Ciclopirox Delivery into the Human Nail Plate

XIAOYING HUI,[1] RONALD C. WESTER,[1] SHERRY BARBADILLO,[1] CHRISTINE LEE,[1] BHIKU PATEL,[2] MITCHEL WORTZMMAN,[2] EUGENE H. GANS,[2] HOWARD I. MAIBACH[1]

[1]Department of Dermatology, University of California–San Francisco, 90 Medical Center Way, Surge 110, Box 0989, San Francisco, California 94143

[2]MEDICIS Pharmaceutical Corp., Scottsdale, Arizona 85258

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ABSTRACT: The human nail penetration of the antifungal ciclopirox was determined for marketed gel containing 0.77% of ciclopirox, an experimental gel containing 2% of ciclopirox, and a marketed lacquer containing 8% of ciclopirox. After 14 days dosing, unabsorbed drug remaining on the surface, drug within the infection-prone area, and the amount that had penetrated through the nail were determined. Ciclopirox delivery into and through the nail was significantly greater from the marketed gel, than from either the experimental gel or the nail lacquer ($p < 0.05$). In addition, the surface nail contained more unabsorbed drug from the lacquer. Further, the drug penetrating into and through the nail was also greater from the marketed gel, leading to a higher Calculated Efficacy Coefficient for the marketed gel, than from the marketed lacquer or the experimental gel. The formulation plays an important role in the enhancement of ciclopirox permeation into and through the human nail plate, and the concentration of ciclopirox in the formulation was not a factor in determining penetration. J Pharm Sci 93:2545–2548, 2004

Keywords: nail; topical formulation; ciclopirox; deep nail concentration; antifungal

INTRODUCTION

Topical therapy of onychomycosis is limited by the infection's deep-seated nature, by the nail's unique properties, its thickness, and relatively compact construction, and by the ineffective penetration of the deep nail plate by topically applied drugs.[1,2]

To achieve an effective chemical concentration into/through the human nail plate, a successful local therapy of onychomycosis is dependent on choosing an appropriate antifungal drug coupled with a method of delivery. This method should maximize the effect of the active principle by aiding its diffusion into the nail bed at levels exceeding the minimum inhibitory concentration against local infection by dermatophytes and yeasts. Ciclopirox has a low molecular weight (207.27) that may benefit the drug penetration into the nail plate and it is lipophilic ($\log P = 2.73$).[3] Thus, a suitable carrier may be needed to enhance drug penetration through the nail barrier. Nail lacquer formulation is a popular choice for nail topical antifungal treatment, and traditional topical formulations such as gel or cream can provide a chemical gradient to drive drug flux as the drug is released. This study describes ciclopirox *in vitro* penetration into the human nail from two gel formulations and a lacquer formulation.

MATERIALS AND METHODS

Chemicals and Formulations

[Pyridinone-6-^{14}C]-ciclopirox was obtained from Perkin-Elmer Life Science (Boston, MA). The radiochemical purity and specific activity of the chemical were determined by HPLC as >99% and

Correspondence to: Xiaoying Hui (Telephone: 415-502-7761; Fax: 415-753-5304; E-mail: xhui@itsa.ucsf.edu)

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43.87 mCi/mmol, respectively. The two gel formulations marketed gel (Loprox Gel) containing 0.77% ciclopirox and experimental gel containing 2% ciclopirox and the lacquer (Penlac™, Dermik Laboratories, Inc., Collegeville, PA) containing 8% ciclopirox were received from MEDICIS Pharmaceutical Corporation (Scottsdale, AZ). The formulations are detailed in Table 1. A trace amount of [^{14}C]-ciclopirox was added to each formulation and mixed thoroughly. Triplicated aliquots were collected each time before the first dosing, after 7 days and 14 days during the dosing period to examine the homogeneity of radioactivity in each formulation.

Experiment Procedures

Details of the nail incubation have been given previously.[1,2] Briefly, a healthy nail plate was mounted in a one-chamber diffusion cell (Permegear, Inc., Hellertown, PA) with the nail surface (top center) open to the air and the inner surface made contact with a small cotton ball acting as a nail-supporting bed. The supporting cotton ball under the nail was wetted by normal saline providing moisture for the nail plate, and the degree of hydration was monitored and controlled during the experiment. The incubation period started 24 h prior to the first dose, and ended 24 h after the final dose. Ten-microliter aliquots containing 0.34 μCi of radioactivity were applied to the surface of the nail plate twice daily, approximately 8 h apart for 14 days. Starting on the second day, each morning before dosing, the surface of the nail was washed with cotton tips in a cycle, as follows: two times with ethanol, then with 50% Ivory® liquid soap (Procter & Gamble, Cincinnati, OH), then two times with distilled water. The washing samples from each cycle were pooled and the radioactivity was measured. After completion of the dosing and the incubation phase, the nail plate was transferred to a cutting holder for sampling. Under the controlled humidity and temperature, we did not observe any abnormal situations such as the nail plate color change, hydration changes, or fungal growth during the 14-day dosing period. The nail plate was secured in position so that the outer dorsal-dosed surface faced the holder. The cutting holder was moved to bring the plate surface just barely in contact with the cutter tip. The drill was then turned on and a fine adjustment moved the stage toward the cutter tip, removing a powder sample from the nail. In this way, a hole approximately 0.3–0.4mm in depth and 7.9 mm in diameter was drilled in each nail, enabling the harvest of powder sample from the center of each nail's ventral surface. These samples are referred to as samples taken from the "ventral/intermediate nail plate center." Then the nail outside the dosing area (and also the sampling area) was cut away and saved as the "remainder nail plate." The layer above the sampling area where the powder samples were also saved as "the dorsal/intermediate center" (Fig. 1). All the nail plate samples were individually collected into a glass scintillation vial and weighed. The nail samples were dissolved and then radioactivities were counted.

Table 1. Formulations

Name	Marketed Gel	Experimental Gel	Lacquer
Ciclopirox concentration	0.77%	2%	8%
Form	Gel	Gel	Lacquer
Vehicle	Octadecanol Dimethicone copolyol Carbomer® Isopropyl alcohol Sodium hydroxide Docusate sodium Purified water	Propylene glycol EDTA Urea Citric acid BHT Hydroxypropyl cellulose Ethyl alcohol Purified water	Ethyl acetate Isopropyl alcohol Butyl monoester of polymethylvinyl ether/maleic acid
Dose (Ciclopirox equivalent/10 μL)	53 μg	136 μg	584 μg

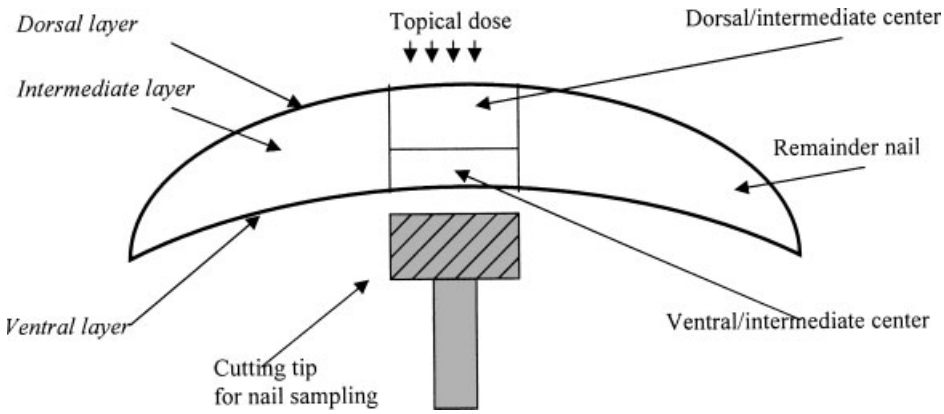

Figure 1. Diagram of a human nail plate and a cutting tip.

RESULTS AND DISCUSSION

Mass balance of this study shows near complete dose accountability (range 94–103%).

Table 2 shows after weight normalization that with the marketed gel group the concentration of ciclopirox equivalent in ventral/intermediate center nail samples was 0.55 ± 0.28 μg eq/mg nail, and the ciclopirox equivalent in the supporting bed cotton ball was 46.26 ± 4.08 μg eq/mg. These were significantly higher than those from the experimental gel and lacquer groups, respectively ($p < 0.05$). On the top surface of the dosed site (dorsal/intermediate center), the concentration of unabsorbed ciclopirox equivalent from the lacquer group was significantly higher than that from the marketed gel and experimental gel groups ($p < 0.05$). It could be of clinical significance that the marketed gel with 0.77% ciclopirox delivered much more drug than the nail lacquer with 8% ciclopirox. Whether the gel formulation would perform as well or better in clinical use where patient function such as socks may alter surface dose is not known. What is known is that this study

Table 2. Summary of Weight Normalized Ciclopirox Equivalent in Nail and Supporting Bed Samples after 14-Day Treatment

Items (Unit)	Normalized Ciclopirox Equivalent[a]			Significant (if p-Value < 0.05)
	Marketed Gel	Experimental Gel	Lacquer	
Dorsal/intermediate center within surface of nail (μg eq/mg)	71.70 (16.79)	103.36 (38.05)	2162.09 (526.44)	Lacquer versus experimental gel Lacquer versus marketed gel
Ventral/intermediate center within infection-prone area (μg eq/mg)	0.55 (0.28)	0.19 (0.11)	0.31 (0.08)	Marketed gel versus lacquer Marketed gel versus experimental gel Experimental gel versus lacquer
Remainder nail (μg eq/mg)	51.97 (62.44)	49.70 (71.95)	563.42 (709.61)	Not significant
Penetration through the nail into the supporting bed cotton ball (μg eq/sample)	46.26 (4.08)	5.96 (1.26)	15.48 (3.06)	Marketed gel versus lacquer Marketed gel versus experimental gel Experimental gel versus lacquer

[a]The data represents the mean (SD) of each group ($n = 5$).

Table 3. Ciclopirox Concentration and Relative Antifungal Efficacy of Three Formulations[a]

Parameters	Marketed Gel	Experimented Gel	Lacquer
Ciclopirox in the deeper layer ($\mu g/cm^3$)	727 (372)	249 (152)	407 (106)
Efficacy coefficient $E_D(MIC_D = 0.04\ \mu g/mL)$[b]	18,175	6225	10,175
Efficacy coefficient $E_V(MIC_V = 0.05\ \mu g/mL)$[b]	14,540	4980	8140

[a]The data represents the mean (SD) of each group ($n = 5$).
[b]See ref. 4.

and previous studies show antifungal drug delivery into the inner human nail plate where the disease resides is formulation dependent, and that antifungal drug delivery can be altered with formulation and delivery enhancers.

Table 3 shows the mean value of the minimum inhibitory concentration (MIC) of ciclopirox for dermatophytes species is 0.04 μg/mL and for yeast species 0.05 μg/mL.[4] After 14 days of exposure, the ciclopirox content measured from the marketed gel was 0.55 ± 0.28 μg/mg for the ventral/intermediate layers. This content, multiplied by the density of the nail sample (1.332 mg/cm^3, measured under current experimental conditions), yields 727 ± 372 $\mu g/cm^3$ of ciclopirox, 18,175 times the MIC for most dermatophytes species and 14,540 times the yeast species (Table 3). The results suggest that the enhanced level of ciclopirox from the marketed gel in the ventral/intermediate layers and supporting bed dramatically exceeds the minimum inhibitory concentration of ciclopirox for most common onychomycosis organisms.

The concentration of ciclopirox was not a factor in determining penetration, but only the nature of the vehicle, with the marketed gel better than that of the lacquer and experimental gel formulation. We do not wish to over interpret these onychokinetic studies; ultimately, clinical confirmation is required. Yet, from other drug delivery experience (blood levels, etc.), enhanced delivery often correlates with enhanced efficacy.

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