Original Article

Ciclopirox for the treatment of superficial fungal infections: a review

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Abstract

Ciclopirox is a broad-spectrum antifungal agent that also exhibits anti-inflammatory and antibacterial activity. The lotion and cream formulations of ciclopirox are effective in many types of infection, including tinea corporis/cruris, tinea pedis, cutaneous candidiasis, pityriasis (tinea) versicolor, and seborrheic dermatitis. The new ciclopirox gel 0.77% formulation is also indicated for the treatment of seborrheic dermatitis of the scalp, interdigital tinea pedis and tinea corporis.

Introduction

Ciclopirox has a mechanism of action that is different from other antimycotic agents[1]. This antifungal compound is a synthetic hydroxypyridone derivative whose chemical formula is 6-cyclohexyl-1-hydroxy-4-methyl-1 (1H)-pyridone[2]. Ciclopirox is available in many forms, including cream, lotion, topical suspension, and gel (Loprox®) and nail lacquer (Penlac™). The cream and lotion formulations contain ciclopirox olamine 1%, while the gel contains 0.77% ciclopirox in a free acid form; these are equivalent in dosage and have the same activity[3]. Ciclopirox in the cream/lotion/topical suspension/gel formulations has been used to treat a variety of fungal infections including tinea pedis, tinea corporis/cruris, pityriasis (tinea) versicolor, and seborrheic dermatitis. The lacquer formulation is indicated in the US for the management of onychomycosis; however, this will not be covered in this paper.

Antimicrobial mechanism

Unlike some other antifungal agents, ciclopirox does not affect sterol synthesis. Ciclopirox inhibits cellular uptake of essential compounds, and at high concentrations can alter cell permeability[4,5]. The plasma membrane of dermatophytes and *Candida albicans* were found to be affected by ciclopirox, as in a freeze-fracture experiment by Gasparini and colleagues[6]. In patients with pityriasis versicolor treated with ciclopirox olamine, cell wall damage and disorganization of internal structures of yeast cells could be seen by electron microscopy[7]. Transmembrane transport was blocked in *C. albicans* and *Saccharomyces cerevisiae* treated with ciclopirox in an experiment using radiolabeled leucine. There was accumulation of leucine within the cell, and at high concentrations leakage of potassium ions and other intracellular material was present[2,8].

Ciclopirox may also act through chelation with polyvalent metal cations such as Fe^{3+} and Al^{3+} [9,10]. Chelation creates a larger, combined polyvalent cation, which has an inhibitory effect on enzymes that are involved in the cellular processes of fungi. For example, the polyvalent cation can affect the cytochromes involved in transport and energy production in mitochondria[4,11]. Catalases and peroxidases, which are metal-dependent enzymes, may also be inhibited by ciclopirox. These enzymes play important roles in degradation of toxic peroxides[11].

In vitro activity

Ciclopirox is effective against a broad spectrum of fungal organisms, including dermatophytes, yeasts, dimorphic fungi, eumycetes, and actinomycetes, acting in a fungistatic or fungicidal manner *in vitro*[4,8,12]. For most sensitive pathogenic fungi, low minimum inhibitory concentrations have been observed, being in the range of 0.9–3.9 μg/ml, which can vary depending on the media used in the assay[4,12].

Pig-skin models, used to determine the inhibitory and fungicidal effects of ciclopirox, have shown favorable results. Two separate studies have compared ciclopirox with different topical antifungal agents containing 1% active

ingredient[13,14]. Both studies demonstrate a 93% inhibitory effect of ciclopirox, which was higher than oxiconazole, naftifine, and bifonazole creams, each having less than 50% activity when compared with controls. Hänel *et al.*[14] observed a higher fungicidal activity for ciclopirox in comparison to the above-mentioned agents. Fungicidal activity was measured against *Trichophyton mentagrophytes* after a 1 h exposure to the drug; ciclopirox had a 98% effect[14]. The various antimycotics showed relative fungicidal activity as follows: ciclopirox cream 1% > naftifine cream 1% > oxiconazole cream 1% > bifonazole cream 1%[13]. This ranking was also true in human skin models.

Ciclopirox shows a greater *in vitro* activity towards *C. albicans* than other antimycotics tested[9]. This was determined in an ultrafiltration tissue activity test; the topical agent was applied to a porcine skin sample, and then layers removed and *C. albicans* inoculated in the deep layers. The sample was then allowed to incubate and cultures were made from the incubated skin tissue to determine the number of colony forming units (cfu). The other agents in this test, in order of activity (greatest to lowest) were tioconazole, oxiconazole, miconazole, econazole, clotrimazole, bifonazole, and naftifine creams[13].

In addition to the above-mentioned pathogens, ciclopirox also exhibits activity against many other species of dermatophytes, yeasts, and moulds; these include other *Trichophyton* and *Candida* species. A list of species that ciclopirox has been found to be active against *in vitro* is in Table 1[8]. Ciclopirox has also shown *in vitro* activity against *Malassezia furfur*[7,15].

Table 1 Common pathogenic species ciclopirox is active against *in vitro* (Not a complete list; modified from Jue, Dawson and Brogden, 1985[8])

Dermatophytes	**Dimorphic fungi**
Trichophyton mentagrophytes	*Blastomyces dermatitidis*
T. rubrum	*Histoplasma capsulatum*
T. verrucosum	
T. tonsurans	**Eumycetes**
T. soudanense	*Madrella grisea*
T. violaceum	*M. mycetomi*
Microsporum canis	*Petriellidium boydii*
M. gypseum	
Epidermatophyton floccosum	**Actinomycetes**
	Nocardia asteroids
Yeasts	*N. brasiliensis*
Candida albicans	
C. tropicalis	**Various fungi**
C. parapsilosis	*Aspergillus* species
Cryptococcus neoformans	*Penicillium* species
Malassezia species	*Phialophora* species
Saccharomyces cereviciae	*Fusarium solani*
Torulopsis glabrata	

Antibacterial activity

Ciclopirox has been compared *in vitro* with other topical antifungals to determine its antibacterial activity. When compared with clotrimazole and miconazole, ciclopirox had a higher MIC range for Gram-positive bacteria, but the MIC range for Gram-negative bacteria was much lower[9]. Ciclopirox shows lower MIC values for both Gram-negative and Gram-positive when compared with ketoconazole (data on file, Medicis Pharmaceutical Corp.). Ciclopirox was found to have the highest *in vitro* activity against both fungi and bacteria when compared to econazole nitrate and butenafine HCl[15]. These factors give ciclopirox an advantage over most other antifungals, especially in the case of Gram-negative bacterial infection secondary to fungal infections, such as what may be present in macerated tinea pedis[7,12,15,16].

A clinical comparison of ciclopirox olamine 1% cream with the cream vehicle and clotrimazole 1% cream was performed in 45 patients with interdigital tinea pedis with complicating bacterial infection. During treatment with ciclopirox, total bacterial counts decreased, while the vehicle and clotrimazole had no effect on the bacterial infection. Post treatment, the bacterial counts returned to baseline values[9].

Ciclopirox has antibacterial activity against many species of pathogenic bacteria, which has been shown by Abrams *et al.*[9] and Kokjohn *et al.*[15].

Penetration through skin

In vitro skin model studies have demonstrated that ciclopirox penetrates skin rapidly. Ciclopirox cream was applied to the stratum corneum in a pig-skin model and adhesive tape strippings were taken at specified time intervals to expose different depths of the stratum corneum[17]. The treated skin was then inoculated with microcondia of *T. mentagrophytes*. There was complete inhibition of fungal activity in the upper most layer of the stratum corneum, which underwent no stripping, after 30 min of contact with drug. As each consecutive strip was taken, there was less inhibition of fungal growth, with a reduction by more than half in the sixth stripping, which represents the layer close to the stratum lucidum[17]. With increased exposure to the drug, there was greater penetration, with 100% inhibition after 18 h of exposure in all layers.

Another *in vitro* study using a porcine model found that after exposure to ciclopirox for 1 h or longer, there was almost complete inhibition of *T. mentagrophytes* growth in the lower layers of the stratum corneum[13]. In yet another *in vitro* pig-skin model, testing inhibition of *T. mentagrophytes*, ciclopirox olamine inhibited 100% of growth at the surface and 93% in the stratum granulosum after 3 h of exposure[14]. This was compared to azole antimycotics in the deeper skin layers; none of the azoles had inhibition over 50%.

Human-skin models have also been used to determine the penetration of ciclopirox. *In vitro* experiments using cadaver skin show similar results to those in the pig-skin models[13,18]. *In vivo* human studies have been performed to determine the penetration on 1% ciclopirox olamine cream. Ciclopirox cream was applied to the forearm in 10 healthy volunteers. Twenty strips were obtained from each site (at which time the stratum lucidum should be reached). After 2 h of contact with drug, a high level of ciclopirox was detected in the uppermost layer, and decreased levels in the deepest layers. The general trend, after up to 24 h exposure, was toward there being a decrease in concentration of drug in the lower layers[17].

Human studies using radiolabeled ciclopirox olamine 1% cream found there to be 1.3% systemic absorption of the dose in healthy volunteers when it was applied topically to 750 cm^2 on the back followed by occlusion for 6 h[19]. The majority of the labeled ciclopirox was excreted renally within 2 days after application.

Ciclopirox penetrates the hair and sebaceous glands via the epidermis and hair follicles[19,20]. A portion of the drug also collects within the stratum corneum, creating a reservoir effect.

Anti-inflammatory activity

Ciclopirox exhibits anti-inflammatory activity. This has been demonstrated in human polymorphonuclear cells where ciclopirox inhibits prostaglandin and leukotriene synthesis[9]. Ciclopirox may also exert its anti-inflammatory effect via inhibition of 5-lipoxygenase and cyclo-oxygenase[21–23].

In the arachidonic acid-induced ear edema assay, anti-inflammatory activity of topical agents may be determined. Ciclopirox significantly reduced arachidonic acid-induced ear edema, as measured in comparison with control-inflamed ears. The large percentage of activity was more than twice as much as observed with naftifine, ketoconazole, fluconazole, or miconazole, and similar to that of the anti-inflammatory agents indomethacin and desoximetasone[9].

The anti-inflammatory properties of ciclopirox have also been shown in a study assessing the modulation of prostaglandin E_2 (PGE_2) release. Ciclopirox caused a 25% reduction in PGE_2 release, which was significant compared to minimal reduction achieved with naftifine and fluconazole. There was no anti-inflammatory activity exhibited by ketoconazole and miconazole[24].

In a double-blind protocol to assess the suppression of delayed erythema response to human exposure to ultraviolet B (UVB) irradiation *in vitro*, ciclopirox exhibited the most anti-inflammatory activity, followed by naftifine and terbinafine (allylamines), ketoconazole, oxiconazole and econazole (azoles), and 2.5% hydrocortisone[25].

Ciclopirox has shown its anti-inflammatory effects in the treatment of inflamed superficial mycoses. The authors of a study comparing ciclopirox olamine 1% cream with ciclopirox 1%-hydrocortisone acetate 1% cream found that there was no significant difference in the anti-inflammatory effect between the two. They noted that ciclopirox may have anti-inflammatory activity similar to a mild corticosteroid, in addition to a broad spectrum antifungal activity, but the former not having side-effects like corticosteroids[21].

Efficacy of ciclopirox in therapeutic trials

Jue *et al.*[8] have summarized a number of earlier studies concerning dermatophytoses of the skin treated with ciclopirox. In an open clinical trial, 40 patients with dermatophytoses were treated with 1% ciclopirox olamine cream or solution. Ciclopirox was applied for 3 weeks, and after 1 week of treatment, direct microscopy was negative in 89% of patients and culture was negative in 97%. Clinical cure was achieved in all patients at the end of the 3 weeks[26].

A double-blind clinical trial was used to compare ciclopirox 1% solution to the vehicle in the treatment of superficial dermatomycoses caused by *T. rubrum*, *T. violaceum*, *T. mentagrophytes*, and *M. furfur*[27]. The assigned preparation was applied twice daily for 4 weeks and a final assessment was performed on the 28th day of treatment. Ciclopirox 1% solution proved superior to the vehicle both mycologically and clinically at day 28, with 59.5% and 28.6% of ciclopirox and vehicle patients, respectively, showing marked clearing or improvement of symptoms and negative microscopic examination[27].

Tinea infections (tinea corporis/cruris and tinea pedis)

The treatment of tinea cruris and tinea corporis was addressed in two multicenter, double-blind, parallel clinical trials[28]. One trial compared ciclopirox olamine cream 1% with the cream vehicle and in the other trial ciclopirox olamine 1% cream was compared with clotrimazole cream 1%. Patients with both types of infection applied the assigned test drug twice daily for 4 weeks. Evaluation occurred during the course of treatment and also during a 2 week follow-up period after the cessation of treatment. Ciclopirox olamine cream 1% was found to be significantly more effective than the vehicle after the first treatment through the end of the evaluation period, with mycological and overall response rates much higher for ciclopirox than the vehicle[28]. In the trial comparing ciclopirox olamine cream 1% with clotrimazole cream 1%, the two preparations were statistically equivalent in the mycological and clinical cure rates[28]. Ciclopirox had a rapid onset of effect in both trials.

Tinea pedis is a common infection that has been treated with ciclopirox in clinical trials. One multicenter double-blind parallel group study compared ciclopirox olamine 1% cream with vehicle[29]. The creams were applied twice daily for 4 weeks. A better clinical response for ciclopirox over the vehicle was seen at each visit, with significant results starting

at the third visit and thereafter. Clotrimazole was also compared with ciclopirox in this study. More patients achieved complete cure when they were treated with ciclopirox than clotrimazole. These results were significant starting at the second visit[29].

Ciclopirox was found to be effective in the treatment of tinea pedis associated with onychomycosis caused by *Trichophyton* species and *Epidermophyton floccosum*[30]. In a clinical trial, ciclopirox olamine 1% cream was applied 2–3 times daily for no less than 3 months. Tinea pedis was cured in 42%, and improved in an additional 45% of patients[30].

Two multicenter, randomized, double-blind, vehicle controlled studies were performed to evaluate the efficacy of ciclopirox gel 0.77% in comparison to the gel vehicle in patients with interdigital tinea pedis[3]. The two studies were identical in method and variables. The treatment period consisted of 28 consecutive days, with gel application twice daily. Patients all tested positive for a dermatophyte infection at baseline. *T. rubrum* (80%) was the most common causative pathogen, followed by *T. mentagrophytes* (13%), *E. floccosum* (6%), and other dermatophytes, or nondermatophytes (6%). Two-weeks post-treatment, mycological cure was seen in 85% of ciclopirox patients, compared to 16% of the vehicle subjects. Ciclopirox was superior in the treatment of all organisms identified. At the endpoint, 66% of ciclopirox subjects were either cleared or had excellent improvement, compared to 19% of the vehicle subjects. Thirty-two percent of vehicle subjects showed no improvement, compared to 5% of ciclopirox subjects[3].

Cutaneous Candidiasis

A double-blind, multicenter clinical trial enrolled 96 patients with cutaneous candidosis[4]. The patients were divided into three groups; one was treated with ciclopirox olamine 1% cream, one with placebo, and the other with an imidazole-type antimycotic. The duration of treatment was 4 weeks, with preparation applied twice daily. At the end of treatment, 83% of the ciclopirox group and 14% of the placebo group were cured. The ciclopirox group was cured more quickly than the imidazole group[4].

Two multicenter, randomized, double-blind trials also found ciclopirox to be effective in the treatment of cutaneous candidiasis[31]. In one study, patients were given either ciclopirox olamine cream 1% or cream vehicle; these were applied twice daily for 4 weeks. At post-treatment visits, 1–2 weeks after cessation of therapy, 74% of ciclopirox patients and 12% of vehicle patients had clinical and mycological cure[31]. In the second study, patients were given either ciclopirox olamine cream 1% or clotrimazole cream 1%. Post-treatment evaluation showed that 74% of ciclopirox patients and 60% of clotrimazole patients were clinically and mycologically cured[31].

Pityriasis versicolor (tinea versicolor)

Pityriasis versicolor has been effectively treated with ciclopirox olamine cream 1%. Ciclopirox was found to be significantly more effective than the vehicle cream in a randomized, double-blind, parallel group study[32]. After 2 weeks of therapy, 49% and 24% of ciclopirox and vehicle patients, respectively, achieved mycological and clinical cure. In a similar, but comparative study between ciclopirox cream 1% and clotrimazole cream 1%, each was applied for 2 weeks[32]. At a two week follow-up examination, 86% and 73% of ciclopirox and clotrimazole patients, respectively, had mycological and clinical cure.

Ciclopirox olamine solution 0.1% was used to treat 90 patients suffering from pityriasis versicolor; it was applied for 4 weeks. Seventy-four percent of patients had clinical cure, and after an additional 4 weeks of treatment, 86% cure was achieved[4]. In a different study, six patients received ciclopirox olamine solution 1% for 1, 2, or 3 days[7]. Twenty-one days after the start of therapy, patients were assessed for clinical changes from baseline. All patients were clinically healed at this time. Shortly after the start of treatment, itching and erythema had ceased[7]. Ciclopirox may have a more rapid effect than clotrimazole[8].

Seborrheic dermatitis

Topical corticosteroids (anti-inflammatory agents) and antifungal agents are the two main classes of treatment for seborrheic dermatitis of both the skin and scalp. Adverse events associated with corticosteroids have caused a shift in treatment strategies for seborrheic dermatitis, with increased interest in antifungal agents. Adverse events, while treating seborrheic dermatitis with corticosteroids, include atrophy, telangiectasias, or perioral dermatitis[34] and can also be associated with dysfunction of the adrenal cortex especially in cases where high potency fluorinated topical steroids are used[35].

The yeast *M. furfur*, a normal commensal in human skin, is probably a factor in seborrheic dermatitis[36]. Ciclopirox has activity against *Malassezia* yeasts, altering their structure both *in vivo* and *in vitro*[7]. The anti-inflammatory activity of ciclopirox, as mentioned previously, and the reduction of *Malassezia* species on the skin is what most likely reduce the clinical signs of seborrheic dermatitis. Relief of clinical signs and symptoms may begin before the initiation of antifungal activity against *Malassezia* yeasts.

In a randomized, double-blind controlled trial; ciclopirox olamine shampoo 1% and vehicle were compared for the treatment of seborrheic dermatitis of the scalp[37]. Ciclopirox shampoo was found to be significantly more effective than the vehicle. The shampoos were applied for 5 min twice daily for 4 weeks. Ninety-three percent of patients receiving ciclopirox olamine shampoo 1% showed improvement or complete clearing at the end of 4 weeks, based on severity of

symptoms and overall assessment by the patient and physician. The vehicle group had only 41% improvement of clearing ($P < 0.00001$). No recurrences were observed at follow-up[37].

In a 56-day randomized, double-blind, placebo-controlled trial, ciclopirox olamine cream 1% was compared with vehicle in the treatment of facial seborrheic dermatitis[38]. Both creams were applied twice daily for 4 weeks, then once daily for an additional 4 weeks. At the end of the treatment duration, disappearance of erythema and scaling in a test lesion, defined as 'treatment response', was reported in 63% of ciclopirox patients, compared to 34% of those receiving vehicle[38].

Ciclopirox 0.77% gel formulation has also proven effective in the treatment of moderate seborrheic dermatitis when compared with vehicle in a multicenter, randomized, double-blind, vehicle controlled study. Within a 28 day treatment period, there was rapid and significant improvement in the patients who used ciclopirox 0.77% gel. Excellent improvement, or complete clearing was experienced by 53% of ciclopirox patients. The first signs of improvement were seen as early as 2 weeks after the initiation of treatment[36].

Cosmetic acceptability was reported to be excellent in 29% of patients receiving ciclopirox gel for the treatment of moderate seborrheic dermatitis of the scalp[36]. A study comparing shampoo containing 1.5% ciclopirox olamine and 3% salicylic acid (CPO/SA) vs. 2% ketoconazole shampoo showed that both were effective for dandruff and seborrheic dermatitis, but only CPO/SA was effective in relieving the itching associated with seborrheic dermatitis of the scalp[39].

Adverse effects

Side-effects are rare while using ciclopirox for the treatment of superficial mycoses. The most common side-effects include burning sensation of the skin, irritation, redness, pain, or pruritus, which is reported in less than 5% of patients in most studies[8]. The gel formulation of ciclopirox contains isopropyl alcohol, which would explain a burning sensation experienced by patients applying gel for the treatment of interdigital tinea pedis[3]. Ciclopirox therapy is rarely discontinued due to adverse events.

There are very few reports of allergic contact dermatitis due to ciclopirox in adults and children[4,40]. A 50-year-old man with interdigital mycoses was being treated with ciclopirox olamine cream 1% and developed allergic contact dermatitis, which spread up to his shins; a secondary infection occurred. Treatment of the dermatitis and discontinuation of the ciclopirox produced clearing after 1 month[40].

Toxicity effects

Toxicity has been tested in several animal models. For acute toxicity screening, 1% ciclopirox olamine was applied to a shaved rabbit skin for 24 h. The animals showed no signs of local or systemic toxicity[4]. In a 20 day trial assessing long-term application toxicity effects in healthy rabbits, the maximal side-effect was reddening of the skin[4]. However, other data on the topical application of ciclopirox in guinea pigs and rabbits state that the cream has produced reversible epidermal changes with no systemic effects[8].

Numerous tests have been performed in animals to determine the carcinogenic, mutagenic and dysmorphogenic effects of topical, oral and subcutaneous administration of ciclopirox. In all studies, there was no potential for any of the above effects[4,8]. Teratogenicity and embryotoxicity tests also reported no effect[4].

Indications and usage

In the US, ciclopirox formulations are approved for use as topical therapy for superficial fungal infections. Ciclopirox olamine cream 1%, lotion 1%, and topical suspension 0.77% are indicated for use in tinea pedis, tinea cruris, and tinea corporis due to *T. rubrum*, *T. mentagrophytes*, *E. floccosum*, and *M. canis*, as wells as cutaneous candidiasis due to *C. albicans*, and pityriasis versicolor due to *M. furfur*[20,41]. Ciclopirox 0.77% gel is indicated for use in the treatment of interdigital tinea pedis and tinea corporis due to *T. rubrum*, *T. mentagrophytes*, and *E. floccosum* as well as topical treatment of seborrheic dermatitis of the scalp[42]. There is little information on the safety of ciclopirox in children under 10 years of age and it is not known whether any drug is excreted in the breast milk of nursing mothers, so caution should be taken when treating these groups of people[20]. Any individual who has shown hypersensitivity to any of its components should not use ciclopirox[20].

In dermatophytosis of the skin, ciclopirox cream, lotion or gel should be gently rubbed into the affected area and surrounding skin twice daily[8]. It is recommended that a 4 week duration of therapy be used for treatment with ciclopirox gel[36,42]. Clinical improvement should occur within the first week of treatment, and if it has not, the diagnosis should be re-examined[8].

Conclusion

Ciclopirox is a broad-spectrum antifungal agent that also has anti-inflammatory properties and activity against Gram-positive and Gram-negative bacteria. This makes it a useful agent for inflamed skin infections and dermatophytoses with secondary bacterial infection. Ciclopirox has a rapid effect, as reported in clinical trials in which ciclopirox was superior to its vehicle and other antifungal agents. Ciclopirox gel 0.77% is a new formulation that has had promising results in the treatment of interdigital tinea pedis and seborrheic dermatitis of the scalp. Ciclopirox olamine cream 1% has been effective

in the treatment of tinea infections, cutaneous candidiasis, pityriasis versicolor, and seborrheic dermatitis.

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