Review

Ciclopirox: an overview

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Drug names
ciclopirox olamine: Loprox, Penlac nail lacquer, Batrafen (in Europe)
clotrimazole: Lotrimin, Mycelex, Fungoid
econazole: Spectazole
fluconazole: Diflucan
ketoconazole: Nizoral
miconazole: Monostat-Derm
naftifine: Naftin
oxiconazole: Oxistat
terbinafine: Lamisil
tioconazole: Vagistat-1

Introduction

Ciclopirox is a hydroxypyridone derivative which differs in structure and mechanism of action from the other known antifungal agents.[1] Ciclopirox is the ethanolamine salt of 6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridone.[2] It is a synthetic antifungal agent with a broad spectrum of *in vitro* activity.[3,4] Ciclopirox olamine 1% is equivalent to 0.77% of the free acid form (ciclopirox 0.77%). The clinical strengths are identical. The percentage content is a weight-based calculation and the olamine moiety weighs more but does not add to the antifungal effect.

Mechanism of action

Ciclopirox does not affect sterol synthesis. It may act through the chelation of trivalent metal cations, such as Fe^{3+}, 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.[1] Ciclopirox also inhibits metal-dependent enzymes, such as catalase and peroxidase, which play a part in the intracellular degradation of toxic peroxides.[1]

Another site of action of ciclopirox appears to be the cell membrane. Using a freeze–fracture technique, it has been shown that ciclopirox may modify the plasma membrane of dermatophytes and *Candida albicans*.[5] Also, in patients with pityriasis versicolor treated with ciclopirox, electron microscope examination has demonstrated damage to the cell membranes and disorganization of internal structures.

With *C. albicans* and *Saccharomyces cerevisiae*, ciclopirox blocks the transmembrane transport of radiolabeled leucine. In fact, when ciclopirox is at the minimal inhibitory concentration (MIC) for *C. albicans*, greater than 90% of leucine accumulates in the intracellular amino acid pool.[6] At higher concentrations of ciclopirox, the integrity of the cell membrane of susceptible organisms is affected with leakage of potassium ions and other intracellular material.[6]

In vitro antifungal activity

Ciclopirox can be both fungistatic and fungicidal.[6] The *in vitro* activity is against a broad spectrum of fungal organisms. The genera include dermatophytes, yeasts, dimorphic fungi, eumycetes, and actinomycetes.

For many organisms including dermatophytes (*Trichophyton* species, *Epidermophyton* species, *Microsporum* species) and yeasts (*Candida* species), the MIC is in the range 0.9–3.9 μg/mL when the culture medium is Sabouraud's dextrose that contains beef peptone which is free of certain metals.[1] Some other fungi and selected strains of aspergilli have a higher MIC, such as 7.8 and 15.6 μg/mL.[1,6]

In a pig skin model, the activity of various topical antifungal compounds, each containing the 1% active ingredient, was evaluated.[7] Ciclopirox cream was observed to be substantially more active than oxiconazole, naftifine, and bifonazole creams.[8] In this model, after the compounds had penetrated the skin for 3 h, at the level of the lowest layer of the stratum corneum, adjacent to the stratum granulosum, ciclopirox 1% cream demonstrated inhibitory and fungicidal effects of 93% and 98%, respectively. The other antimycotics were found to have less than 50% activity compared with controls.[7]

Other *in vitro* studies have investigated the relative activity of ciclopirox 1% cream compared to other topical antifungal agents. Ciclopirox cream 1% and lotion 1% have been reported to have a fungicidal activity against *Trichophyton mentagrophytes* that is superior to the other active agents.[9] Fresh and frozen human and pig skin specimens were inoculated with *T. mentagrophytes* and incubated for 48 h. The following were applied to the skin surface: ciclopirox olamine cream 1%, oxiconazole cream 1%, naftifine cream 1%, and bifonazole cream 1%, with untreated skin samples being used as controls. The horny layer of skin was scraped off, homogenized and plated onto Kimmig agar after 18 h. Following a 96-h incubation period, the number of colony forming units (CFUs) was determined. For untreated skin specimens, CFUs were determined prior to the start of therapy. The various antimycotics demonstrated the following fungicidal activity: ciclopirox cream 1% > naftifine cream 1% > oxiconazole cream 1% > bifonazole cream 1%.[9]

The activity of the different topical antifungal agents against *C. albicans* was measured using the ultrafiltration tissue activity test.[7] The topical agents of interest were applied to the stratum corneum of excised porcine skin. Three hours following application, the skin specimen was stripped to the deeper layer (10 strippings) and then covered with a dry, thin dialysis membrane followed by two thicker membranes that had been inoculated with *C. albicans*. The preparations were placed side by side and incubated for 18 h. The fungal material was rinsed off and plated on Kimmig agar plates enabling the number of CFUs to be determined. Controls were untreated specimens and those treated with cream vehicle. The candicidal activity of antifungal compounds in the deeper stratum corneum layers of pig skin was: ciclopirox olamine cream 1% > tioconazole cream 1% > oxiconazole cream 1% > miconazole cream 2% > econazole cream 1% > clotrimazole cream 1% > bifonazole cream 1% > naftifine cream 1%.

In vitro antibacterial activity

Ciclopirox has *in vitro* activity against many Gram-positive and Gram-negative bacteria.[9] The activity of ciclopirox against Gram-negative strains is an advantage over some azoles, the latter being more active against Gram-positive bacteria. The broad spectrum activity of ciclopirox, which includes both fungal organisms and Gram-negative infections, is of particular advantage in the treatment of macerated tinea pedis. In this presentation, infection due to *Proteus* species and *Pseudomonas aeruginosa* may be present. Enzymes such as elastase and proteases produced by these bacteria enhance their penetration into the stratum corneum which, in turn, may facilitate invasion of other organisms, e.g. fungi including dermatophytes, nondermatophyte molds, and *Candida* species.

The antibacterial spectrum of activity of ciclopirox also extends to *Propionibacterium acnes* and *Corynebacterium minutissimum* (data file, Medicis Pharmaceutical Corp.).

Penetration through skin

Animal studies have demonstrated good penetration of ciclopirox through skin. In pig skin experiments, excised skin from the back of slaughtered pigs was shaved and kept on water agar.[10] Cream was applied to the skin surface and, following prespecified intervals, adhesive tape strippings were obtained to expose the deeper layers of the stratum corneum. Subsequently, the stripped skin surface was inoculated with microconidia of *T. mentagrophytes*. When the contact time of application of cream to pig skin was 30 min, complete inhibition of fungal activity was observed in only the most superficial layer of skin, the stratum corneum, that had not undergone any stripping. In the layer of skin that had undergone two strippings (representing approximately four layers of stratum corneum), there was 95.98% inhibition of fungal activity. With six strippings (i.e. in the layer close to the stratum lucidum), the corresponding inhibition was 49.3%. After a contact time of 120 min, the percentage inhibition of fungal activity in the most superficial layer (no stripping performed) was 100%. Following two strippings and six strippings, the corresponding inhibition of fungal activity was 100% and 99.99%, respectively.[10]

In vivo human studies have been performed to evaluate the penetration of 1% ciclopirox olamine cream. In 10 healthy volunteers, 1% ciclopirox cream was applied to the forearm.[10] From each site, 20 successive strips were obtained. Previous studies had indicated that, after the 20th stripping, the stratum lucidum would be reached. The 20 strippings were collected in groups of five enabling them to be stratified into four layers of progressive depth. Following a contact time of 2 h between the cream and the forearm, a high concentration of drug was detected in the most superficial layer with low levels in the two deepest layers. After a contact time of 6 h, the concentration of

ciclopirox in the most superficial layer was 2.1–9.2 μg/mL. The trend was towards a decrease in the concentration of the drug in the deeper layers of skin. The concentrations of the drug in the four layers from superficial to deep were 4.1, 2.6, 1.6, and 2.1 μg/mL, respectively.[10]

In humans, studies with radiolabeled 1% ciclopirox olamine solution in polyethylene glycol 400 demonstrated an average of 1.3% absorption of the dose when it was applied topically to 750 cm^2 on the back followed by occlusion for 6 h.[3] The biological half-life was 1.7 h. The excretion was renal and 2 days after application only 0.01% of the dose was detected in the urine.[3] There was negligible excretion in the feces.

In human cadaverous skin from the posterior trunk, ciclopirox has been demonstrated to have good penetration. Application of ciclopirox to skin results in levels of drug that exceed the MIC for sensitive organisms in the epidermis and the dermis.[9] Ciclopirox olamine cream 1% with radiolabeled ciclopirox olamine reveals that 1.5–6 h following application there is 0.8–1.6% of the dose in the stratum corneum, with levels in the dermis being 10–15 times the MIC.[3,4]

Ciclopirox penetrates into the hair and into the sebaceous glands via the epidermis and hair follicles.[3,4] Also, the drug exhibits a reservoir effect with a portion remaining in the stratum corneum.

Ciclopirox olamine cream 1% is not associated with delayed hypersensitivity-type contact sensitization, irritation, phototoxicity, or photocontact sensitization.[3,4]

Kligman *et al.*[11] used a shortened modification of Dittmar's *in vitro* human skin assay to predict the efficacy of topical antifungal agents against *T. mentagrophytes*.[12] Cadaver skin was treated with the test agents for 4 h or 24 h. After heat separation of the epidermis at 60 °C for 1 min, the undersurface was point inoculated with a spore suspension of *T. mentagrophytes*. In untreated skin, fluffy colonies that were 3 μm in size developed following incubation for 4–5 days. Application of ciclopirox, econazole, and tolnaftate produced complete inhibition of growth. On the other hand, haloprogin, undecylenate, and hydroxyquinoline in proprietary form were inactive.

Anti-inflammatory activity[9,13–16]

Ciclopirox has anti-inflammatory activity. It may inhibit prostaglandin and leukotriene synthesis in human polymorphonuclear cells. Topical anti-inflammatory activity may be determined using the arachidonic acid-induced ear edema assay. Ciclopirox significantly reduces arachidonic acid-induced ear edema as measured by the percentage change from control inflamed ears. This was at a rate more than twice that observed with naftifine, ketoconazole, fluconazole, or miconazole, and similar to that of the anti-inflammatory agents indomethacin and desoximetasone.[9,15]

Another study, the modulation of prostaglandin E_2 (PGE_2) release (cyclooxygenase metabolite), also supports the anti-inflammatory properties of ciclopirox.[15] In this study, ciclopirox caused a significant reduction (25%) in PGE_2 release, compared to a minimal reduction by naftifine and fluconazole, and no inflammatory activity by ketoconazole and miconazole.

The comparative ability of antifungal preparations to suppress the expected delayed erythema response following *in vivo* human exposure to ultraviolet B (UVB) irradiation generated by a solar simulator was assessed using a double-blind protocol. The most anti-inflammatory preparation was ciclopirox, followed by the allylamines (naftifine and terbinafine), azoles (ketoconazole, oxiconazole, econazole), and 2.5% hydrocortisone.[14]

Ciclopirox may be an antifungal treatment with an inherent anti-inflammatory effect.[16] In a study comparing ciclopirox olamine 1% cream with ciclopirox 1%–hydrocortisone acetate 1% cream in the treatment of inflamed superficial mycoses, both were applied twice daily for 21 days in a randomized, double-blind, parallel group manner. On day 28 (1 week post-treatment), mycologic cures in the two groups were not significantly different. The authors of the study commented that ciclopirox may have both a broad spectrum antifungal activity as well as anti-inflammatory activity, the latter being similar to that of a mild corticosteroid, but without the side-effects associated with corticosteroids.

Efficacy of ciclopirox olamine in the treatment of superficial fungal infections

Ciclopirox has been shown to be effective in the treatment of cutaneous infection caused by dermatophytes (*T. rubrum*, *T. mentagrophytes*, *Microsporum canis*, and *Epidermophyton floccosum*) and yeast infections (*Malassezia furfur* and *Candida* species).[16–31]

In vehicle-controlled studies, ciclopirox was significantly superior to vehicle.[20]

Tinea corporis/cruris

The results of two multicenter, double-blind, parallel group trials reported the effectiveness of ciclopirox in the treatment of tinea corporis/tinea cruris.[28] In one study, ciclopirox olamine cream 1% (ciclopirox 0.77%) was compared with the cream vehicle, and in the other trial ciclopirox olamine cream 1% was compared with clotrimazole cream 1%. Treatment consisted of twice daily applications for 4 weeks followed by a 2-week post-treatment period during which the patients were

evaluated while off antifungal therapy. After the first week of treatment, and through to the end of the trial, ciclopirox olamine cream 1% was significantly more effective than the vehicle alone. At the final post-treatment visit (either 1 or 2 weeks post-treatment), the mycologic response rates in the ciclopirox olamine 1% and vehicle groups were 47/66 (71%) and 26/66 (39%), respectively. The overall response rates in the two groups were 40/66 (61%) and 10/66 (15%), respectively.[28]

In the group of patients with tinea corporis/tinea cruris treated with either ciclopirox olamine 1% or clotrimazole 1%, at the final post-treatment visit (either 1 or 2 weeks post-treatment), the mycologic response rates in the ciclopirox olamine and clotrimazole groups were 25/33 (76%) vs. 27/36 (75%), respectively. The overall response rates in the two groups were 20/33 (63%) and 26/36 (71%), respectively.[28]

Tinea pedis

Multicenter, double-blind, parallel group studies have also demonstrated the efficacy of ciclopirox in the treatment of tinea pedis in humans.[29] In one study, ciclopirox olamine cream 1% (ciclopirox 0.77%) was compared against the vehicle; in another study, ciclopirox was compared against clotrimazole. The creams were applied twice daily for 4 weeks. At all visits, there was a better clinical response in patients treated with ciclopirox cream compared to those using the vehicle. In the ciclopirox group, significantly better results were observed compared to vehicle in the clinical cure rates from visit 3 through to the post-treatment visits, 1 or 2 weeks after completing active therapy. At week 6 (2 weeks following discontinuation of active therapy), in the ciclopirox and vehicle groups, clinical cure, with KOH and culture conversion from positive to negative, was 40/71 (56%) and 6/73 (8%), respectively.[29]

When ciclopirox and clotrimazole were used to treat tinea pedis, more patients in the ciclopirox group achieved clinical cure compared to clotrimazole.[29] In fact, the differences in clinical cure were significant at visits 2 and 3 (during therapy) and at visits 5 and 6 (post-treatment). Also, significantly higher proportions of patients treated with ciclopirox had clinical and mycologic cures at visits 2, 3, 5, and 6 ($P \leq 0.05$). At week 6, the combined clinical and mycologic cure in the ciclopirox group was 33/43 vs. clotrimazole 37/42 ($P \leq 0.05$).

Cutaneous candidiasis

Ciclopirox olamine 1% cream (ciclopirox 0.77%) is also effective in the treatment of cutaneous candidiasis. In randomized, double-blind studies, the active drug ciclopirox or vehicle was applied twice daily for 4 weeks with a follow-up for 1–2 weeks afterwards.[30] By the final post-treatment visit, mycologic and clinical cures were observed in 74% of patients treated with ciclopirox and 12% treated with vehicle. In another double-blind randomized study, ciclopirox olamine cream 1% or clotrimazole cream 1% was applied twice daily for 4 weeks. At the end of treatment, 60% of the patients in the ciclopirox group ($N = 48$) and 50% of patients applying clotrimazole ($N = 48$) were observed to have clinical and mycologic cure. When evaluated 2 weeks post-treatment, 74% of patients in the ciclopirox group ($N = 42$) and 60% of patients in the clotrimazole group ($N = 43$) were cured both clinically and mycologically.

Pityriasis versicolor

Ciclopirox olamine cream 1% (ciclopirox 0.77%) applied twice daily for 14 days is effective and safe in the treatment of pityriasis versicolor. In a randomized, double-blind parallel group study, ciclopirox olamine cream 1% was significantly more effective than vehicle alone after 1 and 2 weeks of therapy, and at 1 and 2 weeks post-therapy.[31] Following 2 weeks of therapy, 49% of 73 patients using ciclopirox were clinically and mycologically cured compared to 24% of 72 patients applying the vehicle ($P < 0.0001$). In an active comparative study between ciclopirox cream 1% and clotrimazole cream 1%, a double-blind, randomized protocol was used with each cream being applied for 2 weeks. At the end of active therapy, clinical and mycologic cures were observed in 77% of patients applying ciclopirox cream vs. 45% using clotrimazole cream. When evaluated 2 weeks following therapy, a combined response had occurred in the ciclopirox and clotrimazole groups in 86% and 73% of cases, respectively.

Summary of clinical studies

In several controlled, multicenter studies lasting 6 weeks, the mycologic cures and clinical improvement in subjects treated with ciclopirox were statistically significantly higher than vehicle for the following indications: tinea pedis, tinea corporis/cruris, and cutaneous candidiasis.[7,11,15,28–30] Furthermore, in a 4-week, controlled, multicenter study, the mycologic cure rate and clinical improvement in pityriasis versicolor was significantly greater with ciclopirox compared with the vehicle.[31] In comparative studies, the clinical improvement after 1 week of treatment with ciclopirox was superior or similar to that observed with clotrimazole.[7,11,30,31]

Adverse effects

Ciclopirox olamine cream 1% (ciclopirox 0.77%) is generally extremely well tolerated. In 514 patients applying the active cream, there was pruritus at the application site in one patient and worsening of the symptoms and signs in another.[3] In 296 patients applying the vehicle, there was worsening of the clinical symptoms and signs in one patient.

Indications and usage

In the USA, ciclopirox olamine cream 1%, lotion 1% and gel 1% (ciclopirox 0.77%) are indicated as topical therapy for dermal infections manifesting as tinea pedis, tinea cruris, and tinea corporis caused by *T. rubrum*, *T. mentagrophytes*, *E. floccosum*, and *M. canis*, and candidiasis due to *C. albicans*.[3] The cream should be applied twice daily, with clinical improvement, including relief from pruritus, generally occurring within the first week of application. The diagnosis should be re-evaluated if no clinical improvement is observed within 4 weeks of starting therapy. Ciclopirox cream is also indicated for the treatment of pityriasis versicolor with clinical and mycologic improvement occurring following 2 weeks of treatment. Ciclopirox cream/lotion/gel formulations are not indicated for the treatment of onychomycosis. The safety and efficacy of application in children less than 10 years of age have not been established.[3] Also, caution should be employed when using ciclopirox olamine in a nursing mother as it is not known whether this drug is excreted in breast milk.[3]

Conclusions

Ciclopirox is a topical antifungal which is a substituted pyridine. The mechanism of action is not related to that of the azoles or the allylamines. Ciclopirox is fungicidal *in vitro*. It is a broad spectrum antifungal agent with activity against some Gram-positive and Gram-negative bacteria. In both vehicle-controlled and active-controlled studies, ciclopirox olamine cream 1% (ciclopirox 0.77%) has been shown to be effective in the treatment of superficial fungal infections including tinea corporis/cruris, tinea pedis, cutaneous candidiasis, and pityriasis versicolor.

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