IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 6, April 2024

Ketoconazole: A Review of its Antifungal Properties and Clinical Applications

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Abstract: *Ketoconazole (KET), an imidazole derivative with well-known antifungal properties, is lipophilic and practically insoluble in water, therefore its clinical use has some practical disadvantages. The aim of the present study was to investigate the influence of PAMAM-NH2 and PAMAM-OH dendrimers generation 2 and generation 3 on the solubility and antifungal activity of KET and to design and evaluate KET hydrogel with PAMAM dendrimers. It was shown that the surface charge of PAMAM dendrimers strongly affects their influence on the improvement of solubility and antifungal activity of KET. The MIC and MFC values obtained by broth dilution method indicate that PAMAM-NH2 dendrimers significantly (up to 16-fold) increased the antifungal activity of KET against Candida strains (e.g., in culture Candida albicans 1103059/11 MIC value was 0.008 μg/mL and 0.064 μg/mL, and MFC was 2 μg/mL and 32 μg/mL for KET in 10 mg/mL solution of PAMAM-NH2 G2 and pure KET, respectively). Antifungal activity of designed KET hydrogel with PAMAM-NH2 dendrimers measured by the plate diffusion method was definitely higher than pure KET hydrogel and than commercial available product. It was shown that the improvement of solubility and in the consequence the higher KET release from hydrogels seems to be a very significant factor affecting antifungal activity of KET in hydrogels containing PAMAM dendrimers.*

Keywords: PAMAM dendrimer; ketoconazole; hydrogel; antifungal activity; aqueous solubility

I. INTRODUCTION

Ketoconazole is an imidazole antifungal that is administered either topically or by mouth. It is taken orally for the treatment of chronic mucocutaneous candidiasis, for treatment of fungal infections of the gastrointestinal tract, for treatment of dermatophyte infections of the skin and fingernails that do not respond to topical administration, and for treatment of systemic infections including blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis. Because of its erratic absorption and slow therapeutic response, ketoconazole should not be used for the treatment of life-threatening fungal infections, including fungal meningitis, or for severe infections in immunocompromised patients Micromedex ..

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Ketoconazole, sold under the brand name Nizoral among others, is an antiandrogen, antifungal, and antiglucocorticoid medication used to treat a number of fungal infections.Applied to the skin it is used for fungal skin infections such as tinea, cutaneous candidiasis, pityriasis versicolor, dandruff, and seborrheic dermatitis. Taken by mouth it is a less preferred option and only recommended for severe infections when other agents cannot be used. Other uses include treatment of excessive male-patterned hair growth in women and Cushing's syndrome.

Fungal infections are characterized by high morbidity and mortality. Every year, at least 1.5 million people are killed, and the lives of more than one billion people are affected by fungal infections (Bongomin et al. 2017). In recent years,

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the frequency of fungal infections has been increasing rapidly. Fungal infections can be divided into superficial and deep infections. Deep fungal infections can cause invasive mycosis, which is an infectious disease caused by fungal invasion of subcutaneous tissues, mucous membranes, and internal organs. About 6 in 100,000 people are infected with invasive fungi each year, although only one-half of fatal cases are diagnosed prior to death (Dignani 2014). Therefore, the lack of timely diagnosis, and treatment, is one of the causes of the high mortality of invasive fungal infections (von Lilienfeld-Toal et al. 2019). At present, invasive fungal infections are mainly caused by species of Aspergillus, Candida, and Cryptococcus (Pathakumari et al. 2020), and echinomycin, flucytosine, polyenes, and triazoles are the drugs used most commonly for their treatment. Superficial fungal infections can lead to cutaneous mycosis and superficial mycosis, which are caused by pathogenic fungi parasitizing keratin tissues, such as hair, nails, and skin. Cutaneous mycosis is one of the most common superficial fungal infections, with an incidence of up to 25% (Havlickova et al. 2008). Cutaneous mycosis is also known as "ringworm." Ringworm infections are caused mainly by species of Epidermophyton, Microsporum, and Trichophyton, with the common skin ringworm infection in human being caused by Trichophyton rubrum. At present, topical drugs used to treat superficial fungal infections include allylamines, azoles, and griseofulvin (Ademe 2020; Khurana et al. 2019).

II. MEDICINAL USES

Topical antifungal

Topically administered ketoconazole is usually prescribed for fungal infections of the skin and mucous membranes, such as athlete's foot, ringworm, candidiasis (yeast infection or thrush), jock itch, and tinea versicolor.[20] Topical ketoconazole is also used as a treatment for dandruff (seborrheic dermatitis of the scalp) and for seborrheic dermatitis on other areas of the body, perhaps acting in these conditions by suppressing levels of the fungus Malassezia furfur on the skin.

Systemic antifungal

Ketoconazole has activity against many kinds of fungi that may cause human disease, such as Candida, Histoplasma, Coccidioides, and Blastomyces (although it is not active against Aspergillus), chromomycosis and paracoccidioidomycosis.[23][13] First made in 1977,[20] ketoconazole was the first orally-active azole antifungal medication.[23] However, ketoconazole has largely been replaced as a first-line systemic antifungal medication by other azole antifungal agents, such as itraconazole, because of ketoconazole's greater toxicity, poorer absorption, and more limited spectrum of activity.

Ketoconazole is used orally in dosages of 200 to 400 mg per day in the treatment of superficial and deep fungal infection.

Ketoconazole 2% gel

Ketoconazole shampoo in conjunction with an oral 5α-reductase inhibitor such as finasteride or dutasteride has been used off label to treat androgenic alopecia. It was speculated that antifungal properties of ketoconazole reduce scalp microflora and consequently may reduce follicular inflammation that contributes to alopecia.

Limited clinical studies suggest ketoconazole shampoo used either aloneor in combination with other treatments[29] may be useful in reducing hair loss in some cases.

Cushing Syndrome is divided into ACTH-dependent forms, either due to a corticotropic pituitary adenoma i.e. a Cushing's disease (CD) or due to an ectopic ACTH production by a neuroendocrine tumor or an unknown source (occult ectopic ACTH syndrome), and ACTH-independent forms, due to adrenal adenoma/carcinoma or nodular adrenal hyperplasia (Boscaro, 2001; Newell-Price, 1998). According to the Committee for Orphan Medicinal Products (COMP) (Opinion dated 23/04/12) the prevalence of the "condition" Cushing's syndrome is approximately 0.9 in 10,000 people in the European Union (EU). This is equivalent to a total of around 46,000 people, and is below the ceiling for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor. The median age at first admission was 41.4 years (range 3.6-77.7) and the female to male ratio was 3:1. Less than 10% of cases occur in pediatrics and unlike in adults no female preponderance is observed (Shah, 2011).

The clinical consequences of excess endogenous cortisol exposure are generally severe: glucose tolerance impairment or diabetes; hypertension; dyslipidemia; clotting disorders; vascular fragility; muscular weakness; osteoporosis; diminished resistance to infection; depression and psychiatric disorders; healing defects; gonadal dysfunction with

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hirsutism and acne (Arnaldi, 2012; Bolland, 2011; Boscaro, 2001; Cavagnini, 2001; Newell-Price, 1998). Obesity and growth arrest are the most common findings in children with CS (Shah, 2011). Because of complications such as hypertension, diabetes mellitus, cardiac abnormalities and alteration in hemostatic parameters, cortisol excess leads to an increased cardiovascular risk (Whitworth, 2005; Arnaldi, 2012) with increased frequency of arterial atherosclerosis (Neary, 2013).

Antifungal mechanisms and immunomodulatory effects of existing antifungal drugs

Currently, antifungal targets have been identified for drugs that treat superficial or systemic fungal infections. Acrylamide targets the fungal enzyme squalene cyclooxylate and then blocks the synthesis of ergosterol, so that squalene accumulates on the cell membrane, increases the cell membrane brittleness, and leads to the rupture and death of fungal cells (Thapa et al. 2015). Although triazole drugs are the most widely used antifungal drugs, with low hepatorenal toxicity, there is widespread triazole resistance among pathogenic fungi. Triazole drugs mainly bind to 14-α-lanosterol demethylase, a key enzyme in ergosterol biosynthesis in fungal cell membranes, with binding causing inhibition of cell membrane synthesis, cell rupture, and death (Chen et al. 2022a). Polyenes, such as amphotericin B (AmB), were among the earliest antifungal drugs; even today, it is still the "gold standard" for the treatment of systemic fungal infections (Mahor et al. 2022). By acting on sterols of the phospholipid bilayer of fungal cell membranes, polyenes can change the permeability of the cell membrane and generate water-soluble pores, thus leading to the loss of intracellular contents and resulting in fungal cell death. However, due to their potential liver and kidney toxicity, polyenes are used in clinical circumstances with caution (Carolus et al. 2020). Although the price of echinocandin drugs is high, the use of echinocandin drugs in clinical treatment is increasing due to their broad spectrum, low toxicity, and high efficiency. The echinocandin drugs (large lipoprotein molecules) target and non-competitively inhibit activity of the catalytic subunit of β-1,3-D-glucan synthase, encoded by fks genes, causing interference with the fungal cell β-1,3-D-glucan synthesis, and resulting in fungal cell wall permeability changes, leading to cell lysis and death (Campoy and Adrio 2017). The drug 5-fluorocytosine exhibits antifungal activity by disrupting fungal DNA and protein synthesis. As mammalian cells lack cytosine deaminase in the antimicrobial pathway, this drug does not have a direct toxic effect on mammals (Delma et al. 2021). Unfortunately, because of the widespread drug-resistant in pathogenic fungi, the use of 5-flucytosine has been greatly reduced. It is only recommended for the treatment of lower urinary tract infections caused by Candida (Pappas et al. 2016). However, it has become one of the most reliable treatments for cryptococcal meningitis and complex Candida infections in combination with AmB (Perfect et al. 2010).

Inadequately treated CS is aLife-threatening condition. In a Danish study (Lindholm, 2001), the mortality rate of non-malignant CS was 3.7 fold higher than in the normal population and was even worse in CD patients not cured by pituitary surgery, in which the mortality rate was 11.5 times higher than in the normal population. CD patients with persistent disease after initial surgery had a standard mortality ratio (SMR) of 3.73 (95% CI: 2.31-6.01), whereas mortality of CD patients with initial remission did not differ significantly from the general population (SMR: 1.23 (95% CI: 0.51-2.97) (Graversen, 2012). Other authors reported that in CD the mortality is significantly affected, even after apparently successful treatment. The probability of 10-year survival was 95.3% with 71.4% of the deaths attributed to cardiovascular causes or infection/sepsis (Ntali, 2013). Persistence of disease, older age at diagnosis, and presence of hypertension and diabetes were the main determinants of mortality. These results are similar to those in Spain (Etxabe, 1994) where mortality in patients with CD was significantly higher (SMR 3.8) than expected in the control population.

About the product Ketoconazole is an imidazole derivative named: (±)-cis-1-Acetyl-4-{4-[2-(2,4-dichlorophenyl)-2-imidazol-1-ylmethyl-1,3-dioxolan-4-ylmethoxy]phenyl} piperazine, was originally used in the treatment of fungal infections and inhibits the synthesis of ergosterol in fungi and cholesterol in mammalian cells. In addition it is an inhibitor of cortisol synthesis resulting from its ability to inhibit several cytochrome P450 enzymes in the adrenal glands. Ketoconazole inhibits primarily the activity of 17α-hydroxylase, but it also inhibits 11-hydroxylation steps, and at higher doses the cholesterol side-chain cleavage enzyme. Therefore, ketoconazole is an inhibitor of cortisol and aldosterone synthesis. Ketoconazole is also an inhibitor of androgens synthesis, inhibiting the activity of C17-20 lyase in the adrenals and also in Leydig cells. Ketoconazole has therefore been demonstrated to be not only an inhibitor of cortisol and aldosterone synthesis but also an inhibitor of androgens synthesis. Ketoconazole could be used in the treatment of all causes of endogenous hypercortisolism, regardless of its aetiology. Ketoconazole was subject to a

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referral procedure, due to public health concerns on the hepatotoxicity risk and in July 2013, the CHMP, taking into account the increased rate of liver injury, concluded that the clinical benefit of oral ketoconazole as an anti-fungal therapy is uncertain as data on its effectiveness are limited and did not meet current standards, and as alternative treatments of fungal infections were available.

In addition,

Ketoconazole may commonly have caused an increase in liver enzyme levels and very rarely, cases of serious liver damage, including deaths, or cases requiring a liver transplant.

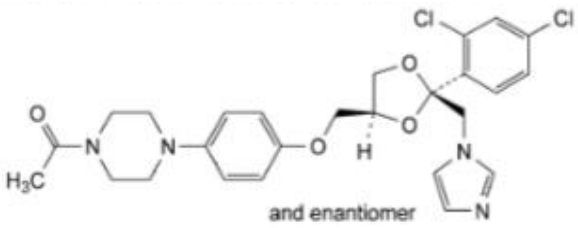
Quality aspects

Introduction The finished product is presented as uncoated tablets containing 200 mg of ketoconazole as active substance.

Other ingredients are: maize starch, lactose monohydrate, povidone, microcrystalline cellulose, colloidal silica and magnesium stearate. The product is available in PVC/Alu blisters. 2.2.2. Active Substance

General information The chemical name of ketoconazole is 1-acetyl-4-[4-[[(2RS,4SR)-2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)1,3-dioxolan-4-yl]methoxy]phe nyl]piperazine and has the following structure:

Chemical compounds:



The (2S, 4R)-Ketoconazole sulfonamide analogs were prepared according to our previously reported methods (Blass et al., 2016). Briefly, (2S, 4R)-Ketoconazole (4) was hydrolyzed with NaOH in refluxing methanol/water and the resulting product was converted to a sulfonamide (3a-3l) using the corresponding sulfonyl chloride (5) in the presence of Net3 and CH2Cl2 (Figure 2). Amphotercin B was purchased from ACTGene Inc. (Catalog number R1397-1 g). (±)-ketoconazole we purchased from Combi-Blocks Inc. (Catalog number QA-7778-1 g).

Broth microdilution susceptibility test: The minimum inhibitory concentrations (MIC75) were determined by the broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) M27-A4 standard (CLSI, 2017)). Briefly, a suspension of C. albicans or C. glabrata culture (~0.5–2.5 × 103 cells/ml) was resuspended in RPMI 1640 media (Fisher Catalog number 11875093). The resuspended culture was further incubated with 100 µl of two-fold serially diluted test compounds (100–0.8 µM and 1.0 µM to 7 nM) at 30 °C for 24-48 h. Positive and negative control (wells without antifungal agents and wells without yeast) were conducted. Increased optical density (OD) corresponds to the Candida growth and was quantified by comparison with untreated Candida control samples. The MIC75 of test compounds was determined visually and spectrophotometrically (OD600) after 24-48 h. Experiments were run in triplicate, and data was reported as a mean.

Cyp3A4 inhibition assay: Human Cyp3A4 Inhibition assay: An IC50 for inhibition human Cyp3A4 metabolism of midazolam to 1-OH-midazolam was determined with 10 concentrations of test compounds (half-log serial dilutions; duplicate points). Assays were conducted in 1 ml 96 well polypropylene plates containing 100 µL of 100 mM potassium phosphate (pH 7.4), 3 mM MgCl2, 2 µM midazolam, 1 mM NADPH (tetra Na salt), Corning Gentest supersomes (product 456202: 3 pmol/ml human Cyp3A4, 47 nmol/min human P450 reductase activity, 14 pmol human cytochrome b5; and product 456201: insect control microsome protein; total final microsome protein concentration 0.15 mg/ml) and test compound. All components except NADPH were added to a prewarmed plate and reactions were initiated by adding NADPH. After 30 min at 37°C, reactions were terminated with 200 µL acetonitrile containing 30 µM prednisone. After centrifugation for 10 min at 2200 x g, 165 µL of supernatants were transferred to analysis plate. Samples were analyzed for 1-OH-midazalam concentration, using prednisone as the internal standard, using a Waters Aquity UPLC in tandem with a Xevo TQ MS mass spectrometer (BEH C18 column; 5-95% acetonitrile gradient with

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0.1% formic acid; ESP + mode). IC50's were determined using GraphPad's Prism v 5.04 nonlinear curve fitting program.

Spectrum of antifungal activity

5-FC is most active against yeasts, including Candida, Torulopsis and Cryptococcus spp., and against the dematiaceous fungi causing chromomycosis (Phialophora and Cladosporium spp.) and Aspergillus spp.14 The MICs of 5-FC vary from 0.1 to c.25 mg/L for these fungal species.

In Emmonsia crescens, Emmonsia parva, Madurella mycetomatis, Madurella grisea, Pyrenochaeta romeroi, Cephalosporium spp., Sporothrix schenckii and Blastomyces dermatitidis, MICs vary from 100 to 1000 mg/L.14 5-FC is also active against some protozoa, including Acanthamoeba culbertsoni both in vitro and in vivo and Leishmania spp. In patients.

The mode of action of 5-FC and the essential role of cytosine deaminase have been proven in Saccharomyces cerevisiae and C. albicans and are probably also valid for other sensitive fungi.14 However, specific research in this field is lacking.

The advantages of topical antifungal therapy over oral antifungals include:

(1) lack of systemic side effects and complications due to limited systemic absorption, (

(2) very low incidence of drug interactions,

(3) ease of use,

(4) comparatively low cost of therapy,

(5) additional benefit of anti-inflammatory activity of several topical antifungals including azoles and allylamines.

The disadvantages of topical antifungals include:

(1) difficult to use in extensive dermatophytic infections,

(2) application of inadequate amount results in poor response,

(3) inability to apply in difficult-to-reach areas (e.g., natal cleft) may leave residual foci of infection,

(4) low effectiveness in onychomycosis due to inadequate penetration, and

(5) rarely contact dermatitis.

MEDICAL USES:

Topical antifungal:

Ringworm, candidiasis (thrush or yeast infection), tinea versicolor, athlete's foot and jock itch are all fungal diseases of the skin and mucous membranes that are treating with topically applied ketoconazole. Topical ketoconazole is also used to treat dandruff (seborrheic dermatitis of the scalp) and seborrheic dermatitis on other parts of the body, possibly by decreasing level of the fungus Malassezia furfur on the skin in these disorders.

Systemic antifungal:

Ketoconazole is effective against Histoplasma,Candida, Coccidioides, and Blastomyces (but not Aspergillus), paracoccidioidomycosis, and chromomycosis, among other fungus that can cause human illness. Ketoconazole was the 1st orallyactive azole antifungal drug, being developed in 1977. Because of ketoconazole's slower absorption, higher toxicity, and restricted spectrum of effectiveness, alternative azole antifungal medications, such as itraconazole, have essentially supplanted it as a first-line systemic antifungal treatment.

Side Effects: Ketoconazole is well tolerated by most patients. Gastrointestinal reactions (about 5 %) or pruritus (about 2 %) occur most frequently, occasionally necessitating a dosage reduction or discontinuing treatment. Gynaecomastia has been reported in a few male patients on either usual or 'higher' doses. Transiently elevated liver enzymes occurred in about 10 % of patients, and symptomatic liver dysfunction during ketoconazole administration has occurred in a few patients but resolved on discontinuing therapy. Various other 'side effects', including dizziness, somnolence, arthralgia, myalgia, headache and many others have been reported, but only in 1 or a few of 1361 patients studied, and their association with drug treatment is open to question. Overall, treatment was permanently discontinued due to side effects in 1.5 % of these patients and temporarily discontinued in 1.3 %. In 62 children treated with the drug 2 cases of side effects were reported —transient fever and chills in one child and persistent nausea and vomiting in another, the latter necessitating discontinuation of therapy.

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Dosage and Administration: For all conditions except vaginal candidosis the initial recommended adult dosage is 200mg once daily. If the clinical response is inadequate, the dose may be increased to 400 or 600mg once daily, but there is little evidence to support an improved response with 'higher' doses. In vaginal candidosis the recommended dosage schedule is 200mg twice daily for 5 days. The duration of treatment should be individualised, and based on clinical and mycological response. Generally, in 'deep' mycoses treatment should be continued for at least 1 week after apparent eradication of the infecting fungus. Continued prophylactic use to prevent relapse may be appropriate in some conditions, although this has not been well studied.

Other:

In rare circumstances, limited clinical research show that using ketoconazole shampoo alone or in conjunction with other therapies can help reduce hair loss.17-22

II. CONCLUSION

Ketaconazole is synthetic antifungal agent which is used to treat various fungal infections like chronic mucocutaneous candidosis, genital candidosis, etc. It has good pharmacokinetic profile like it is well absorbed orally. It also has some adverse effect like Nausea, vomiting, and stomach discomfort. Other side effects contain allergic responses such urticaria and angioedema, as well as anaphylaxis in rare circumstances. Ketoconazole is contraindicated in patients with chronic oracute hepatic disease due to its organization with liver toxicity. Ketoconazole is contraindicated in those known to be oversensitive to it.Therefore from this review we concluded that ketoconzole has plenty of application in various antifungal infections and other disorders like hair loss, along with that it shows hepatotoxityso it is used cautiously.

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