Section A -Research paper

Ketoconazole in Treatment of Acne

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Abstract:

Acne vulgaris is a very common skin disease particularly affecting the young females. It has significant psychological impact and impairs the daily living of affected ones. It has been reported that more than twice of the women seek consultation from dermatologists in comparison to male patients, and more than one third of these visits are by women of age over 25 years. Adult female acne (AFA) is defined as the onset of acne in females over the age of 25 years. Ketoconazole (KTZ) cream has been shown to be effective for the treatment of AFA. KTZ is a broad spectrum azole antifungal, which was originally approved in 1981 for the treatment of systemic fungal infections. It has also been shown to have anti-inflammatory and anti-androgenic activity. It has been shown to be ffective against Cutibacterium acnes; it is also effective against resistant isolates.

Keywords: Ketoconazole, Acne, KTZ.

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Introduction:

Ketoconazole is a broad spectrum azole antifungal, which was originally approved in 1981 for the treatment of systemic fungal infections. It has also been shown to have anti-inflammatory and anti-androgenic activity. It has been shown to be effective against *Cutibacterium acnes*; it is also effective against resistant isolates **(1).**

Structure

Ketoconazole is cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl] piperazine and has the following structural formula: **(fig. 1)(2) .**

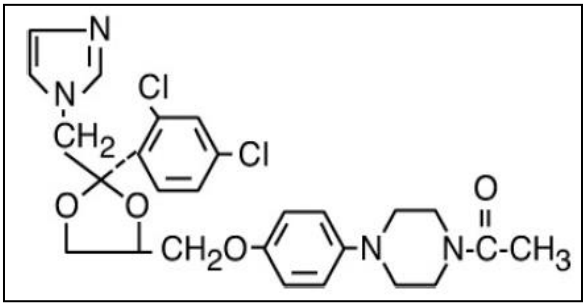

Fig. (1): Ketoconazole Structure **(2)**

Mechanism of Action

Ketoconazole works as an antifungal agent by inhibiting the cytochrome P450 14α-demethylase enzyme. This enzyme is responsible for inhibiting the biosynthesis of triglycerides and phospholipids by fungi. More specifically, ketoconazole

inhibits the synthesis of lanosterol, a necessary precursor for ergosterol biosynthesis. Ergosterol is needed to maintain the integrity of the membrane of fungi **(3).**

Ketoconazole, in high doses, can competitively bind to androgen receptors, such as that of testosterone and dihydrotestosterone, which can decrease the activity of testosterone and dihydrotestosterone. Ketoconazole can also inhibit the enzymes 17-alpha-hydroxylase and 17,20-lyase, which are necessary for the synthesis of steroids in the adrenal cortex, including testosterone **(4).**

Ketoconazole inhibits the activity of the enzyme 21-hydroxylase. This enzyme is essential for synthesizing mineralocorticoids and glucocorticoids, such as cortisol, in the adrenal cortex **(4).**

Pharmacology

Ketoconazole is available in tablet form and as a topical agent in creams, foams, and shampoos. It is also available in mixture products. The oral form of ketoconazole is used for systemic administration and must be taken at least two hours before any antacids **(4)**.

The high pH of the gastric contents would decrease absorption, so appropriate timing of administration is paramount to its absorption and subsequent efficacy. Adult and pediatric patients with achlorhydria should be given ketoconazole tablets with an acidic beverage to decrease pH and allow for optimal absorption **(5).**

Clinical significance

Ketoconazole is a broad-spectrum antifungal agent that exhibits a wide spectrum of activity against dermatophytes, C. albicans, and M. furfur in vitro.

In clinical trials, ketoconazole 2% cream has demonstrated efficacy in the treatment of tinea pedis, tinea cruris, and tinea corporis. Lester, (1995) reported that 82% of patients with tinea pedis, tinea cruris, or tinea corporis had an excellent response to 4 weeks of therapy with once-daily applications of topical ketoconazole. Ketoconazole cream is also effective in the treatment of cutaneous candidiasis and pityriasis versicolor **(6).**

Ketoconazole cream, 2% shampoo, and 2% foam have also been shown to be effective in the treatment of seborrheic dermatitis, owing to the role M. furfur in causation **(7).**

In one study, 78.9% of patients with infantile seborrheic dermatitis achieved a good to excellent response after 10 days of ketoconazole application. Comparable success can be expected in adults. A 1% shampoo formulation is approved for over-the-counter use in the ongoing management of seborrheic dermatitis **(8).**

Ketoconazole in Acne vulgaris

Together with antifungal properties and anti-inflammatory effects, other possible mechanisms of KTZ in acne treatment may be through its antilipase activity and antiandrogenic effect. Lipase is one of the pivotal enzymes and virulence factors of *C. acnes* to stimulate inflammation and follicular hyperkeratosis **(9).**

KTZ inhibits the lipase activity in both antibiotic-susceptible and -resistant *C. acnes*, resulting in a decreased free-fatty acid component in sebum and suppression of comedo formation **(10)**.

Also, systemic KTZ can suppress androgen production through inhibition of cytochrome P450-dependent enzymes in the testes, ovaries and adrenal glands. It is conceivable that topical KTZ may possess a similar effect on the steroidogenesis function of the pilosebaceous units **(11).**

At the same time, KTZ could also affect lipase activity of Malassezia spp., which has a higher lipase activity than C. acnes. Some authors believed that Malassezia spp. is related to refractory acne and other concurrent inflammatory facial dermatoses such as seborrheic dermatosis **(9).**

As KTZ treatment markedly improved acne lesions and is one of the most effective treatments in seborrheic dermatosis, one could propose an additional benefit of treating two commonly found skin disorders by employing this monotherapy **(12)**.

Topical antibiotics should be used in a limited setting and for a restricted duration. Since the increase in antibiotic resistance became a major public concern, many acne treatment guidelines have encouraged the stewardship of antibiotic use **(13).** Thus, using KTZ with an effect on AV comparable with topical clindamycin but causing no risk of antibiotic resistance should be encouraged in the current practice **(9).**

Anwar et al. (1) demonstrated significant improvement in reduction of acne lesions as well as complete recovery using 2.0% ketoconazole for the treatment of mild adult female acne. So KTZ can be used as a preferred treatment option for these patients **(1).**

Contraindications of systemic Ketoconazole

Ketoconazole is contraindicated in patients with acute or chronic liver disease due to its association with hepatotoxicity, which can be fatal. It is contraindicated in adrenal insufficiency because high doses of ketoconazole inhibit adrenocortical function **(4).**

Ketoconazole should not be given to patients with a known hypersensitivity reaction to ketoconazole **(12)**. Ketoconazole should never be co-administered with 3-hydroxy-3-methylglutaryl coenzyme A-reductase inhibitors because it can increase the risk of myopathy **(14).**

Ketoconazole is contraindicated in patients taking benzodiazepines because it can increase plasma concentrations and lead to sedation. Ketoconazole should never be administered to patients on antiarrhythmic drugs, cisapride, pimozide, quinidine, and ranolazine because it can cause QT prolongation and torsade de pointes **(15).**

In patients with increased bone fragility, such as post-menopausal women and the elderly, ketoconazole should be used with caution to avoid the risk of fracture. The CYP3A4 liver enzyme metabolizes ketoconazole, and use requires caution in patients taking drugs that inhibit CYP3A4 or are metabolized by CYP3A4. Ketoconazole can also be present in breast milk, so breastfeeding is not recommended when using the drug **(16).**

Adverse Effects of topical ketoconazole

In clinical trials during which 905 patients were treated with ketoconazole 2% cream, 5% of the patients reported AE including irritation, pruritus, and stinging. One of these patients developed allergic reaction at the site of application **(8).**

In worldwide post marketing experience, rare reports of contact dermatitis have been associated with ketoconazole cream or one of its ingredients, namely sodium sulfite or propylene glycol **(17).**

References:

1. Anwar, A., & Hassan, S. K. U. (2020). Two Percentage of Ketoconazole Cream for the Treatment of Adult Female Acne: A Placebo-Controlled Trial. Cureus, 12(11).
2. Gagini, T., Col RC ina-Vegas, L., Villarreal, W., Borba-Santos, L. P., de Souza Pereira, C., Batista, A. A., Fleury, M. K., de Souza, W., Rozental, S., & Costa, L. A. S. (2018). Metal–azole fungistatic drug complexes as anti-Sporothrix spp. Agents. New Journal of Chemistry, 42(16), 13641–13650.
3. Díaz-Tome, V., Ares, M. T.-R., Varela-Fernández, R., Touriño-Peralba, R., González-Barcia, M., Martínez-Pérez, L., Lamas, M. J., Otero-Espinar, F. J., & Fernández-Ferreiro, A. (2019). Therapeutic Approach in Fungal Keratitis. In Mycotic Keratitis (pp. 189–216). CRC Press.
4. Sinawe, H., & Casadesus, D. (2021). Ketoconazole. StatPearls [Internet], 1.
5. Vinarov, Z., Abrahamsson, B., Artursson, P., Batchelor, H., Berben, P., Bernkop-Schnürch, A., Butler, J., Ceulemans, J., Davies, N., Dupont, D., Flaten, G. E., Fotaki, N., Griffin, B. T., Jannin, V., Keemink, J., Kesisoglou, F., Koziolek, M., Kuentz, M., Mackie, A., … Augustijns, P. (2021). Current challenges and future perspectives in oral absorption research: An opinion of the UNGAP network. Advanced Drug Delivery Reviews, 171, 289–331.
6. Sonthalia, S., Agrawal, M., & Sehgal, V. N. (2019). Topical ciclopirox olamine 1%: revisiting a unique antifungal. Indian Dermatology Online Journal, 10(4), 481.
7. Thomas, L. M., & Khasraghi, A. H. (2020). Topical treatment of seborrhoeic dermatitis and dandruff: An overview. Annals of Tropical Medicine and Public Health, 23(18).
8. Wolverton, S. E., & Wu, J. J. (2019). Topical Drugs for infectious diseases. In Comprehensive Dermatologic Drug Therapy (pp. 476–492).
9. Chottawornsak, N., Chongpison, Y., Asawanonda, P., & Kumtornrut, C. (2019). Topical 2% ketoconazole cream monotherapy significantly improves adult female acne: A double-blind, randomized placebo-controlled trial. The Journal of Dermatology, 46(12), 1184-1189.
10. Unno, M., Cho, O., & Sugita, T. (2017). Inhibition of Propionibacterium acnes lipase activity by the antifungal agent ketoconazole. Microbiology and Immunology, 61(1), 42–44.

11. Ceruti, J. M., Leirós, G. J., & Balañá, M. E. (2018). Androgens and androgen receptor action in skin and hair follicles. Molecular and Cellular Endocrinology, 465, 122–133.
12. Gupta, A. K., & Versteeg, S. G. (2017). Topical Treatment of Facial Seborrheic Dermatitis: A Systematic Review. American Journal of Clinical Dermatology, 18(2), 193–213.
13. Hayashi, N., Akamatsu, H., Iwatsuki, K., Shimada-Omori, R., Kaminaka, C., Kurokawa, I., Kono, T., Kobayashi, M., Tanioka, M., Furukawa, F., Furumura, M., Yamasaki, O., Yamasaki, K., Yamamoto, Y., Miyachi, Y., & Kawashima, M. (2018). Japanese Dermatological Association Guidelines: Guidelines for the treatment of acne vulgaris 2017. Journal of Dermatology, 45(8), 898–935.
14. Vinci, P., Panizon, E., Tosoni, L. M., Cerrato, C., Pellicori, F., Mearelli, F., Biasinutto, C., Fiotti, N., Di Girolamo, F. G., & Biolo, G. (2021). Statin-Associated Myopathy: Emphasis on Mechanisms and Targeted Therapy. International Journal of Molecular Sciences, 22(21).
15. Page, R. L., O'Bryant, C. L., Cheng, D., Dow, T. J., Ky, B., Stein, C. M., Spencer, A. P., Trupp, R. J., & Lindenfeld, J. (2016). Drugs that may cause or exacerbate heart failure: a scientific statement from the American Heart Association. Circulation, 134(6), e32–e69.
16. Wakefield, D., McCluskey, P., Wildner, G., Thurau, S., Carr, G., Chee, S.-P., Forrester, J., Dick, A., Hudson, B., & Lightman, S. (2017). Inflammatory eye disease: pre-treatment assessment of patients prior to commencing immunosuppressive and biologic therapy: recommendations from an expert committee. Autoimmunity Reviews, 16(3), 213–222.
17. Aerts, O., & Goossens, A. (2021). Contact allergy to preservatives. Contact Dermatitis, 835-876.