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KETOCONAZOLE:-A Medication Promise For Fungal Infection

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ABSTRACT:

Ketoconazole is a synthetic imidazole antifungal drug that is used to treat candidosis,genital infections caused by fungal infections ,and chronic mucocutaneous candidosis.Unlike more traditional imidazole antifungals like miconazole and clotrimazole , ketoconazole is a synthetic imidazole derivative that becomes effective when taken orally.Fungal diseases of the skin, including genital candidiasis and dermatophytosis,respond favourably to it.Treatment for persistent mucocutaneous candidiasis has found utility with it.Ketoconazole is also used to prevent fungal infections in immunocompromised patients.Due to its ability to block the synthesis of adrenal to block the synthesis of adrenal sex horm,it has recently been used as a treatment for advanced prostatic cancer.Topical ketoconazole is generally believed to be effective, despite the fact that oral ketoconazole has undergone label changes and market withdrawal due to significant adverse effects.

KEYWORDS : Ketoconazole, Antifungal, Imidazole, Lanosterol.

INTRODUCTION:

For systemic fungal infection, the US Food and Drug Administration approved ketoconazole as a broad-spectrum azole Antifungal in 1981.Azole antifungal inhibit the P450 dependent enzyme Lanosterol 14 demethylase,which results in necrobiosis and prevent the synthesis of ergosterol,a structural components that is vital to the structure of bacterial cell membranes.Ketoconazole was the only oral Antifungal medication on the market for treating systemic mycoses in the 1980s. In 2013,oral ketoconazole was removed from Australia and Europe due to reports of serious side effects, including hepatotoxicity,adrenal deficiency,and drug interactions. In North America,the medications label was changed to no longer include a prescription for the treatment of fungal infections of the skin and nails. Nowadays,treating endemic mycoses with oral ketoconazole is advised only in cases where no alternative antifungal drugs are available.

Topical ketoconazole formulations containing 2% shampoo and seborrheic dermatitis, 1% shampoo,2% cream,2% gel,and 2% aerosol foam have been authorised and approved by the Food and Drug Administration. While 1% shampoos are sold over- the-counter, all 2 % shampoos need a prescription. 1% shampoo and 2% gel are the only ones without generic counterparts. Treatment for superficial fungal infections is challenging,and patient compliance is poor even though extended maintenance periods can improve outcomes. Formulations such as 2% aerosol foam and 2% gel were developed with the goal of improving patient compliance with less messy or recurrent administration as compared to shampoo or cream. Utilizing lipophilic and keratophilic ketoconazole lacquers or nanoemulgels,in vitro and in vivo studies demonstrate enhanced transungual transport and suggest that they might be useful for onychomycosis. When compared to systemic antifungal administration without help,prophylactic administration of topical antifungal like clotrimazole or ketoconazole may result in improved cure and decreased relapse rate of recalcitrant,superficial dermatophyte infections , candida or pityriasis. However more research is needed to determine the efficacy of antifungal prophylaxis. Current research focuses on employing nanostructured lipid carrier,co-polymeric micelles,micro emulsions, liposomes,and niosomes. Nanostructure lipid carriers shield KTZ from photodegradation,while co-polymeric micelles microemulsions enhance thermodynamic strength and percutaneous permeability.Liposomes and noisomers both enhance the skin's ability to cling onto medication, extending its duration of action.

ANTIFUNGAL ACTIVITY :

In vitro, ketoconazole exhibits broad Antifungal activity against a variety of fungi,sharing many of the same mechanism of action as miconazole,an older imidazole antifungal drug. The spectrum of action includes yeasts(Cryptococcus neoformans), dermatophytes (Epidermophyton,Trichophyton), Diamorphic fungi(Coccidioides immitis, Histoplasma capsulatum),and a variety of other fungi.For some now,scientists have disagreed over the function of lipophilic yeast. Among other superficial dermatoses,Pityrosporum folliculitis, pityriasis versicolor,seborrheic dermatitis ,and dandruff pityriasis capitis are all formed by pityrosporumovale(orbiculare). Ketoconazole is a potent anti-
pityrosporum medication that is used to treat seborrheic dermatitis.

Chemical structure :

Ketoconazole
Molecular weight : 531.4
Molecular Formula: C26H28Cl2N4O4
IUPAC Name:1-acetyl-4-(4-{[2-(2, 4-dichlorophenyk)-2-(1H-imiddazole-1-ylmetyl)-1, 3-(dioxolan-4-yl] methoxy} phenyl piperazine ethenone

DOSES FORM OF ACTION:

There are several different dosage forms of ketoconazole, including cream,gel,and ointment,as well as emulgel and polymeric film.

MECHANISM OF ACTION:

The antifungal medication ketoconazole works by inhibiting the cyto P450 14-demethylase enzyme. This enzyme prevents fungi from producing triglycerides and phospholipids. Specifically, ketoconazole inhibit the production of Lanosterol,which is a precursor for the biosynthesis of ergosterol. To maintain the integrity of their membranes,fungi require ergosterol. Without ergosterol,the membrane becomes more fluid and inhibit the growth of fungi. Ketoconazole can compete with androgen receptor,such as those for testosterone and dihydrotestosterone,at high dosages,which reduces the activity of these hormones in prostate cancer. Ketoconazole has the ability to inhibit the enzymes 17,20-lyase,and 17-alpha-hydroxylase,which are necessary for the adrenal cortex to produce hormones. Ketoconazole inhibit 21-hydroxylase,an enzyme. This enzyme is necessary in the adrenal cortex to produce mineralocorticoid such as cortisol and glucocorticoids. Cushing's syndrome can be treated with ketoconazole by inhibiting the enzymes that produce cortisol.

Pharmacokinetic property:

ABSORPTION:

When applied topically, ketoconazole is not absorbed systemically. When 12 healthy individuals were given 2% ketoconazole cream to put on their arms ,chests,and backs,no detectable serum concentrations were discovered. Similar results were seen when this cream was applied repeatedly to dog's abraded skin. In six patients with severe tinea pedis, there was no ketoconazole found in their plasma after applying a 2% lotion. Ketoconazole binds to plasma albumin 84% of the time and blood cells 15% of the time,for a total of 95%binding in plasma.

DISTRIBUTION:

Ketoconazole enters the bloodstream and travels to the skin. Three hours following a 200 mg dose in healthy individuals, ketoconazole was found in suction blister fluid at a maximum concentration of 0.91 mg/L; by nine hours,that concentration had dropped to 0.22mg /L. Subjects skin ketoconazole concentration two hours following the prior treatment ranged from 1.4 to 11.9% p.g/g. Five and ten days after the previous injection,the skin mean concentration had decreased to 2.6 and 1.3 p.g.g/g, respectively. Two hours,five days,or ten days following the prior dosage, ketoconazole did not grow in the roots of the epilated hairs.

ELIMINATION:

Inactive metabolites are created by extensive metabolism and are mostly excreted in the stool. It is likely that hepatic first-pass metabolism is saturable. Ketoconazole's half-life is dose-dependent and increases with time, suggesting metabolic auto-inhibition . A two-compartment model is well suited by the kinetics following oral delivery.

METABOLISM:

Ketoconazole has been shown to cause hepatotoxicity,which is most likely not the results of an immunoallergic mechanism. Ketoconazole is substantially metabolised by hepatic microsomal
enzymes;nevertheless,little is known about the nature,process of metabolisation ,and toxicity of potential metabolites.

INTERACTION:

1.Absorption Interactions:

Since ketoconazole is water insoluble, stomach acidity affects how well it is absorbed . It has been noted that concuuse of medication such cimetidine,which decrease stomach acid production,can obstruct its absorption. For example,a 28-year old woman who had renal failure and cryptococcal arthritis was prescribed 200mg of ketoconazole daily. At the same time,she also received cimetidine, aluminium oxide,and sodium bicarbonate. Even at 400 mg/day, ketoconazole plasma concentrations were less than 1 Wgiml. Next,three adult male volunteers in good health were assessed by Ex.Vander Meer and associates 63. The antifungal plasma levels of the individual are shown at 1,2,4,and 6 hours. When cimetidine was

given two hours prior to 200mg of ketoconazole,the AUC fell by more than 60%. When given two hours after cimetidine and in an acidic solution,the AUC of ketoconazole was more than fifty percent greater than when the drug was administered on its own. Avoiding this interaction can be achieved by administering ketoconazole in an acidic solution. Should antacids or histamine -2 blockers be necessary,they are to be administered at least two hours following the ketoconazole to facilitate complete absorption prior to the stomach's pH being adjusted

2.Metabolic Interaction:

Hepatic microsome enzymatic activity has been demonstrated to be inhibited by derivatives of Imidazole.

ADVERSE EFFECTS:

Among the adverse effects of using ketoconazole are nausea, vomiting,and stomach pain. Ketoconazole Adverse effects are dose-dependent and preventable if taken with meals. Brief elevation in liver enzyme levels in the blood may happen without any symptoms. In addition, oligospermia,hepatits ,Gynecomastia,irregular menstruation,and adrenal cortical suppression can occur .

Additional adverse effects include allergic reactions such urticaria and angioedema,and in rate cases, anaphylaxis. The side effects of ketoconazole medicine includes rash,alopecia,itching,headache, vertigo,somnolence,and impotence.

The most common side effects include diarrhea,vomiting related to dosage,liver damage,and infrequent thrombocytopenia.

CONTRAINDICATIONS:

It is not advised for those who are hypersensitive to ketoconazole to use it. It is not recommended to use it to treat fungal meningitis due to its poor penetration into the central nervous system. It is not advised to provide triazolam concurrently.

As ketoconazole might result in hepatotoxicity,which can be fatal,it is not advised for anyone with acute or chronic liver sickness. Large doses of ketoconazole are not recommended in cases of adrenal insufficiency because they impair adrenocortical function. Ketoconazole should not be given to people who have already had a hypersensitive reaction to the medication. Ketoconazole and HMG-CoA reductase inhibitors should never be combined since the former increases the risk of myopathy. For those on benzodiazepines, ketoconazole is not advised as it can increase sleepiness

TOXICITY:

The FDA warns that oral ketoconazole usage may result in adrenal insufficiency and hepatotoxicity,and that hepatotoxicity linked to ketoconazole use is common. Off label used for ketoconazole are many. Because of these significant hepatotoxic side effects, ketoconazole must be carefully chosen as a medication.

TERATOGENIC STUDY OF KETOCONAZOLE:

A broad spectrum imidazole Antifungal, ketoconazole,has demonstrated efficacy in treating a number of systemic and superficial mycoses. However, research on pregnant rats has shown that when this drug is administered by gavage at larger dosages,there may be teratogenic and embryotoxic effects. Pregnant rats given 80 mg/kg (ten times the recommended human dose) of Ketoconazole have been shown to produce syndactyly and oligodactyly in the foetuses. In another study,which used varying doses of ketoconazole (ten,twenty-five,or fifty mg/kg) in pregnant rats on days six through twenty-one of gestation,a high percentage of stillbirths indicating fetotoxicity and embryo toxicity was discovered along with a high rate of foetal resorption. The FDA has classified ketoconazole as pregnancy category C, meaning that these drugs must only be used throughout pregnancy if the potential benefit outweighs the potential risk to the foetus. This is because there isn't enough controlled study done on humans and studies done on animals have shown that drugs have the potential to cause teratogenic effects. Antifungal medication are frequently used in human medicine. Therefore,to ascertain their reproductive toxicologic effect,it is necessary to determine both material exposure and reproductive outcome.

MEDICAL USES:

Topical antifungal:

Keratin is applied topically to treat fungal disorder of the skin and mucous membranes, including ringwarm, athlete's foot,jock itch,and candidiasis. Topical ketoconazole is also used to treat seborrheic dermatitis on other parts of the body and dandruff . This treatment may work by reducing the amount of the fungus malassezia furfur on the skin in both conditions.

Systemic antifungal:

Among other fungi that can infect humans, ketoconazole is effective against paracoccioidomycosis,chromomycosis,Can-dida,Coccidioides,and blastomyces. Developed in1977 , ketoconazole was the first orally active azole Antifungal medication. Alternative azole Antifungal drugs , such itraconazole, have essentially replaced ketoconazole as a first line systemic antifungal treatment due to its slower absorption, higher toxicity,and narrower spectrum of activity.

Other:

In rare cases,a small body of clinical evidence suggests that hair loss can be lessened by using ketoconazole shampoo either by alone or in combination with other treatments.

CONCLUSION:

A synthetic Antifungal drug called ketoconazole is used to treat a variety of Fungal diseases, including genital candidosis and chronic mucocutaneous candidiasis. It is well absorbed when taken orally and has a favorable pharmacokinetic profile. Additionally,it can cause nausea, vomiting,and upset stomach. Additional adverse effects include allergic reactions such urticaria and angioedema and in rare cases, anaphylaxis . Due to its association with liver damage , ketoconazole should not be administered to patients suffering from acute or chronic liver disease. For people who are known to be hypersensitive to ketoconazole,it is not advised. Based on our analysis,we have determined that ketoconazole is useful in treating a variety of antifungal infections as well as other conditions including hair loss. However,it should be used with caution due to its hepatotoxicity.

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