsule form that you can swallow. Itraconazole inhibits the fungal –mediated synthesis of ergosterol, via inhibition of lanosterol14alpha-demethylase because of its ability to inhibit cytochrome p450 3A4 CC-3, caution should be used when considering interaction with other medication in, particular, it is active against Aspergillus. It is also licensed for use in blastomycosis, sporotrichosis, histoplasmosis and onychomycosis. Itraconazole is also prescribed for synthetic infection, such as aspergillosis, candidiasis, and cryptococcosis, where other antifungal drugs are inappropriate or ineffective.

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