

Topical Ciclopirox Olamine 1%: Revisiting a Unique Antifungal

Abstract

The injudicious use of antifungals, indiscriminate use of corticosteroids for instant relief, persistence of predisposing factors like sweat retention and uncontrolled diabetes, and emerging resistance to antifungals across the globe have rendered the management of an erstwhile simple infection, the superficial cutaneous mycoses highly complicated and tricky. Ciclopirox is an old yet efficacious, versatile, and safe topical antifungal of the hydroxypyridone family. Despite its numerous beneficial properties over the majority of other topical antifungals, it remains underutilized.

Keywords: *Candida*, ciclopirox olamine, dermatophyte, mycoses, pityriasis versicolor, seborrheic dermatitis, tinea

Ciclopirox olamine (CPO) is a hydroxypyridone derivative that differs in structure and mechanism of action from the other known antifungal agents.^[1] This topical antifungal agent has been in use for over three decades and received its US-FDA approval in June 2004. The majority of extant literature revolves around its nail lacquer formulation used for the treatment of onychomycosis; however, its topical cream formulation remain grossly underutilized. The main focus of this article will be on the cream formulation. The pleiotropic effects and certain unique properties of CPO make a strong case for its resurgence as a topical antifungal.

The molecule exists in its free acid form known as ciclopirox and in its salt form as CPO. CPO 1% is equivalent to 0.77% ciclopirox.^[2] Ciclopirox remains the active compound, with no additional antifungal contribution by the olamine group. It is a broad-spectrum antifungal medication with additional antibacterial and anti-inflammatory properties (*vide infra*).

Hydroxypyridones, CPO being the prototype, are the sole class of topical antifungal agents that have a completely different mechanism of action than other topical antifungals (azoles and allylamines).^[3] It acts through the chelation of polyvalent metal cations, such as ferric (Fe^{3+}) and aluminum (Al^{3+}), thereby

causing inhibition of metal-dependent enzymes (cytochromes, catalase, and peroxidase) leading to disruption of cellular activities such as mitochondrial electron transport processes, energy production, and nutrient intake across cell membrane.^[3] It has also been known to alter membrane permeability causing blockage of intracellular transport of precursors. Many other mechanisms have also been postulated [Table 1].^[3-5]

In *in vivo* human studies conducted in healthy volunteers, after 2-h contact time of 1% CPO cream applied to the forearm, a high concentration of the drug was detected in the most superficial layer with low levels in deeper layers.^[6] CPO penetrates into the hair, and through the epidermis and hair follicles in the sebaceous glands, and dermis with a small portion remaining within the stratum corneum (reservoir effect). The systemic absorption of CPO after intravaginal application was found to be very low with an estimated absorption range of 7–9%.^[3]

CPO expresses one of the broadest spectra of antimycotic activity and inhibits nearly all clinically relevant dermatophytes, yeasts, and moulds, including certain frequently azole-resistant *Candida* species, such as *Candida glabrata* and *Candida krusei*.^[3] CPO can be both fungistatic and fungicidal depending on the concentration and the duration of contact with target organisms. CPO also shows fungicidal activity against

Sidharth Sonthalia,
Mahima Agrawal¹,
V. N. Sehgal²

Department of Dermatology and Dermatosurgery, Skinnocence, The Skin Clinic and Research Centre, Gurugram, Haryana, ¹Department of Dermatology and STD, LHMC and Associated Hospitals, ²Dermato Venereology (Skin/VD) Center, Sehgal Nursing Home, Panchwati-Delhi, India

Address for correspondence:
Dr. Sidharth Sonthalia,
Department of Dermatology and Dermatosurgery, Skinnocence: The Skin Clinic and Research Centre, Gurugram - 122 009, Haryana, India.
E-mail: sidharth.sonthalia@gmail.com

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Table 1: Postulated antimycotic mechanisms of action of ciclopirox

- Chelation of polyvalent metal cations, especially iron (Fe³⁺)
- ↓
- Inhibition of metal-dependent enzymes (cytochromes, catalase, and peroxidase)
- ↓
- Disruption of cellular activities such as mitochondrial electron transport processes, energy production, and nutrient intake across the cell membrane
 - Alteration of membrane permeability causing blockage of intracellular transport of precursors
 - Disruption of DNA repair, cell division signals, and disorganization of internal structures (mitotic spindles) of the fungi
 - At higher concentrations, compromising the integrity of the cell membrane of susceptible organisms followed by leakage of potassium ions and other intracellular material
 - Inhibitory effect on secreted aspartyl proteinases, important virulence factors for several types of *C. albicans* infections that favour the adhesion of the yeast to epithelial cells. This may be significant in the action against mucosal candidiasis

non-growing cells, which makes it a desirable antimycotic in onychomycosis where the slow growth of cells prolongs the duration of required therapy to many months.^[1,7] According to the results of Gupta and Kohli,^[4] for dermatophytes, CPO was considerably more effective against all species tested (110 strains of dermatophytes) than itraconazole and ketoconazole, being only minimally inferior to terbinafine. For yeasts (14 strains of *Candida*) and nondermatophyte moulds (9 strains), CPO was the most potent with lowest minimum inhibitory concentration (MIC) values for these fungi, compared with ketoconazole, itraconazole, and terbinafine. Another *in vitro* study comparing the activity of antifungal agents against dermatophytes revealed that ciclopirox had the second lowest MIC value after clotrimazole among the topical antifungals.^[8] CPO has also demonstrated low MIC values and high clinical efficacy against *Malassezia globosa* and *Malassezia restricta*, the predominant species involved in pityriasis versicolor and seborrheic dermatitis.^[4]

It also displays inhibitory effect over *Saccharomyces cerevisiae*, and some *Aspergillus* and *Penicillium* species, although selected strains of aspergilli have higher MIC values compared with dermatophytes.^[5]

CPO has *in vitro* activity against many gram-positive (*Staphylococcus* spp., *Streptococci*, *Micrococci*, among others) and gram-negative (*Proteus* spp. and *Pseudomonas aeruginosa*) bacteria.^[1,2,5] This combined antifungal and antibacterial activity is of particular advantage in the treatment of macerated tinea pedis and “dermatophytosis complex,” both conditions being symptomatic intertriginous fungal affections secondarily infected by bacteria. CPO also exerts activity against *Gardnerella vaginalis* and *Trichomonas vaginalis* while sparing *Lactobacilli* sp.,

making it a useful topical agent for multiple vaginal infections.^[3] It has also been shown to block HIV-1 infection at clinically relevant concentrations [Table 2].

CPO also possesses good anti-inflammatory activity that involves inhibition of prostaglandin and leukotriene synthesis in human polymorphonuclear cells. This is mediated by inhibition of 5-lipoxygenase and cyclooxygenase enzymes. It has been reported to be as potent as indomethacin and desoximetasone, and many *in vivo* studies have reported its anti-inflammatory activity to be superior to most of the other topical antifungals (naftifine, terbinafine, econazole, ketoconazole, miconazole, fluconazole, and oxiconazole).^[2,6,9]

In a double-blind protocol, CPO demonstrated the highest anti-inflammatory property (more than allylamines like terbinafine, azoles, and even 2.5% hydrocortisone).^[10] Anti-inflammatory activity of CPO 1% cream has been reported to be similar to that of a combination of CPO 1% and hydrocortisone 1% cream.^[11] The implication of the robust anti-inflammatory effect of CPO is its great potential to be used as a single-agent nonsteroidal preparation even for inflamed tinea. The prevalent counterfactual approach of many physicians in India of prescribing antifungal-steroid combination instead of plain antifungal to patients with tinea to provide rapid relief in pruritus is considered to have substantially contributed to the genesis of the emergent epidemic of antifungal therapeutic failures. Sharing the concept and facts that back the strong anti-inflammatory effect of CPO with such physicians may prove instrumental in checking this inappropriate prescribing behavior with a reduction in the incidence of cases of dermatophytosis worsened because of steroids.

Currently Available Formulations of Ciclopirox (In India)

- Shampoo (for seborrheic dermatitis) – Available in concentrations of 1% and 1.5%
- CPO (for dermatophytic and yeast infections) – 1% cream
- Nail lacquer (for onychomycosis) – 8% to be used daily over the affected nail(s).

The cream formulation, unfortunately, is not stable at room temperature and requires special excipients to make the drug stable and effective for topical use.

The standard recommended dose and duration of application of CPO 1% cream are listed in Table 3.^[12]

Indications and Efficacy of CPO 1% in the Treatment of Different Superficial Mycoses

Dermatophytic (tinea) infections

The results of two multicentric studies that compared CPO cream 1% (ciclopirox 0.77%) with the cream vehicle and clotrimazole cream 1%, respectively, in patients with tinea

Table 2: Nonfungal microorganisms (bacteria, viruses, parasitic agents etc.) against which ciclopirox displays inhibitory activity

Category of microorganism	Examples
Gram-positive bacteria	<i>Staphylococcus aureus</i> <i>β-haemolytic Streptococci (group A)</i> <i>Micrococcus luteus</i> <i>Micrococcus sedentarius</i> <i>Corynebacterium minutissimum</i> <i>Brevibacterium spp.</i>
Gram-negative bacteria	<i>Pseudomonas aeruginosa</i> <i>Proteus mirabilis</i> <i>Escherichia coli</i> <i>Klebsiella pneumoniae</i>
Other bacteria	<i>Mycoplasma spp.</i> <i>Gardnerella vaginalis</i>
Parasitic agent(s)	<i>Trichomonas vaginalis</i>
Viruses	HIV-1

Table 3: Standard recommended dosing and duration of application of ciclopirox olamine 1% cream in different indications

Indication	Application protocol	Duration of therapy
Tinea corporis/cruris	Twice-a-day	4 weeks
Tinea pedis	Twice-a-day	4 weeks
Pityriasis versicolor	Twice-a-day	2 weeks
Seborrheic dermatitis		
Twice-a-day		4 weeks
Maintenance with Once-a-day (optional/situational)		4 weeks
Vulvovaginal candidiasis		
Twice-a-day		4 weeks

corporis/cruris showed that the mycological and overall response rates were better in the CPO treated group compared with the vehicle alone while they were almost equal to the clotrimazole-treated group.^[13]

CPO demonstrated results superior to clotrimazole in tinea pedis. A prospective, randomized, double-blind, placebo-controlled 8-week clinical study of 100 patients in which ciclopirox gel applied once or twice daily significantly reduced the signs and symptoms, compared with the vehicle with much higher rates of mycologic cure, complete cure, and bacterial count reduction with CPO than the vehicle.^[14] The 2007 Cochrane review of topical antifungals for tinea pedis identified good evidence that CPO is efficacious relative to placebo in the management of fungal infections of the skin.^[15]

Inflammatory signs and symptoms of tinea pedis have also been shown to respond preferentially to CPO cream 1% as compared with clotrimazole cream 1% in a multicenter, double-blind study of 4 weeks of treatment. The differences

between treatment groups were especially marked early in the trial. Clinical response rate (improvement and cure) was significantly higher in the CPO group than in the clotrimazole group at week 1 (93% vs 71%, *P* value <0.001). At week 2, 26% of 43 patients in the CPO group had a clinical cure, whereas only 2% of those in the clotrimazole group experienced a clinical cure.^[16]

Pityriasis versicolor (PV)

CPO cream 1% applied twice daily for 14 days is a well-known efficacious and safe therapy for PV.^[17]

Seborrheic dermatitis (SD)

In a recent systematic review on topical treatments for facial SD published by Gupta and Versteeg, topical CPO was accorded a strong recommendation (Grade A practice recommendation) based upon its consistent efficacy established in multiple high-quality randomized controlled trials (RCTs).^[18] Various other comparative trials have established relatively superior efficacy, longer duration of persistence of improvement, and/or lesser adverse effects with the use of ciclopirox-based cream/shampoo compared with formulations containing ketoconazole.^[19-22]

Recently, CPO cream demonstrated superior results over placebo in reducing the severity scoring in the treatment of patients affected with atopic dermatitis of the head and neck who tested positive with immunoglobulin E antibodies to *Malassezia sympodialis* and/or *Malassezia furfur*.^[23]

Candidal infection – vulvovaginal candidiasis (VVC)

The overall incidence of Non candida albicans species (NCAS) causing VVC is on the rise; additionally, the resistance of *Candida albicans* as well as NCAS to azoles, polyenes, and now even echinocandins (invasive candidiasis) is becoming colossal. Formation of biofilms is a huge contributory factor towards drug resistance. CPO has traditionally been one of the most popular antimycotics for the treatment of vulvovaginal candidiasis.^[3] In addition to offering anti-fungal activity against all the major candidal species, CPO is claimed to be effective against azole-resistant *Candida* species also like *C. glabrata*, *C. krusei*, and *C. guilliermondii*. In addition to anticandidal efficacy, the additional inhibitory effect of CPO on *Gardnerella vaginalis* and *Trichomonas vaginalis* (*vide supra*) makes it an obvious choice over azoles in mixed infections of the female lower genitalia. The effects of CPO cream and pessaries have been found to be similar to miconazole and terconazole creams, and clotrimazole vaginal tablets, respectively.

Candidal infection – extravaginal

The RCT by Bagatell reported that 1% CPO cream demonstrated clear superiority of CPO over placebo and faster onset of improvement and better combined cure rates than clotrimazole.^[24]

Ciclopirox topical suspension 0.77% applied twice daily for 7 days to the affected diaper area in babies (6–29 months old) provided statistically significant improvement in severity scores as well as mycological cure.^[25]

A phase III study on the use of CPO cream in paediatric population reported excellent safety profile in 95% of the children, and 92% cases showed clinical improvement within a week of application. The authors concluded 1% CPO cream to be a safe and feasible treatment for superficial cutaneous mycotic infections, especially *Candida* spp. infection, in children aged between 3 months and 10 years.^[26]

Adverse Effects and Use in Special Situations

Local adverse events are infrequent and include a burning sensation, irritation, redness, pain, or pruritus, and have rarely led to discontinuation of therapy.^[3] Allergic contact dermatitis to CPO is rare excepting an anecdotal report.^[26] A recent review opines that CPO compares very well with oral antimycotic agents in terms of the benefit/risk ratio because of its excellent tolerability and complete absence of serious adverse effects.^[3] It is a pregnancy category B drug and safe to use in patients >10 years of age.^[27,28]

CPO could be the answer to the emerging antifungal resistance. Even after more than two decades of frequent use of CPO for tinea, PV, and VVC, not even a single case of clinical or *in vivo* resistance has been reported. Potential of dermatophytes for developing resistance to CPO by biochemical or molecular means is extremely low. The most plausible reasons behind the inability of superficial fungi (both dermatophytes and yeasts) of mounting or evolving mechanisms to resist CPO are its fungicidal mode of action, unique anti-fungal mechanism of action, and a steep dose–response curve.

In conclusion, the unique mechanism of action, *in vitro* and *in vivo* efficacy, broad-spectrum antimycotic coverage, additional anti-bacterial and anti-inflammatory activity, well-established safety and excellent tolerance, lack of drug resistance at present coupled with an extremely low likelihood of the development of resistance in future, and easy affordability make CPO 1% cream potentially an ideal topical antifungal for superficial cutaneous mycoses. However, there is a strong need to generate more and fresh evidence to assess its value in the current therapeutic armamentarium of dermatophytosis and other superficial cutaneous mycoses. Its versatility remains unexploited, especially in the wake of the pharmaceutical-driven focus on the development and sale of “newer azoles.” Most importantly, CPO can be instrumental in reducing the menace of steroid-abuse and management of treatment-refractory dermatophytic infections, tinea incognito, mixed infections, and recurrent VVC.

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Conflicts of interest

There are no conflicts of interest.

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