Topical Ciclopirox – Recalling a Forgotten Ally in the Fight against Cutaneous Mycoses

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Background:

The injudicious use of antifungals, unselective use of corticosteroids for direct relief, persistence of predisposing features like sweat retention, and uncontrolled diabetes, and developing resistance to antifungals across the globe have rendered the management of an erstwhile simple infection, the superficial cutaneous mycoses highly complicated and tricky. Ciclopirox (CPX) is an old yet efficacious, versatile, and safe topical antifungal of the hydroxypyridone family. Despite its numerous beneficial properties over majority of other topical antifungals, it is being under-utilized owing to aggressive focus and tactics of the pharmaceutical industry on promoting 'newer azoles'.

Focus:

In this lecture, I shall detail the numerous properties of CPX that make it a near ideal topical antifungal. The antifungal spectrum of ciclopirox is one of the broadest and includes nearly all clinically relevant fungi (dermatophytes, yeasts and moulds). It is also effective against many azole-resistant dermatophytes and Candida albicans and Non-albicans Candida spp. like C. glabrata and C. krusei. The mechanism of action of ciclopirox, a fungicidal agent, is different from that of other topical antifungals that usually inhibit ergosterol synthesis. The drug chelates trivalent metal cations especially iron resulting in inhibition of metal-dependent enzymes that protect the fungal cell by scavenging reactive oxygen species, disrupts cellular activities such as mitochondrial electron transport processes, blocks intracellular transport of precursors by cell membrane alteration, and disrupts DNA repair. This set of multilevel fungicidal mechanisms being unique to ciclopirox minimizes the possibility of development of drug resistance, which till date has never been reported clinically. The drug also has potent anti-bacterial (against Gram Positive as well as Gram Negative bacteria) and bears anti-inflammatory effects comparable to 2.5% hydrocortisone. Ciclopirox olamine 1% cream, equivalent to 0.77% ciclopirox penetrates into the deep layers of the skin, and mucosae. It is indicated for tinea, pityriasis versicolor, seborrheic dermatitis, vulvovaginal and cutaneous candidiasis, usually as twice-a-day application for 2-4 weeks. For onychomycosis, its 8% nail lacquer formulation is used. The topical drug is devoid of systemic adverse effects. Only mild transient local reactions have been reported in less than 5% of treated patients. It is perhaps one of the best and most versatile topical antifungal with potential of being instrumental in the management of frequently encountered rampant antifungal therapy failure.

Newer Horizons for CPX:

I shall end the lecture with the newfangled properties of topical CPX as the latest anti-bacterial topical being used in ICU patients with MDR cutaneous bacterial infections, as well as the potential role of ORAL CPX as a potent anti-cancer agent.

Ciclopirox olamine (CPO) is a hydroxypyridone derivative that varies in structure and mechanism of action from the further recognized antifungal agents. 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. 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). 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. It has also been known to alter membrane permeability causing blockage of intracellular transport of precursors. Many other mechanisms have also been postulated.

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. 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%.

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. 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 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. According to the results of Gupta and Kohli, for dermatophytes, CPO was considerably more effective against all species tested (110 strains of dermatophytes) than itraconazole and ketonazole, 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. 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.

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.

CPO has in vitro activity against many gram-positive (Staphylococcus spp., Streptococci, Micrococci, among others) and gram-negative (Proteus spp. and Pseudomonas aeruginosa) bacteria. 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. It has also been shown to block HIV-1 infection at clinically relevant concentrations.

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