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KETOCONAZOLE

shampoo 2%

2.6.2 Pharmacology written summary

Primary Pharmacodynamics

Ketoconazole is an imidazole antifungal agent (Roy, et al 2023; Buxton, 1988; Van Tyle, et al 1984; Sohn, 1982). Ketoconazole exhibits antifungal activity, similar to its predecessors clotrimazole and miconazole, by inhibition of uptake of precursors of RNA and DNA, synthesis of oxidative and peroxidative enzymes and increasing membrane permeability (Martindale, Ketoconazole 2007). Ketoconazole differs from miconazole in that it can be given orally (Sohn, 1982).
Ketoconazole has a potent antimycotic action against dermatophytes and yeasts (Van Tyle, et al 1984; Borgers, et al. 1983; Nagpal, et al. 2003; Kyle and Dahl, 2004).
Ketoconazole acts rapidly on the pruritus, which is commonly seen in dermatophyte and yeast infections. This symptomatic improvement often occurs before the first signs of healing are observed. Ketoconazole is superior also to miconazole in that it has a lower degree of inactivation once absorbed (Borgers, et al. 1983). Another possible mechanism of ketoconazole is inhibition of the transformation of yeast forms to hyphal forms, the yeast form being more susceptible to phagocytosis by leukocytes. Ketoconazole blocks testosterone synthesis during long-term oral administration. The drug may find usefulness given in high doses to suppress steroid synthesis in conditions such as prostatic carcinoma, Cushing's syndrome, or hirsutism (Pont, et al. 1982; Sinawe and Casadesus, 2022).

Ketoconazole in a form of shampoo primarily exerts its pharmacodynamic effect through its antifungal properties (Van Tyle, et al 1984; Borgers, et al. 1983; Nagpal, et al. 2003; Kyle and Dahl, 2004). In the context of ketoconazole shampoo, this mechanism of action allows it to effectively target and eliminate fungi that cause conditions such as dandruff (caused by Malassezia yeasts) and seborrheic dermatitis (Jiang, et al. 2005). By controlling fungal overgrowth on the scalp, ketoconazole shampoo helps alleviate symptoms associated with these conditions, including itching, flaking, and inflammation (Jiang, et al. 2005; Van Cutsem, et al. 1991).

It's important to note that while ketoconazole shampoo primarily acts as an antifungal agent, it may also have additional effects, such as anti-inflammatory properties, which can contribute to its therapeutic efficacy in conditions like seborrheic dermatitis (Van Cutsem, et al. 1991; Marsella, et al 1997). However, the primary pharmacodynamic action of ketoconazole shampoo remains its antifungal activity targeting the fungal pathogens responsible for scalp-related conditions (Jiang, et al. 2005).

Mechanism of Action

Ketoconazole appears to block enzymes in the steroid biosynthetic pathway (Daneshmend and Warnock, 1988). Their data indicates that ketoconazole primarily inhibits C-17, 29-desmolase, the enzyme responsible for androstenedione biosynthesis. Fungi often infect the skin surface and subsequently invade the stratum corneum to avoid being shed from the skin surface by desquamation. Pharmacologic agents applied to the surface of the skin in the form of creams, lotions, or sprays, readily penetrate into the stratum corneum to kill the fungi (fungicidal agents), or at least render them unable to grow or divide (fungistatic agents). Thus, topical therapies work well to rid the skin of topical fungi and yeasts. Azole drugs such as miconazole, clotrimazole, and ketoconazole are fungistatic, limiting fungal growth but depending on epidermal turnover to shed the still-living fungus from the skin surface (Kyle and Dahl, 2004).
Therapy for cutaneous candidiasis is dominated by topical antifungal agents. Azole antifungal cream (e.g., bifonazole, ketoconazole, neticonazole hydrochloride, lanoconazole and luliconazole) is most effective (Pappas, et al, 2004). Both topical and systemic ketoconazole are reported to be effective against pityriasis versicolor (Nagpal, et al. 2003).
The effects of miconazole and its new derivative ketoconazole on Candida albicans have been evaluated by light and electron microscopy. The growth characteristics and morphology of C. albicans in culture for various periods of time in a solution consisting of Eagle's minimum essential medium supplemented with amino acids and fetal calf serum are emphasized. This medium, normally used for culturing mammalian cells, promotes a rather fast growth of C. albicans and favours the development of pseudomycelium. The obvious interest in using such culture conditions for drug evaluation is the prevalence of pseudomycelium, which in vivo is the predominant pathological form of C. albicans. Suppression of pseudomycelium formation is found in the 10-9 to 10-7 M concentration range of the imidazoles. Growth retardation and the destruction of both yeast and pseudomycelial forms brought about by incubating the cells with 10-9 to 10-4 M of the drugs are reported. At low doses these changes include the alteration of cell division, an increase in cell volume and a progressive deterioration of subcellular organelles at the cell periphery. At higher doses the involvement of all other organelles is observed finally leading to complete cell necrosis (Borgers, et al. 1979).

Spectrum of Activity

Ketoconazole has a potent antimycotic action against yeasts, including Malassezia and dermatophytes. Its broad spectrum of activity is already well known (Roy, et al 2023; Domosławska and Zduńczyk, 2021; Moriello, 2017; Jiang, et al. 2005; Hay, 1985). The antifungal properties of ketoconazole were investigated both in vitro and in vivo (Odds, et al 1980; Van Cutsem J 1983; Van den Bossche, et al. 1980; Van Tyle, et al 1984; Fromtling, 1988; Strippoli, et al 1997).
The antifungal potency of ketoconazole in vitro was studied in Sabouraud's broth for 715 fungal strains belonging to 85 species and several strains were tested in other media, including

Eagle's minimal essential medium. Ketoconazole is highly active in vitro and possesses broad spectrum activity. Its in vitro activity is largely dependent on the medium used. Ketoconazole's activity is increased in medium enriched with serum and in Eagle's minimal essential medium. Ketoconazole is very potent in the topical treatment of skin dermatophytosis, skin candidiasis, and in vaginal candidiasis of laboratory animals. Ketoconazole is superior to griseofulvin in the oral treatment of skin dermatophytosis. Furthermore, ketoconazole is orally highly active in skin candidiasis in guinea pigs, in vaginal candidiasis in rats, and in gastrointestinal candidiasis in various animal species. In systemic candidiasis and in disseminated dermatophytosis in guinea pigs cure with oral ketoconazole is achieved. No side effects are observed (Van den Bossche, et al. 1980).

The in vitro activity of ketoconazole was first reported by Dixon et al. in 1978. These investigators studied 175 isolates of pathogenic yeasts and filamentous fungi and observed that ketoconazole was comparable to miconazole in all cases and was more active than miconazole against isolates of Coccidioides immitis. It was, however, less active against isolates of Sporothrix schenckii. Other in vitro studies also have confirmed the broad-spectrum activity of ketoconazole against pathogenic yeasts and dermatophytes and dematiaceous fungi. A recent study by Shadomy et al. demonstrated that emergence of ketoconazole-resistant clinical isolates of systemic and pathogenic fungi was not apparent but that in vitro data did not necessarily correlate with the clinical outcome of treatment, a common problem among tests with the antifungal azole derivatives. The relative inhibition factor (RIF), an in vitro measure of antifungal activity, of ketoconazole was tested by Odds et al. (1984). The RIF approaches 100% for a drug that either does not or only poorly inhibits the growth of a test fungus; the RIF approaches 0% for a drug that effectively inhibits fungal growth. The RIF values for 26 isolates of Candida species, 6 isolates of dermatophytes, and 8 isolates of Aspergillus species were 54, 18, and 55%, respectively. Activity was greatest at neutral pH. Thus, ketoconazole had substantial activity against all fungi tested in this assay; the data support ketoconazole as a broad-spectrum antifungal agent (Fromtling, 1988).

In vitro, ketoconazole has a relatively broad spectrum of antifungal activity (Dixon, et al. 1978; Ishibashi and Kaufman, 1986; Kaur and Kakkar, 2010), including the following organisms: dermatophytes (Microsporum, Trichophyton, Epidermophyton), fungi (Candida, Cryptococcus, Torulopsis, Pityrosporum), dimorphic fungi (Histoplasma capsulatum, Coccidiodes, Paracoccidiodes) and eumycetes.
- ***Actinomycetales:*** It is not likely that ketoconazole in the normal recommended dose (200 milligrams orally) will be effective in the treatment of oral or cervicofacial actinomycosis. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of isolates of Actinomycetales appear to be greater than 300 micrograms/milliliter (mcg/ml). Peak plasma concentrations of ketoconazole following a normal dosage are 3 to 4.5 mcg/ml. Based on this data Actinomycetales would not be sensitive to ketoconazole when given in the currently suggested doses.

- ***Actinomycetales: Torulopsis glabrata***

- ***Candida albicans*** (Uno, et al. 1982; de Brabander, et al. 1980; Van den Bossche, et al. 1980; Minagawa, et al. 1983). Ketoconazole reduces hyphal development of Candida albicans at concentrations lower than those necessary to inhibit growth or budding of the yeast. The compound interferes with the biosynthesis of ergosterol. Sterols with a methyl group at C-14 accumulate in the fungal cell; this is found both in vitro and in candida sampled from experimentally infected ketoconazole-treated animals. This imidazole derivative has been found to be highly effective in the treatment of experimental rat vaginitis . In this study of the effect of ketoconazole on experimental rat vaginal candidosis, authors found that the drug had effects on the vaginal epithelium in addition to having an antifungal effect (Kinsman OS, et al 1986).

- ***Trichophyton rubrum***

Several reports have demonstrated the efficacy of topical ketoconazole in dermatologic conditions that are not exclusively related to fungi. Some basic pharmacologic studies have indicated effects of ketoconazole on cholesterol production in keratinocytes, on the 5-lipoxygenase enzyme, and on the metabolism of all-trans-retinoic acid in the skin. These observations have led to the hypothesis that topically applied ketoconazole may possess antiinflammatory properties. This hypothesis was tested in an animal model in which living and killed Staphylococcus aureus applied to the backs of guinea pigs resulted in inflammation with erythema and hyperkeratosis. Ketoconazole 0.5% or 2% was applied topically once daily in an ointment base, either as monotherapy or in combination with hydrocortisone acetate 1%. In addition, untreated, excipient-treated, and hydrocortisone acetate-treated animals were included in the study design. All groups consisted of 10 animals that were observed and scored daily up to 3 days after the experimental therapy was stopped. In the animal model involving killed bacteria (i.e., no infection), topical ketoconazole had antiinflammatory activity comparable to that of hydrocortisone acetate. The activity of ketoconazole on the skin of animals infected with living bacteria (i.e., active bacterial infection) was superior to that of steroid therapy, which suggests some antibacterial effect of topically applied ketoconazole. The combination therapy was highly active under both conditions. These results suggest that, apart from the known antimycotic effects of ketoconazole, this molecule might also have effects against gram-positive bacteria at the high concentrations obtained after local application (Van Cutsem, et al. 1991).

Ketoconazole is also effective in topical applications for treating seborrheic dermatitis and dandruff. Recently, topical use of 2% KCZ shampoo has been reported to have had a clinically therapeutic effect on androgenetic alopecia. The present study was conducted with the purpose of quantitatively examining the stimulatory effect of KCZ on hair growth in a mouse model. Coat hairs on the dorsal skin of seven-week-old male C3H/HeN mice were gently clipped, and either 2% KCZ solution in 95% ethanol or a vehicle solution was topically applied once daily for three weeks. The clipped area was photographed, and the ratio of re-grown coat area was then calculated. The results demonstrated that 2% KCZ had a macroscopically significant

stimulatory effect compared with the vehicle group ($p<0.01$, $n=10$). Repeated experiments showed similar effects, confirming the efficacy of KCZ as a hair growth stimulant. Although the therapeutic mechanism of topical KCZ for hair growth is unclear, our results suggest that topical applications of the substance are useful for treating seborrheic dermatitis accompanied by hair regression or male pattern hair loss (Jiang, et al. 2005).

Synergism

There is synergistic action between ketoconazole and host defense cells. This synergism may explain, in part, the effectiveness of ketoconazole in eradicating deep fungal infections secondary to continuous active blood levels achieved after a single daily dose which inhibits growth and tranformation of deep fungal infections (Borgers, et al. 1983).

Secondary pharmacodynamics

Ketoconazole is primarily used as an antifungal medication, but it also exhibits secondary pharmacological effects due to its interaction with various enzymes and receptors in the body. Some of the secondary pharmacological effects of ketoconazole include:

Inhibition of Steroid Synthesis**:** Ketoconazole inhibits the enzyme cytochrome P450 14α-demethylase, which is involved in the synthesis of ergosterol, an essential component of fungal cell membranes (Sinawe and Casadesus, 2022; Ankley, et al. 2007). This same enzyme also plays a role in the synthesis of steroid hormones in humans, including cortisol and testosterone (English, et al. 1986). Therefore, ketoconazole can inhibit the synthesis of these hormones, leading to effects such as decreased cortisol levels and decreased testosterone levels (Kyle and Dahl, 2004; Sinawe and Casadesus, 2022).

Anti-Androgenic Effects: Because ketoconazole inhibits testosterone synthesis, it can have anti-androgenic effects (English, et al. 1986). This property has led to its use in the treatment of conditions such as hirsutism (excessive hair growth) and androgenic alopecia (male pattern baldness) in certain cases (Pont, et al. 1982).

Inhibition of Drug Metabolism**:** Ketoconazole can inhibit various cytochrome P450 enzymes involved in drug metabolism, such as CYP3A4. This inhibition can lead to increased plasma concentrations of drugs metabolized by these enzymes, potentially resulting in drug interactions and increased risk of adverse effects (Sinawe and Casadesus, 2022; Ankley, et al. 2007).

It's important to note that while these secondary pharmacological effects of ketoconazole can be beneficial in certain clinical contexts, they can also contribute to its potential for adverse effects and drug interactions (Micromedex_Ketoconazole, 2024; Van Tyle, et al 1984).

However, this application is for Ketoconazole shampoo, which is applied topically and has negligible systemic absorption. Therefore no drug interactions or adverse effects are expected.

Safety Pharmacology

Ketoconazole shampoo is generally considered safe when used as directed. It's important to understand its safety profile, particularly regarding local irritation or sensitization reactions (Sinawe and Casadesus, 2022). Nonclinical study performed on rabbits eye's shows that topical ketoconazole does not influence closure of experimentally produced corneal epithelial defects in rabbits and is well tolerated in the eye (Ishibashi and Kaufman, 1986).
The safety of ketoconazole 2% shampoo was evaluated in 2890 subjects who participated in 22 clinical trials. Ketoconazole2% shampoo was administered topically to the scalp and/or skin. Based on pooled safety data from these clinical trials, there were no ADRs reported with an incidence ≥1% (SmPC Nizoral 2% shampoo, Thornton & Ross Ltd. UK, 23/10/2020).

Pharmacodynamic Drug Interactions

Ketoconazole shampoo is primarily used to treat fungal infections of the scalp, such as dandruff or seborrheic dermatitis. As for pharmacodynamic interactions, these occur when drugs affect the same physiological or biochemical pathways, potentially leading to additive or antagonistic effects.
However, since ketoconazole shampoo is primarily applied topically to the scalp and has negligible systemic absorption, it's less likely to cause pharmacodynamic interactions with other drugs compared to oral medications. Drug interactions of theoretical, if not practical significance include warfarin, chlordiazepoxide, methylprednisolone, cyclosporin and drugs known to induce microsomal enzymes (Kaur and Kakkar, 2010; Mayer, et al 2008; Dahlinger, et al 1998). In each case. some dosage adjustment for ketoconazole or the interacting drug may be required (Daneshmend and Warnock, 1988).
Additionally, in accordance with SmPC of Nizoral 2% shampoo, (Thornton & Ross Ltd. UK), which is used as parallel product for development of [redacted] shampoo 2% [redacted] no interaction studies have been performed (SmPC Nizoral 2% shampoo, Thornton & Ross Ltd. UK, 23/10/2020).

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