Azole Resistance in Dermatophytes: Prevalence and Mechanism of Action

Mahmoud Ghanouni, PhD, Case Western Reserve University, Cleveland, OH 44106

ABSTRACT

Background. Azole antifungal agents (e.g. fluconazole and ketoconazole) have been widely used to treat superficial fungal infections caused by dermatophytes, and, unlike the allylamines (such as terbinafine and naftifine), have been associated with resistance development. Although a considerable number of published manuscripts describe resistance to azoles among yeast and moulds, reports describing resistance of dermatophytes are starting to appear. Objective. In this review, we discuss the mode of actions of azole antifungals and mechanisms underlying their resistance as compared with the allylamine class of compounds. Methods. Data from published and original studies were compared, summarized, and their clinical implications discussed. Results. The incidence of azole resistance in dermatophytes is reported to be as high as 19% among the worldwide population. In contrast to the cidal allylamines, static drugs such as azoles inhibit the growth of the organism, permitting occurrence of mutations in enzymes involved in sterol biosynthesis, which serves as the drug target. Additionally, unlike allylamines, the ergosterol precursors accumulating as a consequence of azole action are not toxic. Conclusions. Azole antifungals, unlike allylamines, potentiate resistance development in dermatophytes.

MECHANISM OF ACTION

• There are two main classes of antifungal agents for the treatment of dermatophytosis, azoles and allylamines, along with griseofulvin, ciclopirox, and tolnaftate.

• With some exceptions, including griseofulvin and ciclopiroxolamine, antifungal agents commonly used to treat dermatophytoses target the ergosterol biosynthetic pathway. (See Fig. 1) Ergosterol is the major sterol component of the fungal plasma membrane and is essential for the proper functioning of several membrane-bound enzymes. [1]

• Imidazoles, and also in part the more recent triazoles fluconazole, itraconazole, voriconazole, and luliconazole, share a common mechanism of ergosterol depletion and accumulation of sterol precursors. The accumulation of these precursors, including 14a-methylated sterols (lanosterol, 4,14-dimethylzymosterol, and 24-methylated lanosterol) results in altered plasma membrane structure and function. [2]

• By contrast, the allylamines are potent inhibitors of squalene epoxidase, an enzyme involved in the biosynthesis of ergosterol (inhibition of sterol-Δ²⁴-reductase and sterol-Δ²⁴,Δ²⁸ isomerase). [3] This inhibition affects early steps in sterol synthesis and results in accumulation of squalene, which is toxic to the fungal cells. This cell toxicity accounts for the cidal activity of allylamines as compared to azoles, which are static agents.

INCIDENCE OF AZOLE RESISTANCE IN NON-DERMATOPHYTE FUNGAL STRAINS

• The increase in Candida-related bloodstream infections worldwide has been widely publicized, and though the great majority of Candida species remain susceptible to azoles, an emergence of azole-resistant C. glabrata strains from the SENTRY Antimicrobial Surveillance Program (fluconazole 7.7%, posaconazole 5.1%, and voriconazole 6.4% of C. glabrata strains tested) has been reported. [4]

• Similar azole resistance has been reported in recurrent vaginitis and oropharyngeal candidiasis. Taken together, these reports suggest that frequent exposure to azole drugs is a risk factor for the development of resistance.

• Similarly, an increase in the incidence of azole resistance in moulds, such as Aspergillus fumigatus, has recently been recognized. An alarming discovery from testing soil and other environmental samples showed cross-resistance to six widely used triazole fungicides and to voriconazole, posaconazole, and itraconazole, raising concerns that exposure to products will produce airborne A. fumigatus spores that are highly resistant to the medical triazoles. [5]

Fig. 1. Dermatophytosis. Ergosterol pathway and sites of action.

DRUG RESISTANCE IN DERMATOPHYTES

• While azole resistance in dermatophyte strains has been reported in the literature, resistance to allylamines has been published in only one report, which showed resistance development in one patient treated with terbinafine. [6] Increased drug efflux has been reported to be the resistance mechanism of azoles, including fluconazole, itraconazole, ketoconazole, and tioconazole.

• By contrast, modification of the target enzyme squalene epoxidase by gene mutation (substitution of a single amino acid in the squalene epoxidase gene) is considered to be the resistance mechanism in the allylamine terbinafine. These mutations lead to substitutions in amino acids, which are likely involved in the binding of terbinafine to squalene epoxidase. For example, single amino acid exchanges in the region of the protein Erg1 resulted in high terbinafine resistance in both filamentous fungi and yeast. [7]

CONCLUSION

• Widespread use of the limited numbers of antifungal agents, particularly the azoles, to treat systemic fungal infections has led to the development of drug resistance. Thus, drug resistance in pathogenic fungi, including the dermatophytes, is of increasing importance.

• However, it is clear that azoles have a high potential for inducing resistance in these pathogenic fungi. The prevalence of azole resistance in dermatophytes has been reported to be as high as 19% in certain areas worldwide.

• In contrast, the potential of allylamines (terbinafine or naftifine) to potentiate resistance is very low. The primary mode of action of allylamines is the inhibition of squalene epoxidase, leading to not only superficial fungal infections but also systemic disease. Importantly, azole resistance has been encountered in strains present in the environment, which may eventually cause human infections.

References.


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