The Role of Ketoconazole in Seborrheic Dermatitis

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Although the prominent broad-spectrum activity of ketoconazole was reported in the early 1980s, its effect against Malassezia *species was most pronounced; thus, it was developed for the treatment of various skin infections in which a link with these fungal species was proposed. Later, a number of ancillary properties were described for ketoconazole that comprised its anti-inflammatory, antiseborrheic, and antiproliferative profile. The incorporation of ketoconazole in an adapted vehicle could further promote its efficacy. Recently, a new formulation—an anhydrous gel containing ketoconazole 2%—was launched in which all of the ancillary properties were optimized.*

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Seborrheic dermatitis (SD)—or seborrheic eczema, as the disorder is often named in many European countries—is a common superficial inflammatory disease that evolves with periods of flares and remission. The typical distribution and clinical aspect of SD affect areas of the skin that are rich in sebaceous glands, particularly the scalp, face, nasolabial folds, eyebrows and postauricular regions, chest, and upper back. The lesions are sharply marginated, erythematous, pruritic papules covered with a greasy scale. Their color is pink to salmon-red rather than dark red.

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SD affects approximately 2% to 5% of the population worldwide. It is more common in adolescents and young men, but it also is seen in elderly patients, patients with neurologic conditions (eg, parkinsonism, syringomyelia, depression, endocrine disorders), and immunocompromised patients, such as those patients with AIDS.[1] Dandruff may be a symptom of psoriasis or fungal infections, but in most instances, it may be regarded as a mild form of SD. In some cases, the excessive flaking of dead skin, which is typical of dandruff, may be accompanied by redness and irritation, thus fulfilling the definition of SD.

Although SD has been encountered for many years, the etiology of the disorder is poorly understood. The disease is regarded as multifactorial, but several hypotheses have been formulated in the past centuries. In the 19th century, seborrhea was supposed to be, as the name indicates, the most important eliciting factor. Unna[2] coined the term *seborrheic dermatitis* in 1887 because of his hypothesis that the disorder was an eczematous condition; he gave little attention to the microorganisms present in the lesions, which he called *Flashen Bazillen (bacilles bouteilles)*. In 1904, Sabouraud[3] was the first to give attention to the microorganisms, which he recognized as yeasts and thus renamed them *Pityrosporum*. Sabouraud[3] initiated the infectious theory that is ongoing to date, though the name of the yeast has been changed several times.

The Infectious Hypothesis

Currently, yeasts of the genus *Pityrosporum* are classified as *Malassezia* in honor of the first description of fungi in the scales of dandruff by Malassez[4] in 1874. In the 1960s and 1970s, Kligman et al[5] opposed the fungal origin of SD and proposed a hyperproliferative cause because of the presence of an increased cell turnover in the epidermis.

After the genus *Pityrosporum* was proposed as the causative agent of dandruff and SD by Sabouraud[3]

in 1904, the evolution of its taxonomy and nomenclature became chaotic. In 1977, *Pityrosporum ovale* (oval form), *Pityrosporum orbiculare* (round form), and *Malassezia furfur* (mycelial form) were considered different configurations of the same organism. In addition, *Malassezia pachydermatis* was identified as a nonlipophilic yeast in animals. In 1990, Cunningham et al[6] identified 3 different serovars on the basis of different surface antigens. The current knowledge is derived from the 1995 work of Guillot and Guého[7] and based on the differences displayed after ribosomal RNA sequence and nuclear DNA comparisons.

Six of 7 identified species are lipophilic and are encountered in man (*Malassezia globosa*, *Malassezia restricta*, M *furfur*, *Malassezia sympodialis*, *Malassezia slooffiae*, *Malassezia obtusa*), whereas M *pachydermatis* is not lipophilic and is found mostly in animals. Sugita et al[8,9] described 2 new species: *Malassezia dermatis* in 2002, found in patients with atopic dermatitis, and *Malassezia yamatoensis* in 2004, found in patients with SD. In 2005, Cabanes et al[10] described *Malassezia equi* (tentative name), a lipophilic yeast mainly present in horses. *Malassezia nana*, as reported by Hirai et al[11] in 2004, also is a novel lipid-dependent yeast species isolated from animals. M *nana*, M *dermatis*, and M *equi* are genetically close to M *sympodialis*; it is not excluded that these yeasts evolved from M *sympodialis* because of specific animal hosts.[10]

Susceptibility of *Malassezia* Species to Ketoconazole

Ketoconazole was introduced in 1979 as the first orally active imidazole compound with activity against a wide spectrum of yeast, dimorphic fungi, and polymorphic fungi.[12] The drug was recognized for its prominent anti-*Candida*, antidermatophyte, and particularly anti-*Malassezia* properties. The promising clinical results of oral ketoconazole in SD were discovered by coincidence.[13] Because of the agent's possible interference with hepatic functions after oral intake, the efficacy of topical ketoconazole in SD was investigated. The preferential location of *Malassezia* species to the superficial skin layers caused several topical ketoconazole formulations to be successfully introduced.[14-17] It became clear that ancillary mechanisms unrelated to the drug's outstanding activity against *Malassezia* species play an important role in the relief of the SD symptoms.

The potency of ketoconazole to inhibit the growth of various new *Malassezia* species and strains has been reported in 2 publications,[18,19] which mostly confirm the initially reported comparative data with other azoles.[20] Hammer et al[18] showed the superiority of ketoconazole over econazole and miconazole nitrate

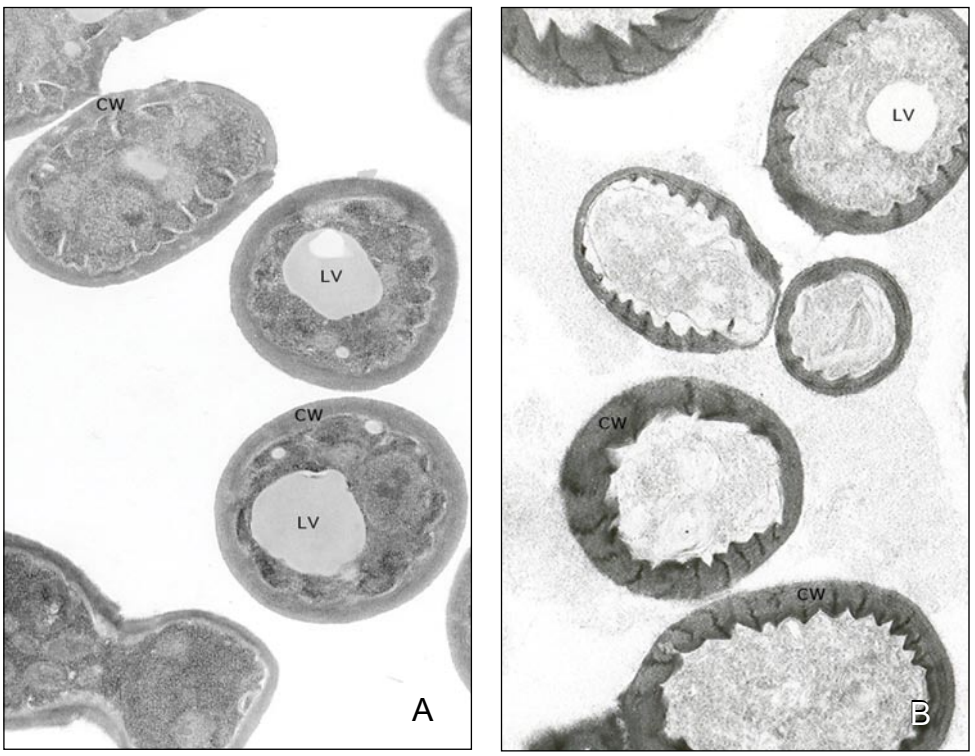

Figure 1. *Malassezia sympodialis* exposed to solvent (transmission electron microscopy, original magnification ×20,100)(A) and 0.1 μg/mL ketoconazole for 24 hours (transmission electron microscopy, original magnification ×24,000)(B). Note the induction of mummification after treatment (ie, the occurrence of cytoplasmic necrosis in the treated culture, even though the surrounding cell wall apparently remains comparable to the solvent exposed cells). CW indicates cell wall; LV, lipid vesicle.

(10−100 times more potent) on a large number of clinical isolates of *M furfur*, *M sympodialis*, *M slooffiae*, *M globosa*, and *M obtusa*. A study by Faergemann et al[19] comparing ketoconazole with pramiconazole, a triazole antifungal,[21] confirmed the potency of ketoconazole against 7 different *Malassezia* species (Figure 1). In the latter study, the obtained minimum inhibitory concentration values ranged from 0.002 to 0.1 μg/mL.[21] In addition, the Faergemann et al[19] study reported the potent inhibitory effects of ketoconazole on the production of hyphae in *M sympodialis* from 0.01 μg/mL onward. To our knowledge, there are no reports in the literature of resistance to *Malassezia* species with ketoconazole.

Although less pronounced than with miconazole nitrate, bacteriostatic effects of ketoconazole against Gram-positive bacteria such as *Staphylococcus aureus* have been reported.[12] The in vitro data were confirmed in vivo after topical application of ketoconazole to skin lesions induced by *S aureus*.[22]

In recent years, there has been a resurgence of interest in *Malassezia* species, not as an infective agent but as a source of inflammatory or immunologic reactions. However, no unambiguous proof has been found regarding the direct relation between *Malassezia* and immunologic (humoral, cellular) abnormalities; only proinflammatory reactions have been reported.[23]

Ancillary Properties of Ketoconazole

Anti-inflammatory Profile—Yeasts of the genus *Malassezia* could exert proinflammatory reactions through production of inflammatory mediators or changes in lipase activity.[24] Lipases or other toxic substances are known to induce complement activation via alternative pathways, which may result in an inflammatory response.[22] However, an important argument against infectious yeast involvement in mediating inflammation is that seborrheic symptoms equally can be induced by killed yeasts.[25] The anti-inflammatory effect of ketoconazole has been proposed in several clinical studies, including studies involving SD.[17,26] The effect of ketoconazole has been attributed to the inhibition of 5-lipoxygenase activity bearing on the production of leukotrienes derived from arachidonic acid.[27] However, it cannot be excluded that the resolution of inflammatory signs are seen subsequent to barrier restoring effects or antimicrobial effects.[22]

Antiseborrheic Profile—Sebum hypersecretion is one of the hallmarks in most cases of SD. It repeatedly has been reported that both oral and topical ketoconazole lower the sebum content of seborrheic skin.[28,29] Recent investigations[30] have supported this observation and showed that cultured human keratinocytes that are exposed to nonlethal concentrations of ketoconazole accumulate lipids, which suggests interference with the normal flow of cellular lipids (Figure 2). Thus, there appears to be a high therapeutic index for ketoconazole (ie, the drug is toxic for human fibroblasts at 100 μg/mL only, whereas its killing effect against *Malassezia* species is already present from 0.01 μg/mL onward).[31]

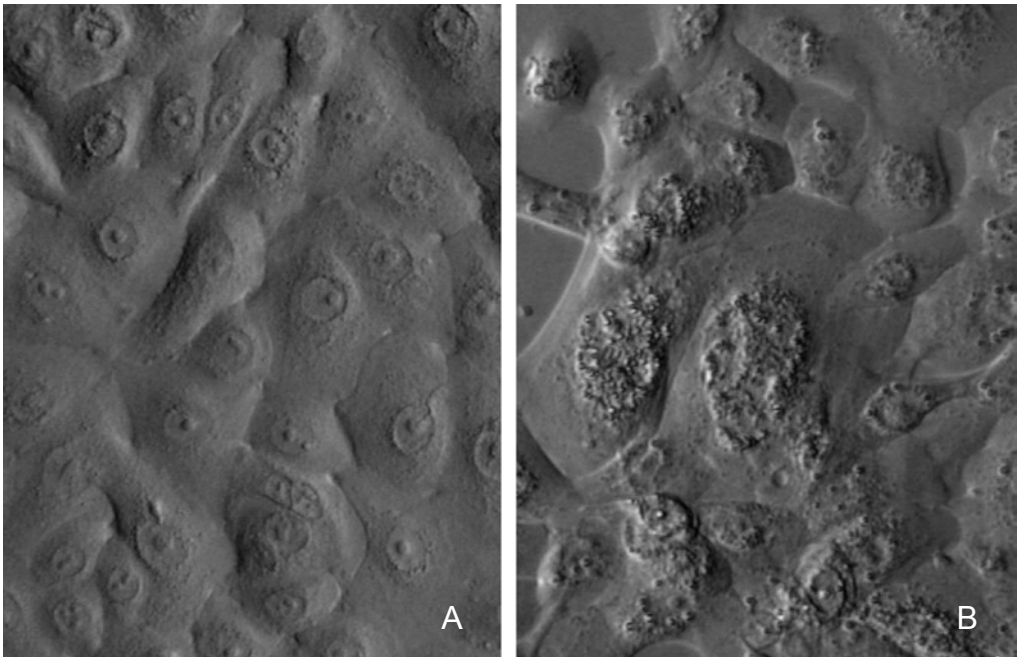

Figure 2. Human keratinocytes exposed to solvent (A) and 50 μg/mL ketoconazole for 96 hours (B). Ketoconazole-induced lipid vacuoles are accumulated in the cytoplasm (phase-contrast microscopy, original magnifications ×960).

Antiproliferative Profile—Ketoconazole appears to have a potent antiproliferative effect in human keratinocyte cultures, which is an activity that is more pronounced than its effect on keratinocyte differentiation.[32] Moreover, recently obtained data[30] indicate that there is a great difference between the ability of ketoconazole to inhibit human keratinocyte growth ($<10^{-7}$ mol/L) and induce proper keratinocyte toxicity ($>10^{-4}$ mol/L).

The observed antiproliferative effect of ketoconazole cannot be attributed solely to its interference with retinoic acid metabolism because more potent retinoic acid–interfering drugs display less antiproliferative activity.[32]

The inhibition of the cholesterol biosynthesis of ketoconazole has been proposed to contribute to the normalization of the hyperkeratotic state.[22]

Ketoconazole in a New Anhydrous Gel Formulation

There are a number of topical formulations, including creams, shampoos, and powders, that contain different concentrations of ketoconazole.[14-17] The search to optimize the ancillary properties of ketoconazole to treat SD led to the development and recent introduction of a ketoconazole 2% formulation in an anhydrous gel.[33] Some physicochemical properties of the gel, such as the presence of ethanol, enable the drug to be better solubilized than the former greasy cream formulation, which may foster better penetration into the superficial skin layers and sebaceous glands, and, importantly, may enable high local drug concentrations to be reached. Moreover, ethanol may solubilize part of the excessive lipids present in the skin of patients with SD, thus limiting one of the possible etiologic factors of the disease.

In contrast to the ketoconazole cream formulations, ketoconazole gel 2% does not contain sulfites; thus, the adverse irritative and sensitizing potential is alleviated.[34] This effect may be relevant to explain the limited reporting of irritative side effects in clinical trials.[33,35]

In a confirmatory double-blind, vehicle-controlled, 2-arm, phase 3 trial, 459 subjects at 24 centers across the United States were enrolled.[35] Ketoconazole gel 2% applied once daily for 2 weeks achieved statistical significance at the primary end point compared with vehicle-treated subjects ($P=.001$). Earlier studies in more than 900 subjects in the European Union and United States were 4-arm phase 3 studies (ketoconazole gel 2%; vehicle; ketoconazole gel 2% plus desonide 0.05%; vehicle plus desonide 0.05%). All 3 active drug groups achieved the primary efficacy end point, meaning that clinical signs and symptoms were cleared or almost cleared at day 30 (ie, after 2 weeks of once-daily treatment).[35]

Comment

Some newly identified properties of ketoconazole—ancillary to its well-known antifungal profile and especially its outstanding activity against *Malassezia* species—in conjunction with an optimized formulation make the ketoconazole anhydrous gel a preferred alternative to the existing topical products to treat SD. Moreover, the broad range of pharmacologic effects of ketoconazole, concurrent to its antifungal profile, make it worthwhile to consider clinical investigations in other indications (eg, *Malassezia folliculitis* because of the antifungal, anti-inflammatory, antilipidic, and antiproliferative properties; acne because of the antiproliferative, antiseborrheic, and anti–Gram-positive bacterial effects; rosacea because of the anti-inflammatory and antiproliferative properties; certain types of atopic dermatitis because of the antifungal, anti-inflammatory, and anti–Gram-positive bacterial effects).

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