[BRIEF REPORT]

Penetration of (^{14}C)-Efinaconazole Topical Solution, 10%, Does Not Appear to be Influenced by Nail Polish

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ABSTRACT

Onychomycosis is a common nail disorder with significant medical impacts and aesthetic consequences. Patients seek treatment for several reasons, including the unsightliness of the nail(s). Even with successful management, it takes months for the diseased nail to appear cosmetically normal. Patients commonly apply nail polish to mask the appearance of the dystrophic nail, though it is contraindicated with the currently available topical lacquers for onychomycosis. The authors' nonclinical study using a cadaver nail model showed that penetration of efinaconazole topical solution, 10%, a new antifungal being developed for the treatment of mild-to-moderate toenail onychomycosis, was not influenced by application of nail polish. Polishes showed an increase in surface tackiness with repeated efinaconazole topical solution, 10% application. The medical and aesthetic significance of the authors' findings have yet to be assessed clinically.
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Onychomycosis is a common, progressive nail disorder that often involves several nails.[1–4] The disease is unsightly and may be uncomfortable or painful. Sufferers commonly apply colored nail polishes to conceal the diseased appearance of their nails rather than seeking treatment, even though without effective treatment this practice is likely to worsen the condition of the nails.

Onychomycosis requires treatment, as it can lead to progressive destruction and deformity of the nails.[5,6] It can also serve as a source for more widespread fungal infection, spreading to other digits, body areas, or even close contacts, such as family members.[7] Patients will often seek medical intervention for onychomycosis because of its aesthetic impact.[8] Studies have shown that more than 90 percent of patients feel that others view infected nails as unpleasant to look at, and 44 to 74 percent of patients feel embarrassed.[9–11] This embarrassment is more prevalent and severe in women[2,12] and younger people, where appearance is of greater importance to their personal relationships.[11] In this way, onychomycosis has a negative impact on a patients' social and professional lives and their sense of well-being.[13]

Successful treatment of onychomycosis is a long-term process. Clinical results appear after months, as it takes time for a clear nail to grow from the nail matrix. In the short term, therapies do little to alleviate the embarrassment of a dystrophic nail. However, use of colored nail polish during active treatment is not recommended with currently available topical products (ciclopirox or amorolfine), as both nail lacquers require frequent nail debridement.

Efinaconazole topical solution, 10%, is a new topical antifungal with unique physicochemical properties, potent antifungal activity, and a low surface tension formulation,[14] which are all believed instrumental in enhancing penetration and achieving clinical success. The ability of efinaconazole topical solution, 10%, to penetrate the nail coated with nail polish has not been studied.

The objective of this study was to compare the *in vitro* nail absorption of radiolabeled efinaconazole through

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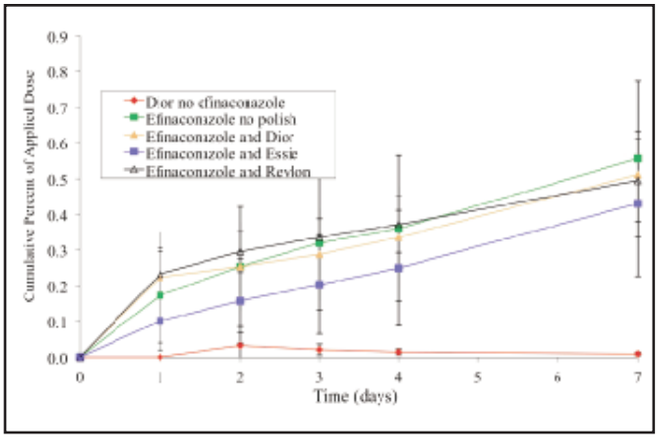

Figure 1. Cumulative permeation of (^{14}C)-efinaconazole, 10%, solution in the receptor phase. Percent of applied dose, mean ± SD

TABLE 1. Cumulative permeation of (^{14}C)-efinaconazole, 10%, solution in the receptor phase

NAIL POLISH TREATMENT	CUMULATIVE AMOUNT OF EFINACONAZOLE IN RECEPTOR (SD) AT STUDY END (DAY 7) µg/CM^2
No nail polish	17.6 (7.0)
Dior (999 Red Royalty)	16.1 (6.1)
Essie (488 Forever Yummy)	13.6 (6.4)
Revlon (550 Cherry)	15.6 (3.6)

human nails that have been coated with cosmetic nail polish to those left uncoated.

METHODS

Human cadaver thumbnails (Science Care), free of apparent disease or pathology, were obtained from multiple donors. Nail thickness range was assessed by randomly measuring the nails at multiple sites using a snap gauge micrometer. Nails were then selected by size and thickness to assure sample-to-sample consistency. Test nails were placed in Bronaugh® chambers, rinsed with saline, wiped with acetone, and allowed to dry thoroughly prior to application of nail polish using standard application procedures. They were then polished with three brands of red-colored nail polish (Dior 999 Red Royalty, Essie 488 Forever Yummy, and Revlon 550 Cherry). In addition, a set of uncoated nails was included as an untreated comparator. After application of two coats of the colored nail polish, nails dried thoroughly over the weekend at room temperature before application of one coat of (^{14}C)-efinaconazole 10% solution (slightly overlapping for adjacent applications until the nail was entirely coated).

A solution of 1mCi/mL (^{14}C)-efinaconazole (Amersham, Buckinghamshire, United Kingdom) was spiked by adding sufficient amounts of (^{14}C)-efinaconazole in toluene, evaporating to near dryness and then adding the total weight of the formulation base in thirds. Between each third, the formulation was mixed manually with a positive displacement pipette tip and centrifuge. Mixing and centrifuging was performed several times to ensure homogeneity and to achieve a radiolabel concentration of approximately 0.15µCi/dose. Nails were coated with 12.7mg/cm^2 (^{14}C)-efinaconazole (dose determined by weight) on Days 1, 2, 3, 4, and 7 (avoiding the weekend). Nails were not occluded after application of the efinaconazole solution. After Day 4, nails were left unoccluded and undisturbed through the weekend until the final application on Day 7. Photographs of the nails in select chambers were taken throughout the study.

Following the seven-day exposure period, nails were removed from their respective chambers, placed inside labeled scintillation vials, and stored at -20ºC. Nail polish from the surface of the nail was carefully and completely removed with cotton balls dampened in acetone. In addition, any radiolabeled efinaconazole on the surface of the nails was removed in the process, leaving only radiolabeled efinaconazole that penetrated into the nail. Care was taken to ensure no acetone or efinaconazole spread to the underside of the nail. Brushes were visually inspected and photographed if nail polish residue was seen.

Nails were then dissolved in Soluene 350® tissue solubilizer (PerkinElmer) and the amount of residual (^{14}C)-efinaconazole that penetrated into the nail determined by liquid scintillation counting using PerkinElmer Ultima Gold XR. The donor side of each diffusion cell was soaked in 5mL 95% ethanol for at least three hours and analyzed for radioactivity to account for any efinaconazole present in the top of the diffusion cell. Statistical analysis was performed on these data using a one-way analysis of variation (ANOVA), and significant means were tested using the Dunnett's multiple comparison test, with statistical evaluation occurring at each measured time point.

RESULTS

Permeation (receptor phase levels) of (^{14}C)-efinaconazole following application of efinaconazole topical solution, 10%, to uncoated nails was 0.56 percent of the applied dose at Day 7 (Figure 1). When efinaconazole topical solution, 10%, was applied to nails coated with Essie, Revlon, or Dior nail polish, permeation rates were 0.43, 0.50, and 0.51 percent of the applied dose, respectively (Figure 1). It should be noted that large variation in the data set for the uncoated nails required the rejection of outlier data points (those that were at least one

order of magnitude greater or lesser than the median level of radioactivity measured, likely due to leaks in the set up or air bubbles below the surface of the cell). All analyses and statistics were performed following the removal of these outliers.

In this study, the level of efinaconazole permeating through nails either uncoated or coated with nail polish was not statistically significantly different at all time points indicating that nail polish did not appear to inhibit the permeation of efinaconazole under these test conditions. Cumulative concentrations of efinaconazole in the receptor at Day 7 ranged from 13.6 to 17.6µg/cm^2 (Table 1).

Nail polish quality appeared to be in good condition following first application and visually maintained a good appearance through the end of the study. It was noted that after the first application, nail polish color was observed on all brush applicators, with the greatest amount associated with Essie nail polish. It was also observed that the overall tackiness of nail polish persisted after drying and was progressively affected with repeated application.

COMMENT

When developing a topical antifungal medication for onychomycosis, active ingredients must penetrate through the dense keratinized nail plate into the deeper layers and nail bed. Moreover, the active drug must be present in free form to be effective. Antifungal drugs are known to possess a high affinity to keratin, and this can have a deleterious effect on their efficacy, as they cannot penetrate through the nail plate.[15] The keratin binding properties of efinaconazole topical solution, 10%, allow for much greater permeation through the nail, as compared to ciclopirox and amorolfine.[15]

However, there are a number of practical considerations when treating a disease over many weeks that can have a significant impact on outcome. This is the first study to show that drug permeation of a topical antifungal, efinaconazole topical solution, 10%, does not appear to be affected by prior application of cosmetic nail polish. This finding may have important implications in the management of onychomycosis, as patients may be able to cosmetically conceal the appearance of dystrophic nails during treatment, which would then likely encourage adherence to the regimen during the long treatment period.

This study, however, has significant limitations. First, this study did not determine whether treatment efficacy is affected by nail polish use; the Phase 3 studies that establish the efficacy of efinaconazole topical solution, 10%, prohibited nail polish use. Second, the study used non-diseased cadaver nails, which is a proxy for determining permeation in living patients with onychomycosis. Third, this study did not exhaustively study a wide range of polishes, in terms of colors, clear coat use, or substrate (e.g., ultraviolet-treated gels). Finally, this study observed qualitative changes to the polish as evidenced by transfer of polish to the brush surface and tackiness to the polish surface. Whether these qualitative effects matter to patients is unknown. Overall, this study provides evidence that nail polish does not appear to affect permeation of efinaconazole topical solution, 10%, through the nail.

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REFERENCES

1. Gupta AK, Jain HC, Lynde CW, et al. Prevalence and epidemiology of onychomycosis in patients visiting physicians' offices: a multicenter canadian survey of 15,000 patients. *J Am Acad Dermatol.* 2000;43:244–248.
2. Szepietowski JC, Reich A, Garlowska E, et al. Factors influencing coexistence of toenail onychomycosis with tinea pedis and other dermatomycoses: a survey of 2761 patients. *Arch Dermatol.* 2006;142:1279–1284.
3. Roberts DT. Onychomycosis: current treatment and future challenges. *Br J Dermatol.* 1999;141(Suppl 56):1–4.
4. Szepietowski JC. Selected clinical aspects of onychomycosis. *Mikol Lek.* 2004;11:119–128.
5. Scher RK, Coppa LM. Advances in the diagnosis and treatment of onychomycosis. *Hosp Med.* 1998;34:11–20.
6. Crissey JT. Common dermatophyte infections. A simple diagnostic test and current management. *Postgrad Med.* 1998;103(2):191–1,197–200,205.
7. Seebacher C, Brasch J, Abeck D, et al. Onychomycosis. *Mycoses.* 2007;50:321–327.
8. Szepietowski JC, Reich A; for the National Quality of Life in Dermatology Group. Stigmatisation in onychomycosis patients: a population-based study. *Mycoses.* 2008;52(4): 343–349.
9. Drake LA, Scher RK, Smith EB, et al. Effect of onychomycosis on quality of life. *J Am Acad Dermatol.* 1998;38(5 Pt 1): 702–704.
10. Elewski BE. The effect of toenail onychomycosis on patient quality of life. *Int J Dermatol.* 1997;36:754–756.
11. Szepietowski JC, Reich A, Pacan P, et al. Evaluation of quality of life in patients with toenail onychomycosis by Polish version of an international onychomycosis-specific questionnaire. *J Eur Acad Dermatol Venerol.* 2007;21(4):491–496.
12. Schein JR, Gause D, Stier DM, et al. Onychomycosis: baseline results of an observational study. *J Am Pod Med Ass.* 1997;87(11):512–519.
13. Drake LA. Quality of life issues for patients with fungal nail infections. *AIDS Patient Care.* 1995;9(Suppl 1):S15.
14. Bhatt V, Sarpotdar P, Pillai R, et al. Development of an optimal formulation for efinaconazole a novel antifungal agent for the treatment of onychomycosis by topical application. Poster presented at 71st Annual Meeting, American Academy of Dermatology, March 1–5, 2013; Miami Beach, Florida.
15. Elewski BE, Rich P, Pollak R, et al. Efinaconazole 10% solution in the treatment of toenail onychomycosis: two phase 3 multicenter, randomized, double-blind studies. *J Am Acad Dermatol.* 2013;68:600–608.