REVIEW ARTICLE

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EBERCONAZOLE – AN ANTI-FUNGAL MOLECULE REVISITED

Dermatology

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KEYWORDS

INTRODUCTION

Man, in his environment is frequently and commonly bombarded with many infective agents including ubiquitous fungi. Little wonder that an estimated 20 to 25 % of the global population is affected with fungal infections [1]. The increased prevalence of dermatophyte infections in the tropics is governed by cultural, socioeconomic and climatic factors[2].

Dermatophytoses are fungal infections of keratin in the skin and nails. Dermatophytes are molds that require keratin for nutrition and must live on stratum corneum, hair, or nails to survive [3].

Human infections are caused by *Epidermophyton, Microsporum,* and *Trichophyton* spp. These infections differ from candidiasis in that they are rarely if ever invasive. Transmission is person-to-person, animal-to-person, and, rarely, soil-to-person. The organism may persist indefinitely. Most people do not develop clinical infection; those who do may have impaired T-cell responses from an alteration in local defenses (e.g., from trauma with vascular compromise) or from primary (hereditary) or secondary (e.g., diabetes, HIV) immunosuppression.

Topical antifungal agents are helpful in the treatment of dermatophytoses since the infection is often limited to the superficial layers of skin. However, selecting a suitable antifungal agent is difficult as the market is flooded with many products. Besides, difficulties in diagnosis, deviation from classical clinical presentation, emergence of drug resistance, poor compliance and increase in immuno-suppressed conditions add to the challenge and complexity of treatment. The cure rate is high, but relapses and exacerbations are common.

Topical preparations with good local bioavailability are the most commonly used and preferred first line agents in the treatment of localized dermatophytoses. Patient compliance resulting in good therapeutic response is enhanced by shortened treatment period, fewer side effects, minimization of recurrence, and ease of application.

Eberconazole

Eberconazole, a newer antimycotic agent is an imidazole derivative and is a broad-spectrum antifungal agent. In vitro studies have shown that eberconazole has broad antimicrobial spectrum of activity, to be effective in dermatophytosis, candidiasis, infection and diseases caused by other yeasts such as *Malassezia furfur,* the causative agent of pityriasis versicolor. Its effectiveness against most triazole-resistant yeasts (*Candida krusei* and *Candida glabrata)* and also fluconazole resistant *Candida albicans* has been demonstrated *in vitro.* It has also been shown to be effective against Gram-positive bacteria [4].

Eberconazole is diverse from other imidazoles as it has been to shown to have anti-inflammatory activity, which favors its use in the management of inflamed dermatophyte infections. The anti-inflammatory activity is comparable to acetyl salicylic acid and ketoprofen [4], and is attributable to the inhibition of 5-lipooxygenase and to a lesser extent of cyclooxygenase-2.

Spectrum of activity

Eberconazole is distinct from other imidazoles Eberconazole has been shown to have broad antimicrobial spectrum of activity *in vitro,* to be effective in dermatophytosis, candidiasis, and infection by other yeasts such as *Malassezia furfur* and causative agents of pityriasis versicolor in *vitro and* animal studies. Its effectiveness against most triazole-resistant yeasts (*Candida krusei* and *Candida glabrata)* and also fluconazole resistant *Candida albicans* has been demonstrated *in vitro.* It has also been shown to be effective against Gram-positive bacteria [59].

Mechanism of action

Eberconazole exerts fungicidal or fungistatic activity depending on concentration, being fungicidal at higher concentration and fungistatic at lower concentrations. Eberconazole prevents fungal growth by inhibiting ergosterol synthesis, an essential component of the fungal cytoplasmic membrane leading to structural and functional changes. It prevents the fungal ergosterol synthesis by inhibiting lanosterol 14-demethylase enzyme that is responsible for the formation of 14-methylsterols (precursor of ergosterols). Studies have shown that eberconazole binds to the phospholipid fraction of the cell and affects sterol synthesis intracellularly. At high concentrations, it causes the leakage of small molecules such as potassium ions [8,9].

Eberconazole exhibited the lowest minimal inhibitory concentration (MIC) for majority of the dermatophyte strains ($P<0.05$), when compared with the *in vitro* activity of clotrimazole, ketoconazole and miconazole against 200 strains of dermatophytes belonging to 19 species of fungi. This suggests an advantage of eberconazole over other widely used agents.

Efficacy and Safety

In vitro comparison of *activity* of eberconazole with that of clotrimazole, ketoconazole and miconazole against 200 strains of dermatophytes belonging to 19 species of fungi. Among the four drugs tested, eberconazole exhibited the lowest minimal inhibitory concentration (MIC) for majority of the dermatophyte strains ($P<0.05$), suggesting an advantage of eberconazole over other widely used agents.

Double blind, randomized control studies showed that the overall efficacy and safety of eberconazole cream in patients with cutaneous was slightly higher. However, eberconazole showed a significantly greater efficacy than clotrimazole in the treatment of dermatophytosis. Noteworthy is that in an Indian study, with a treatment duration of 4 weeks followed by another 4 weeks follow-up, confirmed the earlier findings that eberconazole 1% is significantly effective against cutaneous dermatomycoses. The therapeutic efficacy was 97.44% [8].

Eberconazole is clinically effective in the treatment of topical fungal infections, with a good safety profile and good tolerability. It has acceptable topical availability with no detectable systemic drug levels, and does not appear to cause skin sensitivity.

The most frequent adverse effect after the first application was coldness, and after repeated increasing-doses was itching. No signs or symptoms of skin reactivity were observed following re-exposure to the product [10,11].

Formulation advantage

Eberconazole has been marketed as a cream with a characteristic lipophilic-hydrophilic molecular structure for better penetration of fungal cell membrane and prolonged duration of action. The galenic components of this topical azole favor and optimize the drug's action in the skin, fatty acid esters facilitate penetration in the skin and make the cream easy to spread, while polyacrylamides produce a filmogenous effect and facilitate the continuance of the active principle in the skin.

More recently, a creamy lotion has been introduced to enhance spreadability [12].

CONCLUSION

The need for newer antifungals has been propelled by the complexities mentioned above in the treatment of dermatomycosis. Eberconazole with its efficacy and safety profile finds an important place amongst the commonly used antifungals, and scores above similar molecules, being patient-friendly and dermatologist-prescribed.

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