Original Article

Interdigital tinea pedis (dermatophytosis simplex and complex) and treatment with ciclopirox 0.77% gel

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Abstract

The most common presentation of tinea pedis (athlete's foot) is that involving the interdigital spaces. Tinea pedis interdigitalis may present as asymptomatic dermatophytosis simplex or dermatophytosis complex, which is symptomatic, with secondary bacterial infection. In the dermatophytosis complex presentation there may be inflammation, maceration and odor, with bacterial involvement. Ciclopirox gel offers advantages in the treatment of tinea pedis, especially in the dermatophytosis complex presentation, with antifungal, antibacterial, and anti-inflammatory activity; furthermore, the gel formulation is fast drying, which is an advantage when the toe web area is moist.

Introduction

Tinea pedis is a common fungal infection in adults, affecting between 30 and 70% of the population[1]. It often develops in persons with hyperhidrosis[1,2], particularly among men between the ages of 20 and 40 years[3]. Elderly, diabetic, and immunocompromised patients are also at risk[4]. The etiologic pathogens most commonly associated with tinea pedis are *Trichophyton rubrum*, *T. mentagrophytes*, and *Epidermatophyton floccosum*[1–3].

The most common presentation of athlete's foot is tinea pedis interdigitalis, which is generally chronic, and usually affects the toe web between the fourth and fifth toes, although other spaces may be involved. Interdigital tinea pedis may be mimicked by bacterial infections that have a similar presentation, hyperkeratotic lesions, and erythrasma caused by *Corynebacterium minutissimum*[5]. Other differential diagnoses include psoriasis, contact or atopic dermatitis, candidal infection, and eczema[2,3]. The interdigital presentation can be subdivided into two categories, dermatophytosis simplex and dermatophytosis complex[6]. Interdigital tinea pedis has mostly been treated in the past with antifungal agents; however, in dermatophytosis complex, there is bacterial involvement, and the agent of choice should have both antifungal and antibacterial properties. Ciclopirox 0.77% gel is such a candidate because it has a broad spectrum of activity with antifungal, antibacterial and anti-inflammatory properties.

Dermatophytosis simplex

Dermatophytosis simplex represents the uncomplicated form of interdigital tinea pedis. It is characterized by scaling, and at times, fissuring[7]. This type of tinea pedis is relatively asymptomatic, but pruritus may periodically occur[6]. Dermatophytes are shown to be the causative pathogen in up to 85% of clinically diagnosed cases, with the percentage of organisms that can be recovered decreasing as the disease progresses[8]. Generally, dermatophytes are recovered from the toe spaces in the simplex form by means of KOH preparation or culture[6].

Dermatophytosis complex

Tinea pedis interdigitalis (dermatophytosis complex variety) is a more severe presentation, and typically manifests with inflammation, maceration and odor in the toe web space[9]. Pruritus may be present. In addition, the affected toe web may appear white, macerated, hyperkeratotic, with erosions and fissures. The malodor may be associated with colonization caused by bacteria such as *Micrococcus sedentarius*, *C. minutissimum*, and *Brevibacterium epidermidis*[6,9,10]. Sulfur compounds produced by these odor-causing bacteria may possess fungicidal properties, which, in part, may account for the reduced recovery of fungal organisms from tinea pedis lesions.

Leyden and Kligman[8] demonstrated that a correlation exists between dermatophytosis complex and bacterial infection.

In subjects with moderate interdigital tinea pedis ($n = 43$), characterized with scaling and maceration, dermatophytes were recovered in 55.8%. In the same subjects, *Staphylococcus aureus* comprised 9.8% of the total flora, an increase from normal toe webs ($n = 48$) and simplex form ($n = 39$), (0 and 4.1%, respectively). In dermatophytosis complex, *Proteus* species were recovered in 11.6% of patients, whereas no *Proteus* species were present in normal toe webs and dermatophytosis simplex. In severe, strongly symptomatic, cases of dermatophytoses complex, an increase in *S. aureus* and *Proteus* species was demonstrated, as well as a drastic increase in Gram-negative bacteria ($n = 58$). In normal interspaces and simplex tinea pedis, Gram-negative bacteria made up only 0.05% and 0.06% of the total flora, respectively. The prevalence of Gram-negative bacteria increased with moderate maceration to 0.92% of the total flora, and in severe dermatophytosis complex, an increase of 3.16% was reported. Dermatophytes were recovered in only 36.2% of subjects with dermatophytosis complex[8].

Occlusion of fungus-infected interspaces with plastic film was reported to increase the symptoms of dermatophytosis complex; in those subjects with normal toe webs, occlusion had little effect[8]. Occluded interspaces in patients with dermatophytosis simplex, in which antimicrobial ointment was applied, did not become symptomatic. This suggested that dermatophytes that cause dermatophytosis simplex create an environment favorable to bacteria, especially when the interspaces become hydrated while under occlusion[8]. The bacteria that grow may force the dermatophytes further into the stratum corneum[8]; and an interaction between the bacteria and dermatophytes may create symptomatic tinea pedis[11].

The bacteria that become overgrown within the toe web spaces are typically resident bacteria that have antibiotic resistance[11,12]. Dermatophytes produce a variety of antibiotics, including penicillin[11] and streptomycin-like substances[7]. The bacteria that are common in dermatophytosis complex, Gram-positive *S. aureus*, *M. sedentarius*, *B. epidermidis*, and *C. minutissimum*, and the Gram-negative species *Proteus* and *Pseudomonas*, are routinely resistant to penicillin. This allows proliferation of such bacteria, and in turn, they produce a variety of proteolytic enzymatic substances capable of digesting an array of proteins[7,13]. Normal interspaces are resistant to the effects of these substances, probably due to the protective barrier properties of the stratum corneum[7]. The most severe type of tinea pedis interdigitalis occurs when Gram-negative species overgrow within the interspaces (i.e. Gram-negative athlete's foot)[1,8].

Treating tinea pedis interdigitalis

Many studies involving the use of antifungal agents for the treatment of interdigital tinea pedis do not define what severity of disease subjects are experiencing at the onset of therapy. Studies that score the severity of tinea pedis generally rate signs and symptoms (e.g. erythema, fissures, scaling, hyperkeratosis, odor, maceration, pruritus, and burning/stinging, or a variation thereof) on a severity scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe), and include only those patients whose total score would correspond to a moderate or severe presentation, for example, a cumulative score of 6 or higher. This may allow for more accuracy in evaluating the efficacy of the antifungal agent.

Agents that have been evaluated for the treatment of moderate to severe tinea pedis (according to the above scale) include topical formulations of butenafine[14–16], terbinafine[17–19], clotrimazole[17], oxiconazole[19,20], naftifine[19] and miconazole nitrate[21] (Table 1). In these studies, the tinea pedis interdigitalis may have been of the dermatophytosis simplex variety, although it is difficult to be sure whether it was the dermatophytosis complex variety that was being treated. No trials specifically included maceration, odor, or inflammation (the most common signs and symptoms of bacterial infection) as a necessary inclusion criterion for entry into the study, and to our knowledge, none of the studies reported the change in bacterial counts during therapy from baseline to the end of therapy.

Dermatophytosis simplex

Topical therapy with an antifungal agent is often the first choice in the treatment of dermatophytosis simplex[22]. Imidazoles, allylamines, butenafine, tolnaftate, salicylic acid, tolcicate, and undecylenic acid have been used in the past, with good efficacy[2,4,8,23,24]. In some instances, it may become necessary to use oral antifungal therapy, for example, terbinafine, itraconazole, or fluconazole.

Dermatophytosis complex

Purely antifungal agents generally do not have an optimal effect on the symptoms of dermatophytosis complex. However, when both antifungal and antibacterial agents are used, there has been a high rate of response reported (75% improved with combined therapy compared to 50% improvement with antibacterial agent and no change with antifungal agent)[8]. It is thought that agents that suppress bacteria and fungi, and also have a drying effect are most effective[6]. A reduction in inflammation may in some instances be achieved by the use of a mild topical corticosteroid[25]; alternatively, the desired agent used to treat dermatophytosis complex may have inherent anti-inflammatory properties, as well as antifungal and antibacterial properties.

Ciclopirox for the treatment of interdigital tinea pedis

Ciclopirox (available in cream, lotion, topical suspension and gel) is approved for use in the treatment of tinea pedis and offers advantages for the treatment of dermatophytosis

Table 1. Clinical trials including only those subjects with a moderate to severe presentation of tinea pedis interdigitalis treated with topical antifungal agents other than ciclopirox

Antifungal Agent	Study type	*n*	Regimen	Efficacy results at end of study*	Assessment of tinea pedis at baseline for inclusion in study
Butenafine[14]	Double-blind randomized, placebo-controlled	105	4 weeks, twice daily	MC = 83% Effective treatment rate = 68% Good global response or clearing = 84.9% Patient assessment as greatly improved = 93.4%	‡Erythema = min. 2 and Pruritus and/or scaling = min. 2
Butenafine[15]	Double-blind, randomized, placebo-controlled	271	1 week, twice daily	MC = 74% (98/132) CC = 23% (30/132)	†Combined score for erythema, and/or pruritus, and/or scaling = min. 4
Butenafine[16]	Double-blind, randomized, placebo-controlled	80	4 weeks, once daily	MC = 88% CR = 78% CC = 23% Improved global assessment = 95%	‡Erythema = min. 2 and Pruritus and/or scaling = min. 2
Terbinafine[18]	Double-blind, randomized, placebo-controlled	159	1 week, twice daily	MR = 88% CR = 79% Global assessment = 78% clearing or improvement	‡Minimum score of 6, including: Erythema = min. 2 or Two other signs = min. 2 for each
Oxiconazole Nitrate[20]	Double-blind, randomized, Placebo-controlled	404	4 weeks, twice daily	MC = 65.3% CC = 38.8%	‡Minimum score of 6, including: Erythema = min. 1.5 and Pruritus = min. 2
Terbinafine vs. Clotrimazole[17]	Double-blind, randomized	193	1 week, or 4 weeks twice daily	*Terbinafine:* MR = 81% (1 week); 85% (4 week) CR = 83% (1 week); 91% (4 week) *Clotrimazole:* MR = 30% (1 week); 68% (4 week) CR: 56% (1 week); 78% (4 week)	‡Minimum score of 6, including: Erythema = min. 2 and Two other signs = min. 2 for each
Miconazole Nitrate vs. Tolnaftate[21]	Double-blind randomized	44	2 weeks, twice daily for both	*Miconazole Nitrate:* CR = 95.4% Negative KOH = 95.4% *Tolnaftate:* CR = 83.3% Negative KOH 58.3%	Cutaneous manifestations of acute moderate-severe, symptomatic tinea pedis
Naftifine vs. Oxiconazole vs.Terbinafine[19]	Double-blind, randomized	90	2 weeks, once daily for all	*Naftifine:* Clin Cure = 75.0%; MC = 75.0% *Oxiconazole:* Clin Cure = 30.8%; MC = 26.9% *Terbinafine:* Clin Cure = 83.8%; MC = 80.6%	‡Cumulative min. score of 3 (min. = 0, max. 8 × 3 = 24) for all signs and symptoms

Clin Cure, clinical cure; CC, complete cure (clinical and mycological); CR, clinical response; MC, mycological cure; MR, mycological response.
‡Based on a scale of 0–3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe);
†Based on a scale of 0–4 (0 = absent, 1 = mild, 2 = moderate, 3 = moderate severe, 4 = severe).

complex. This agent has *in vitro* fungicidal activity against *T. rubrum*, *T. mentagrophytes*, *E. floccosum*, *Candida albicans*, and *Microsporum canis*[26]. Antibacterial activity has been reported against *S. aureus*, *C. minutissimum*, *Proteus* and *Pseudomonas species*, as well as other organisms not commonly recovered in tinea pedis[27–29].

Ciclopirox also offers anti-inflammatory properties that are similar to those of a mild corticosteroid, but without the unwanted side-effects associated with the latter (e.g. atrophy and adrenal suppression)[30]. The gel formulation of ciclopirox offers a special advantage in that the vehicle contains some isopropyl alcohol[31], which creates a drying effect in the toe web. Any burning sensation from the alcohol generally disappears after a short time[32].

Clinical trials evaluating the use of ciclopirox for tinea pedis

All but one known trial evaluating ciclopirox for tinea pedis interdigitalis have not reported a change in bacterial counts at any time during treatment. The severity and presentation of tinea pedis is not specified, so it may be that both presentations, dermatophytosis simplex and complex, were included in these studies, or perhaps only the simplex variety. A summary is given below.

In two multicenter, double-blind trials, ciclopirox 1% cream (applied twice daily for 4 weeks) was significantly more effective, mycologically and clinically, compared with vehicle ($P < 0.05$, and $P < 0.001$, respectively), and clotrimazole 1% cream ($P = 0.05$) in the treatment of interdigital and plantar tinea pedis ($n = 214$)[33].

Ciclopirox 1% cream was found to be effective in the treatment of tinea pedis associated with onychomycosis in an open clinical trial when applied 2–3 times daily for between 3 and 24 months; the primary aim of the study was to evaluate the efficacy of ciclopirox cream in the treatment of onychomycosis[34]. Upon clinical and mycological examinations, tinea pedis was cleared in 42% and improved in an additional 45% of patients ($n = 33$)[34].

In a double-blind, parallel-group, multicenter study with 178 patients enrolled, ciclopirox 1% lotion (applied for 4 weeks) ($n = 89$) was compared with vehicle ($n = 89$) in the treatment of tinea pedis (75% with interdigital presentation)[35]. One hundred and thirty-four patients were evaluable for efficacy, 67 in each group. Ciclopirox was significantly better than vehicle for combined clinical and mycological cure 2 weeks post-treatment ($P = 0.001$)[35].

Ciclopirox 0.77% gel has been use in two recent multicenter, randomized, double-blind, vehicle controlled studies[32]. A total of 374 subjects with interdigital tinea pedis (75% with moderate to severe presentation) were enrolled and applied either ciclopirox 0.77% gel or the gel vehicle twice daily for 28 days. At the endpoint (2–3 weeks post-treatment), 40% of the ciclopirox subjects ($n = 160$) were cured (100% clinical cure and clearing of tinea pedis) in comparison to 4% of the vehicle subjects ($n = 157$). Pruritus, maceration, fissures, and hyperkeratosis decreased a great deal more in patients who were administered ciclopirox. Mycological cure and complete cure was achieved in significantly more ciclopirox subjects (85 and 40%, respectively) than vehicle subjects (6 and 4%, respectively) 2 weeks post-treatment ($P = 0.05$)[32].

Ciclopirox for treating dermatophytosis complex

A recent double-blind, randomized, vehicle controlled study, which enrolled 100 patients presenting with moderate dermatophytosis complex, compared once daily and twice daily application of ciclopirox 0.77% gel for 4 weeks with placebo applied twice daily for 4 weeks (A. Gupta *et al*., submitted for publication). There was no significant difference found between the once daily and twice daily application of ciclopirox 0.77% gel. However, once and twice daily application of ciclopirox gel was significantly more effective than placebo at the end of treatment (week 4), and 4 weeks post-treatment for reduction in clinical signs and symptoms ($P < 0.05$), reduction in severity of tinea pedis according to subject evaluation ($P < 0.05$), as well as reduction in bacteria after 2 weeks of treatment ($P < 0.05$). There was also a greater reduction in bacterial counts in the ciclopirox groups at weeks 4 and 8. Mycological cure was achieved at weeks 4 and 8 in 25/28 (89.3%) and 21/26 (80.8%) of subjects, respectively, who applied ciclopirox twice daily; in 25/30 (83.3%) and 24/29 (82.8%) of subjects, respectively, who applied ciclopirox gel once daily; and in 8/17 (43.8%) of subjects (for both weeks) who applied placebo. Complete cure was achieved in more subjects treated with ciclopirox than placebo 4 weeks post-treatment (53.8% of twice daily application group, 41.4% of the once daily application group, and 11.8% of the placebo group) (A. Gupta *et al*., submitted for publication). To the authors' knowledge, this is the only study that has evaluated the change in bacterial counts during the course of therapy for interdigital tinea pedis. When treating dermatophytosis complex it is important to evaluate both mycological cure and the decrease in bacterial counts.

Conclusion

Tinea pedis interdigitalis may be classified into the dermatophytosis simplex and dermatophytosis complex varieties. Dermatophytosis simplex is an uncomplicated form of tinea pedis interdigitalis; it may progress to a more symptomatic form that is more difficult to treat. The simplex variety typically presents with scaling and may be pruritic. The more severe presentation is termed tinea pedis interdigitalis, dermatophytosis complex. It may manifest with inflammation, maceration, odor and pruritus of the affected toe web space. Ciclopirox 0.77% gel is effective in the management of both the simplex and complex presentation of tinea pedis interdigitalis. In particular, the antifungal, antibacterial and anti-

inflammatory properties of ciclopirox are of advantage when there is a combination of a fungal and a bacterial infection present, as it is in the complex presentation. Furthermore, the gel formulation helps to dry out the moist toe web space.

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