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Topical Antifungals used for Treatment of Seborrheic Dermatitis

Abstract

Seborrheic dermatitis is a common inflammatory condition mainly affecting scalp, face and other seborrheic sites, characterized by a chronic relapsing course. The mainstay of treatment includes topical therapy comprising antifungals (ketoconazole, ciclopirox olamine) and anti-inflammatory agents along with providing symptomatic relief from itching. Oral antifungals and retinoids are indicated only in the severe, recalcitrant cases. The objective of this review is to discuss various topical antifungals available for use in seborrheic dermatitis of scalp, face and flexural areas, discuss their efficacy and safety profiles from relevant studies available in the literature along with upcoming novel delivery methods to enhance the efficacy of these drugs.

Keywords: Seborrheic dermatitis; Antifungal agents; Ketoconazole; Ciclopirox

Review Article

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Introduction

Seborrheic dermatitis (SD) is a common, chronic inflammatory disease that affects around 1-3% of the general population in many countries including the U.S., 3-5% of patients consisting of young adults. The incidence of the disease has two peaks: one in newborn infants up to three months of age, and the other in adults of around 30-60 years of age [1].

It is a multifactorial disease that requires several predisposing factors for its progress. Presence of these factors leads to reproduction of opportunistic yeast *Malassezia spp* [2]. The fungus uses lipids from the skin surface to produce unsaturated and saturated fatty acids which, when left in the individual's skin milieu, induce an inflammatory response. The sebum in the skin aids the growth of *P. ovale* (i.e. *Malassezia*) and hence the development of SD. The fact that SD responds to treatment with antifungal medication represents concrete evidence of the association between *Malassezia* and SD [1]. Even if the yeast is not critical to the disease pathogenesis, it is at least an exacerbating factor [3].

Dandruff and SD are considered the same basic condition differing only in magnitude [4]. The development of effective drugs for treating dandruff/SD requires appropriate outcome assessment measures like presence and level of skin flakes for the quantitation of the condition of the scalp and assessment of therapeutic resolution [5]. Other such outcome assessment measures employed by various studies establishing the efficacy of a drug in SD mainly include total clearance of lesions at the end of treatment phase/maintenance phase, mean change in symptom scores, i.e. erythema score, scaling score & pruritus score and patient assessment methods (usually visual analogue score method) [6].

Treatment of SD most commonly involves the use of shampoos containing anti-fungal materials to control the *Malassezia* population, thereby reducing the release of proinflammatory materials. Shampoo matrices are complex delivery vehicles for an active material (antifungal agent), which must be retained on the scalp after rinsing to be effective [7]. There are various antifungals available in the market and the authors have attempted to review the efficacy and safety profile of these agents for SD involving scalp, face and flexural areas.

Discussion

Treatment considerations

Treatment for SD should aim for not just achieving remission of lesions but also to eliminate itching and burning sensation and prevent recurrence of the disease [6]. A variety of treatment options are available for the treatment of SD. Antifungal and topical corticosteroids are the first line agents [8]. There have been reports of successful use of tacrolimus as well [9]. Behavioral modifications such as frequent skin cleansing, resolute commitment to personal hygiene and frequent outdoor recreation, especially in summer, have been found to lessen the symptoms [6]. Other therapeutic modalities include salicylic acid, zinc pyrithione and coal tar, which are applied topically and function to soften and remove the thick hardened crusts that sometimes occur in SD. Oral therapies like antifungals and retinoids or physical therapies like PUVA may be beneficial when multiple anatomic sites are involved, for patients who are unresponsive to traditional topical therapies and/or for those with severe SD [6,8]. In this article, the authors have focused on topical antifungal agents with published reports of efficacy in SD, which are available in various formulations such as ointments, creams, gels and shampoos in the market.

Topical antifungals available for SD

Table 1 lists various antifungals available for use in SD and Figure 1 explains the mechanism of action of azole and allylamine groups of antifungals. These are further described in detail as follows.

Table 1: Topical antifungals available for Seborrheic Dermatitis.

Class	Antifungal Agent	Formulations Available	Mode of Application	Mechanism of Action
Azoles	Ketoconazole	2% Shampoo, 2% Cream	Shampoo: 1-3 times per week for 4-8 weeks. Cream: Twice a day	Inhibition of fungal lanosterol 14-α demethylase enzyme resulting in depletion of ergosterol and accumulation of toxic sterols in fungal cell membrane
	Fluconazole	2% Shampoo, 0.5% Gel	Shampoo: 2-3 times per week for 4 weeks Gel: 1-2 times daily	
	Clotrimazole	1% Cream, Lotion	Twice daily	
	Sertaconazole	2% Cream, Lotion	Twice daily	
	Miconazole	2% Cream, Gel	Twice daily	
	Oxiconazole	1% Cream, Lotion	Once daily	
	Bifonazole	1% Cream, Shampoo	Once daily	
	Flutrimazole	1% Shampoo, 1% Gel	Shampoo: 1-2 times per week for 4 weeks Gel: Once daily	
	Climbazole	1% lotion, 0.5% Shampoo	Lotion: Overnight application Shampoo: 2 times per week for 4 weeks	
Hydroxypyridone	Ciclopirox olamine	0.77% Gel, 0.77% Cream, 1% Shampoo	Shampoo: 1-3 times per week for 4 weeks; for prophylaxis once weekly Cream: Twice daily	Inhibition of essential enzymes by creating a large polyvalent cation through chelation, thus interfering with mitochondrial electron transport processes and energy production.
Allylamine	Terbinafine	1% Cream	Once daily	Interfere with synthesis of ergosterol by inhibiting
Benzylamine	Butenafine	1% Cream	Twice daily	squalene 2,3-epoxidase that is responsible for converting squalene to squalene oxide

Ketoconazole: Ketoconazole is an imidazole derivative first approved by the FDA in 1981. It is available in 1% and 2% shampoo and cream formulations [10]. In 2007, ketoconazole foam, 2%, was approved in the United States for the topical treatment of SD when used twice daily for 4 weeks in patients 12 years and older [11]. There are reports of better efficacy of 2% formulations as compared to the ones with 1% ketoconazole [12]. Absorption of ketoconazole through the skin is insignificant, with no ketoconazole detected in plasma after topical application of ketoconazole cream or shampooing. Approximately 5% of the drug is found to penetrate into the hair keratin 12 hours after a single shampoo. It is classified as a pregnancy category C drug [10]. Various studies conducted on ketoconazole have used it in varying doses. The most frequent dose was 2% twice daily every day over face and 2% twice a week over scalp [6].

Other formulations of this drug have also yielded similar efficacy as the cream formulation. Elewski et al. [13] evaluated the efficacy and safety of twice-daily treatment with ketoconazole 2% foam for seborrheic dermatitis on the scalp, body, and face on 1162 patients and concluded that it was as effective as twice daily use of ketoconazole 2% cream. Another study evaluated the efficacy and safety of a once-daily, ketoconazole 2% gel treatment in moderate to severe seborrheic dermatitis in 459 patients and observed that a significantly greater percentage of subjects were successfully treated with this gel compared with vehicle (25.3% vs. 13.9%, P = 0.0014) [14].

The Cochrane Skin Group recently conducted a meta-analysis for studies published so far on the use of topical antifungals for SD and they concluded that as compared to placebo group, participants taking ketoconazole were 31% less likely to have symptoms persisting at four weeks of follow-up. It was usually well tolerated but common side effects included increased skin redness or itching, burning sensation and hair loss [6]. The US FDA in 2013 has issued a safety guideline stating that angioedema can be caused by ketoconazole 2% shampoo [15].

Ortonne et al. [16] in a single-blinded study observed 62 patients with SD over scalp, face and chest who were treated topically with a 2% ketoconazole foaming gel or with a 0.05% betamethasone dipropionate lotion for 4 months. At the end of

treatment, the response rate for ketoconazole 2% foaming gel was significantly higher than that for betamethasone dipropionate 0.05% lotion according to the global evaluation by the physician (89 vs. 62%, P <0.05) and the patient (89 vs. 65%, P <0.05). There was also a significant reduction of the count of P. ovale organisms on the scalp in the ketoconazole group (P <0.001) compared to the betamethasone group, in which the count was not much affected during therapy. The treatment was also better tolerated in the ketoconazole group (5 vs. 16 patients with side-effects, P <0.001). The authors thus concluded that ketoconazole 2% foaming gel offers an excellent alternative to topical corticosteroids in the treatment of SD [16]. In another study, the efficacy of 2% ketoconazole cream was compared with 1% hydrocortisone cream in the treatment of infantile SD in paediatric population of age two months to two years. The authors concluded that efficacy of both the drugs in the treatment of infantile SD was not significantly different and they recommended that ketoconazole provides another option for the treatment of infantile SD, so as to avoid the side effects of topical corticosteroids especially when applied over large surface area and/or following long-term use [17].

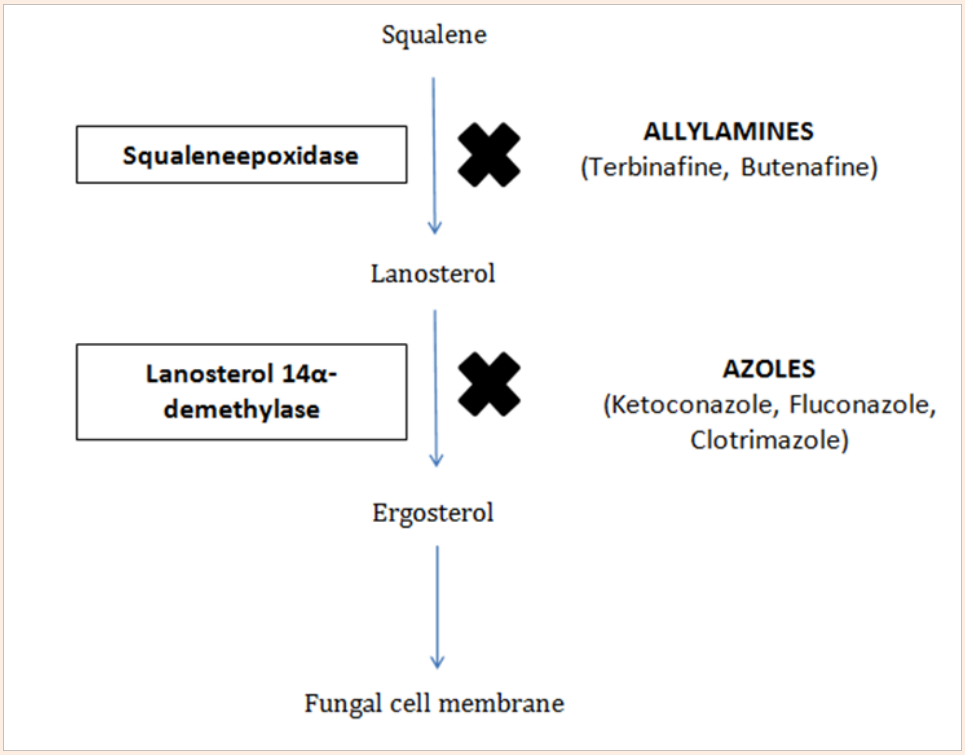

Figure 1: Flowchart depicting the mechanism of action of azole and allylamine groups of antifungals.

Clotrimazole: Clotrimazole is a broad spectrum antifungal agent of the imidazole family. Topical clotrimazole is classified as a pregnancy category B drug. In general, it is well tolerated by most patients. Occasionally, patients may experience irritation with a burning sensation at the site of application. Allergic contact dermatitis with erythema, edema, urticaria, and pruritus has been reported rarely [10]. However there is a paucity of studies in the literature on use of this drug in SD.

Sertaconazole: Sertaconazole is also a broad spectrum antifungal agent of the imidazole family. It is available in cream, lotion and shampoo formulations. Topical sertaconazole is classified as a pregnancy category C drug [18]. It is also well tolerated when applied topically with occasional local site irritation/burning sensation. The unique benzothiophene ring in the chemical structure offers higher lipophilicity and greater retention of drug in the stratum corneum) for up to 48 hours, leads to greater mycological cure rates and lesser chance of relapse [19]. Treatment with sertaconazole also results in the induction of cyclooxygenase-2 (COX-2) and the subsequent release of prostaglandin E2 (PGE2), thereby providing anti-inflammatory therapeutic benefits [20]. It is usually well tolerated, however rarely few side effects like pruritus, contact dermatitis, burning sensation, application site erythema have been noted [18].

A study was undertaken to compare efficacy of sertaconazole 2% cream vs. clotrimazole 1% cream for the treatment of SD of face. One hundred twenty eight patients were advised to use these creams twice daily for four weeks. The measured outcome patient satisfaction rates were higher in the sertaconazole group [21]. Another study showed that topical sertaconazole is equally effective at clearing SD as tacrolimus 0.03% topical preparation

[22]. A study conducted by Lotti et al. [23] in 132 patients of SD, the group of patients receiving sertaconazole 2% cream showed improvement comparable with the group receiving ketoconazole 2% cream [23].

Miconazole: Miconazole is available in 2% cream, 2% gel and shampoo formulations. It is a pregnancy category B drug. It has good penetration in stratum corneum following topical application to skin [10]. A randomized, double-blind, comparative, parallel group, multicenter study conducted in Switzerland showed that miconazole shampoo, when used twice a week is at least as effective and safe as ketoconazole shampoo in treating scalp SD [24].

Another randomized, double-blind, comparative, parallel group, multicenter study was carried out on 274 patients (145 miconazole, 129 ketoconazole). Treatment was twice-weekly for 4 weeks. Assessments included symptoms of erythema, itching, scaling ['Symptom Scale of Seborrhoeic Dermatitis' (SSSD)], disease severity and global change [Clinical Global Impressions (CGIs) and Patient Global Impressions (PGIs)]. They concluded that miconazole is at least as effective and safe as ketoconazole in treating scalp SD [24].

Bifonazole: Bifonazole is a substituted imidazole antifungal agent which possesses a broad spectrum of activity *in vitro* against dermatophytes, moulds, yeasts, dimorphic fungi and some Gram-positive bacteria. It is available in 1% cream and shampoo preparations. Compared with the majority of topical antifungal drugs, which need to be applied at least twice daily, bifonazole offers the convenience of once daily administration, which may improve patient compliance [25].

In a randomized study conducted by Zienicke et al. [26] 100 patients were enrolled and treated with either bifonazole 1% cream or the corresponding vehicle once daily for 4 weeks. All patients were also evaluated after 6 weeks of follow-up. Clinical evaluation was based on the following parameters: erythema, papules, infiltration, scaling, itch. In addition, mycological evaluation was performed using adequate contact plates for quantitative determination of *Malassezia* furfur. There was a statistically significant improvement in all these parameters in the patient group that applied bifonazole.26 In another study conducted over twenty-five patients with SD localised to the face, bifonazole cream was applied once daily and 21 (84%) patients were free of lesions at the end of four weeks. It has also been reported to have an anti-inflammatory action [27].

Climbazole: Pople et al. [28] observed that climbazole application to scalp results in an upregulation in expression of a number of genes including those encoding proteins involved in cornified envelope formation and further studies demonstrated that this does translate into increased protein expression. This climbazole-driven increase in cornified envelope proteins may improve the scalp skin barrier, which is known to be weaker in dandruff/SD. These studies suggest climbazole, besides its antifungal activity, is delivering positive skin benefits helping to relieve dandruff symptoms effectively [28]. A double-blind, comparative, prospective, longitudinal study was conducted on 60 patients of scalp SD for six weeks. Patients were assigned randomly to one of two treatment groups- 1% ketoconazole shampoo and 1% climbazole shampoo for once daily application. After six weeks, it was found that both drugs were effective in treating symptoms such as itching, peeling, dry or oily skin, but 1% ketoconazole shampoo showed superior efficacy, with a statistically significant difference in all symptoms. Eighty percent of patients in the ketoconazole group and 13 percent of the climbazole group were observed to achieve clinical cure at end of treatment ($p = 0.0001$) [29].

Fluconazole: Fluconazole, a member of the triazole antifungal family, was approved by the FDA for oral use in the early 1990s [10]. After oral administration, fluconazole accumulates in eccrine sweat and diffuses rapidly and extensively in the stratum corneum. Its concentration in the skin is higher than in the serum. The prolonged skin retention of fluconazole (7 days after stopping treatment) has been attributed to its high affinity to stratum corneum due to an interaction between fluconazole and keratin [30]. However skin distribution after topical administration has not been studied extensively. Though facial SD has been reported to be respond to fluconazole 2% shampoo in a study [31], there is a lack of studies in the literature studying the use of topical fluconazole in SD.

Flutrimazole: Flutrimazole is another imidazole antifungal agent whose antifungal activity against *Malassezia furfur spp* in guinea pigs *in vivo* has been shown to be better than sertaconazole, though lower than ketoconazole and bifonazole [32]. In a study conducted by Noguera et al. [33] it was concluded that flutrimazole gel 1% has a similar efficacy to ketoconazole gel at a dose of three applications per week for 28 days.

Luliconazole, Eberconazole: Luliconazole 1% cream and eberconazole 2% cream are relatively newer imidazole antifungal drugs which possess fungicidal properties and are well tolerated [34,35]. However there is a paucity of studies evaluating their role in this disease.

Ciclopirox Olamine: Ciclopirox is a synthetic hydroxypyridone derivative which in addition to being a broad spectrum antifungal agent, possesses a broad-spectrum antibacterial activity and anti-inflammatory properties [36]. Unlike azoles, this drug does not inhibit sterol synthesis, but acts through the chelation of trivalent metal cations, such as Fe3+, for which it has a high affinity. The polyvalent cation has an inhibitory effect on enzymes, for example, cytochromes which play a role in mitochondrial electron transport processes and energy production. Ciclopirox also inhibits metal-dependent enzymes, such as catalase and peroxidase, which play a part in the intracellular degradation of toxic peroxides [37].

It is available in 0.77% cream, 0.77% gel and 1% shampoo formulations for use in SD. Ciclopirox 0.77% gel and 0.77% cream formulations were approved by the FDA in 2004 and the 1% shampoo preparation was approved by the FDA in 2010 [38]. Ciclopirox has demonstrated both fungicidal and fungistatic activity *in vitro* against a broad spectrum of pathogenic fungi, including dermatophytes of the *Trichophyton*, *Microsporum* and *Epidermophyton species*, yeasts of the *Candida species*, *Malassezia species*, *Cryptococcus neoformans, Sacchromyces cerevisiae* and *Candida glabrata*. MIC values of this drug for *Malassezia furfur*

range from 0.001 to 0.125µg/ml.36 The drug is well tolerated and rarely side effects like burning sensation or eye stinging has been observed, but they are usually mild in nature [39]. It is classified as a pregnancy category B drug [10].

To date, ciclopirox has been used in 13 studies so far.6 In a multicenter, randomized, double-blind, vehicle controlled study of 178 subjects, the efficacy of ciclopirox gel in treating SD of the scalp was evaluated and it was observed that more ciclopirox-treated subjects achieved over 75% improvement in the global evaluation scores, based on a scale of 0-5 (100% clearance to flare of treatment area), compared with vehicle at days 22, 29, and endpoint ($P < 0.01$) [40]. Another randomized, parallel-group, double-blind, vehicle-controlled trial was designed to compare three different application frequencies of ciclopirox 1% shampoo: once, twice, and three times weekly. The authors observed that the increase of therapeutic index from the 1× group to the 3× group was too small to conclude that increased frequency leads to increased efficacy of treatment. Furthermore, there were no increased side effects noted on increasing the frequency of usage [41].

There are several studies comparing the efficacy of ciclopirox with ketoconazole in SD as well. A randomized, open labeled clinical study was conducted by Chosidow et al. [42] to compare ciclopirox olamine 1% cream and ketoconazole 2% foaming gel in patients with mild to moderate facial SD. The authors found that at the end of the maintenance phase, treatment response to ciclopirox olamine was greater than to ketoconazole in both intention-to-treat (ITT) and per protocol (PP) populations.42 However, while the group applying ciclopirox was using it twice daily, the group applying ketoconazole gel was using it only twice a week during the initial phase. This may be a confounding factor. Another study with a randomized, double-blind, parallel group design was conducted on 350 patients who were divided into three groups: 1.5% ciclopirox shampoo (150), 2% ketoconazole shampoo (150) and placebo (50) respectively. The study period was four weeks. Assessments included scalp area affected, the severity of scaling, erythema, itching and scaling, and overall signs and symptoms. They observed that while the two shampoos were similar in efficacy in reducing both the area of involvement of scalp affected by SD and erythema, patients rated the ciclopirox shampoo as superior to placebo ($P < 0.001$) and ketoconazole shampoo ($P < 0.05$) on the basis of overall signs and symptoms [39].

Shuster et al. [43] also observed that a low relapse rate of SD is maintained by shampooing hair with ciclopirox once every one or two weeks [43].

Terbinafine: Though there are reports of its weak action against *M. furfur*, it has been shown to improve SD when administered in oral [44,45] as well as topical [46,47] formulations. In a study conducted on 35 patients with SD over face, terbinafine 1% cream was applied twice daily for four weeks. The severity of the signs (erythema, scaling, infiltration) was assessed using a 4-point score (0=absent, 1=mild, 2=moderate, and 3=intense) at baseline and at the 2nd and 4th weeks of the therapy. Also, self-assessment was done by the patients on a 100 mm visual analogue score (VAS) at each visit. Complete remission was observed in 10 (32.3%) patients at the end of the therapy. Statistically significant reductions in the scores of all parameters were observed at both the second and fourth weeks of the therapy [47].

In another study, the efficacy of terbinafine 1% cream was compared with ketoconazole 2% cream and placebo in 90 patients with facial SD. After four weeks of therapy, there was not any significant difference between ketoconazole and terbinafine groups ($P > 0.05$). There were no serious side effects and also the recurrence rate and side effects were not statistically different in the three groups [46].

Butenafine: Butenafine, like the allylamines, inhibits squalene epoxidase and is fungicidal *in vitro* [48]. In an open study, ten patients over the age of 50 years with classical signs of facial SD were enrolled and butenafine hydrochloride cream 1% was applied to the entire face twice daily for three weeks. The authors reported that there was significantly greater improvement compared with baseline in the disease status [48]. However the lack of control population and small sample size are major limiting factors. Further randomized, controlled trials are required to establish its efficacy in SD.

Novel methods of delivery of topical antifungal agents

Since the drugs discussed so far in the management of SD provide complete remission in only a small proportion of cases, it is necessary to look for therapeutic options which aim to increase the local drug delivery and hence efficacy of treatment in this chronic, relapsing disease. It should be noted that studies focusing on the following novel drug delivery mechanisms are required for SD which will help dermatologists in achieving higher remission rates in this disease.

The stratum corneum has a unique hierarchical structure, which is filled with multiple lipid bilayers and the embedded corneocytes. The lipid phase is continuous throughout the stratum corneum, and therefore the penetrating substances must interact with this phase whether they penetrate transcellularly or intercellularly. In order to facilitate the passage of molecules through the stratum corneum, transdermal permeation enhancers have been extensively studied [49].

These novel delivery methods are described as follows:

I. Micelle: A micelle is defined as a group of surfactant molecules dispersed in a liquid and have shown to increase the efficacy of topical drugs like clotrimazole and fluconazole for superficial fungal infections [50].

II. Solid lipid nanoparticles: These are carriers in which the drug is entrapped within a solid lipid core matrix. They are recommended as good carriers for lipophilic drugs like clotrimazole and miconazole [50].

III. Microemulsions: Microemulsions are defined as thermodynamically stable mixtures of oil and water stabilized by surfactants and co-surfactants, with size in the nanometer range. A microemulsion gel developed for topical delivery of fluconazole for the treatment of invasive fungal infections was developed and found very effective in enhancing percutaneous absorption of the drug [50,51].

IV. Vesicular delivery systems: Vesicles are defined as highly ordered assemblies of one or several concentric lipid bilayers. They are formed when certain amphiphilic molecules such as phospholipids or surfactants are placed in water. They increase the penetration of the lipidic components of topical drugs like antifungals into the stratum corneum leading to alteration in the intercellular lipid matrix. They are of many types- liposomes, niosomes, transferosomes, ethosomes, and penetration enhancer vesicles [50].

a. Liposomes: Liposomes are single or multilayered vesicles that completely enclose an aqueous phase within one or several phospholipid bilayer membrane(s) [52]. They are either adsorbed onto the skin surface leading to the release of drugs, or penetrate via the lipid-rich channels either intact, or after losing some lipid lamellae. Liposomal gels of ketoconazole and ciclopirox olamine have been used successfully [52,53].

b. Niosomes: It comprises of two essential components- cholesterol and non-ionic surfactants. They release drug in a sustained manner and also provide improved drug concentration at the site of action. Niosomes of terbinafine and ketoconazole have shown promise [50,54].

c. Proniosomes: Since aqueous suspensions of niosomes may exhibit problems of physical instability, they can be stored as dry granular material, also known as 'proniosomes' which are converted into niosomes upon hydration. There is evidence of prolonged release of ketoconazole using a proniosomal gel [55].

d. Transferosomes: These are also known as ultradeformable or flexible liposomes, and thus are able to pass into deeper skin layers intact. Transferosomal formulations of miconazole showed a higher rate of permeation of drug into deeper skin layers [56].

e. Penetration enhancer vesicles: Oleic acid induces penetration into skin due to subcutaneous lipid fluidization and phase separation. Oleic acid vesicles have been used to deliver clotrimazole with enhanced penetration as well as sustained release of upto five days after application [57].

Practical Approach

In cases of mild to moderate SD involving scalp, 2% ketoconazole shampoo applied thrice weekly or ciclopirox olamine 1% shampoo applied twice weekly usually leads to remission. The recurrent lesions can be prevented by once weekly use of ciclopirox 1% shampoo or twice weekly use of ketoconazole 2% shampoo. Leave-on preparations of ketoconazole and climbazole may also be prescribed for overnight use. In case of mild to moderate SD involving face and other sites (other than scalp), the topical antifungal of choice is ketoconazole 1% cream or terbinafine 1% cream. Bifonazole 1% cream and clotrimazole 1% cream are other therapeutic options and the effect of these preparations is enhanced by co-administration of anti-inflammatory drugs like topical corticosteroids. In moderate to severe cases of SD, in addition to the above treatment options, oral antifungals, oral retinoids or oral steroids should be considered.

In all cases, general measures like avoiding use of hair oil & maintaining adequate hygiene and use of oral antihistamines to control pruritus should be used.

Conclusion

Thus we conclude that ketoconazole and ciclopirox olamine preparations remain the most effective and thus widely used topical modalities in the treatment of SD involving scalp and face. Other modalities are effective in mild to moderate seborrheic dermatitis, especially when used in combination with other drugs, like topical corticosteroids. In future, studies are required to test the efficacy of newer topical delivery systems in SD in order to achieve better results with topical antifungals.

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