ELSEVIER

Journal of the European Academy of Dermatology and Venereology
4 (Suppl. 1) (1995) S17–S21

JEADV

Amorolfine nail lacquer: a novel formulation

Jean-Paul L. Marty *

Unité de Recherche en Dermopharmacologie et Cosmétologie, Faculté de Pharmacie, Université Paris Sud, 5 rue J.B. Clément, 92296 Châtenay-Malabry, France

Abstract

Onychomycosis is difficult to treat. Systemic therapy with the potent oral azoles may be restricted by their potential side-effects; an attractive alternative is topical application of an antifungal directly to the nail. Several such formulations have been developed, including creams and lotions which are largely ineffective due to poor drug penetration into and through the nail structure. Nail keratin is thick and compact; its permeability is low. Transungual drug diffusion depends on the characteristics of the nail (especially degree of hydration) and the properties of the chemical (molecular weight and size, and lipophilic/hydrophilic profile). A nail lacquer containing 5% amorolfine was recently introduced; the volatile vehicle evaporates, leaving an occlusive film on the surface of the nail. The film acts as a drug depot, while at the same time increasing the hydration of the nail and the thermodynamic activity of the drug, thereby enhancing diffusion, particularly of hydrophilic compounds. Amorolfine has been shown to penetrate human nail from the film at clinically effective concentrations. In addition, the effect is long lasting: a single application of lacquer provides protection for 1 week. Release and rate of diffusion can be optimized by selecting the components of the lacquer formulation (solvent, polymer, plasticizer). Transungual drug delivery via nail lacquer is a major addition in the dermatologist's therapeutic arsenal.

Keywords: Amorolfine; Nail lacquer; Transungual drug delivery; Nail diffusion

1. Introduction

Successful local therapy of onychomycosis is dependent on choosing an appropriate antifungal coupled with a method of delivery which maximizes the effect of the active principle by aiding its diffusion into the nail bed at levels exceeding the minimum inhibitory concentration (MIC) against local infection by fungi, dermatophytes and molds.

Local treatments are an interesting alternative to long-term systemic therapy, especially when the nail matrix is not affected. Transungual diffusion of the active principle is the necessary and

* Corresponding author. Tel.: +33 1 4683 5351.

SSDI 0926-9959(94)00075-1

limiting condition for all local application. Diffusion depends on the physicochemical composition of the nail and of the excipient containing the active principle.

In addition to delivery of the active principle to the nail, other problems exist in applying drugs to the nail surface: how to apply the preparation evenly, how to maintain it in place long enough to ensure adequate penetration at fungicidal levels, and thereby avoiding multiple applications and enhance compliance.

2. Differential permeability of nail

The basic constituent of the nail is keratin, a scleroprotein responsible for the mechanical resistance of the nails. The hardness of the nail plate depends not only on the junctions between the cells and their architectural arrangement, but also on the tranverse orientation of the keratin filaments with respect to the axis of nail growth. The multiplicity of the lateral bonds between keratin fibers (disulfide bridges, hydrogen bonds, acid-base bonds, electrostatic bonds) accounts for the hardness of nail keratin and its high resistance to the diffusion of active principles.

Nail contains little lipid (0.5 to 1.5%, depending on age), in contrast to the stratum corneum (10%) [1]. The lipid comprises cholesterol, which appears to be responsible for maintaining nail elasticity and cell cohesion, hydrocarbons and mainly unsaturated fatty acids. The latter account for 2/3 of the total lipid, and consist mainly of oleic acid. Phospholipids tend to be found in abundance in the dorsal layer of the nail, in association with calcium. Solvent extraction of cholesterol leaves the nail dry and brittle.

Water is the main nail plasticizer. Its concentration in nail tissue (7% to 12%) is directly related to ambient relative humidity, and is lower than in the stratum corneum (15% to 25% under normal conditions). In dry air, nails quickly lose water; they can be rehydrated up to a maximum concentration of 25% in high ambient humidity. Nail is less able to bind water than the stratum corneum, which can absorb several times its dry weight [1,2].

Like the stratum corneum, nail tissue is constantly losing water; under normal conditions, transungual diffusion of water (1.8 to 3.1 $mg/cm^2 \cdot h$) is similar to transepidermal water loss from the palms and soles (2.0 to 3.0 $mg/cm^2 \cdot h$). It is 10-fold higher than that from other anatomical areas (0.15 to 0.35 $mg/cm^2 \cdot h$). Given the relative thicknesses of stratum corneum and nail, the permeability of nail to water is some 1000-fold greater than that of the stratum corneum [3,4].

The nail plate is also permeable to many polar and non-polar substances with widely differing molecular weights (30 to 665), as shown in toxicological studies (formaldehyde, phenol, fluoruracil, detergents, pesticides, mercurials, hydroquinone etc), therapeutic trials (antifungal agents, antipsoriasis drugs) and diffusion studies [5].

Aliphatic alcohols are useful for analysing the mechanism of diffusion across biological membranes, owing to their respective solubility in water and lipids. The data reported by Walters et al. for dilute aqueous solutions of these alcohols with samples of human nail in vitro show that the permeability constant falls steadily from methanol to octanol, and then rises up to decanol. These results differ from those obtained with the same substances under identical experimental conditions in stratum corneum, in which membrane permeability increases with the length of the hydrocarbon chain [6].

These comparative data suggest that the stratum corneum is a lipophilic membrane; the increase in diffusion is due to a favorable partition coefficient of lipophilic alcohols in the hydrophobic areas of the membrane. Nail, on the other hand, behaves primarily as a water gel (for alcohols comprising 1 to 8 carbon atoms). A lipophilic route of diffusion has been demonstrated for the diffusion of alcohols with a longer hydrocarbon chain. Similar qualitative data have been obtained when aliphatic alcohols have been applied pure to the nail surface and not in dilute aqueous solution. However, permeability constants are on average five times lower than those obtained with the dilute aqueous solutions. The parallel diffusion profiles show that the concentration of the diffusing molecule is a predominant factor in the mechanism; the difference in degree of diffusion

suggests that water facilitates diffusion through the nail [7].

This physicochemical difference in the characteristics of nail permeability suggests that there are two routes by which substances penetrate nails:

- The hydrophilic pathway, which is used by most compounds, particularly if polar, and which accounts for the diffusion of water, urea, electrolytes and the ionized forms of ionizable molecules; the water contained in the vehicle plays an important role in promoting diffusion.
- A secondary lipophilic pathway, through the extracellular lipid network, for use by strictly non-polar compounds.

This selective diffusion of hydrophilic substances through a water gel contrasts with that in the stratum corneum and restricts the diffusion of many active principles that were developed for dermatological use because their lipophilic properties enabled them to diffuse through the extracellular lipids of the stratum corneum [8].

The excipients developed for use on skin are thus inappropriate for releasing active principles on the nail, as shown by the inefficacy of diffusion promoters such as DMSO [9]. Where ionizable substances are concerned, water solubility is maximal when ionization is complete; given that the nail is hydrophilic, vehicle pH can thus play a fundamental role, as has been suggested in the case of miconazole [10], where a high concentration of active principle is achieved in the vehicle for maximal diffusion.

3. Transungual drug diffusion

The topical formulations conventionally used in dermatology (creams, gels, water- or oil-based lotions, powders) are specifically adapted neither to the nail nor to the mean treatment duration (6 to 12 months) required for the growth of a healthy nail. Following application to the nail, such formulations are readily removed by rubbing, wiping and washing; their impermanence at the site of application readily accounts for their inefficacy. Apparently simple formulations have been proposed instead: alcoholic solutions containing high concentrations of active principle, e.g. 28% ticonazole, and nail lacquers or film-generating solutions containing 8% ciclopirox or 5% amorolfine.

A film-generating solution is a novel therapeutic formulation developed to deliver effective doses of antifungal to the entire nail tissue over a short duration (one day, in the case of ciclopirox) or for longer periods (up to 1 week, in the case of amorolfine). Because 5% amorolfine remains at the site of application, the number of applications can be reduced, while effective treatment is ensured by high bioavailability of the active principle.

A film-generating solution basically consists, in addition to the active agent, of the following: a volatile solvent (ethanol, ethyl/butyl/methyl acetate, methylene chloride, methyl ethyl ketone, isopropanol) and a non-water-soluble polymer (methacrylic acid copolymers, vinyl polymers) which leaves a thin continuous film following evaporation of the solvent. Plasticizers (triacetin, dibutyl phthalate) can be added to give the film the characteristics required for molding to the nail, including enough mechanical flexibility to prevent flaking and removal. The solvent itself can be composed of a mixture of compounds to accelerate drying and result in an even and reproducible film.

This formulation is very similar to that of a nail lacquer, one of the most widely used products in cosmetics. It maintains the active principle in a polymer film depot on the nail surface, from which the antifungal evenly diffuses through the nail plate keratin to reach the nail bed. The concentration (or thermodynamic activity) of the active principle in the film after solvent evaporation is extremely high; by the laws of diffusion, this enhances penetration [8].

According to Spruit [11], application of an 0.05 mm film of nail lacquer reduces transungual water diffusion from 1.6 to 0.4 $mg/cm^2 \cdot h$, leading to hyperhydration of the upper layers of the nail plate. This also enhances the diffusion of the amorolfine applied to the nail surface.

The specific aims addressed in formulating a

film-generating solution were to give the active principle maximal affinity for nail keratin and obtain the highest possible thermodynamic activity compatible with maintaining the active principle in true or supersaturated solution. Thus, in the case of Loceryl™, the amorolfine concentration in the film-generating solution is 5%; solvent evaporation leaves a film with a final amorolfine concentration of 25%. The high post-evaporation concentration enhances transungual diffusion of the active principle.

The concern to maximize diffusion must take into account the stability of the active principle and any physicochemical incompatibilities. The final product must be as clinically effective as possible, at the same time as having a maximal risk/benefit ratio and zero systemic diffusion. This means that the vehicle constituents must be non-irritant and non-allergenic and be well tolerated locally. The formulation chemist is also under purely technological constraints arising from the use of organic solvents: special techniques need to be employed, particularly in the choice of inner packaging, to ensure maximal stability during storage. Application of the lacquer to the nail surface requires a device coping with the viscosity of the solution and giving a consistent and reproducible dose. A calibrated spatula gives a uniform coat of 18 μl of solution per nail; thus 90 ± 8 μl (mean $\pm$ standard deviation) is required to treat five nails.

The film-generating solution, in the case of amorolfine, is an excipient giving substantial intraungual diffusion, which is enhanced by the hydrating effect of the film; the active principle penetrates rapidly following a single application. Thus 6 h after single application in vitro, the nail concentration of amorolfine is 56 $\mu g/g \cdot cm^2$, with a residual concentration of 188 $\mu g/g \cdot cm^2$ after 7 days. These tissue concentrations are 140- and 470-fold higher, respectively, than the MIC against *Candida albicans* [12]. The vehicle composition helps modulate the release of amorolfine into the nail and maintain it at high levels over 7 days [13]. These data have been confirmed in vivo, after treatment for one month: two weeks after the last application, subungual tissue still showed an overall antifungal activity far exceeding the mean MICs against test organisms [14].

4. Conclusion

A nail lacquer is a novel formulation solution to the problem of a transungual drug delivery system for maximal antifungal efficacy. The film on the nail surface acts as a depot of active principle, permitting optimized and sustained diffusion of amorolfine (for up to 7 days). Continuous penetration of the active principle leads to the high tissue concentrations required for the effective treatment of onychomycosis.

References

[1] Baden HP, Goldsmith LA, Fleming B. A comparative study of the physicochemical properties of human keratinized tissues. Biochim Biophys Acta 1973;322:269–278.
[2] Finlay AY, Frost P, Keith AD, Snipes W. An assessment of factors influencing flexibility of human fingernails. Br J Dermatol 1980;103:357–365.
[3] Spruit D. Measurement of water vapor loss through human nail in vivo. J Invest Dermatol 1971;56:359–361.
[4] Walters KA, Flynn GL, Marvel JR. Physicochemical characterization of the human nail: 1. Pressure sealed apparatus for measuring nail plate permeability. J Invest Dermatol 1981;76:76–79.
[5] Walters KA, Flynn GL. Permeability characteristics of the human nail plate. Int J Cosmet Sci 1983;5:231–246.
[6] Walters KA, Flynn GL, Marvel JR. Physicochemical characterization of the human nail: Permeation pattern for water and the homologous alcohols and differences with respect to the stratum corneum. J Pharm Pharmacol 1983;35:28–33.
[7] Walters KA, Flynn GL, Marvel JR. Physicochemical characterization of the human nail: Solvent effects on the permeation of homologous alcohols. J Pharm Pharmacol 1985;37:771–775.
[8] Marty JP, Dervault AM. Voie percutanée. In: Dubertret L (ed.), Thérapeutique dermatologique. Paris: Médecine Sciences Flammarion, 1991;649–663.
[9] Walters KA. Penetration of chemicals into, and through, the nail plate. Pharm Int 1985;April:85–89.
[10] Walters KA, Flynn GL, Marvel JR. Penetration of the human nail plate: the effects of vehicle pH on the permeation of miconazole. J Pharm Pharmacol 1985;37:498–499.
[11] Spruit D. Effect of nail polish on the hydration of the fingernail. Amer Cosmet Perf 1972;87:57–58.

[12] Pittrof F, Gerhards J, Erni W, Klecak G. Loceryl™ nail lacquer: realization of a new galenical approach to onychomycosis therapy. Clin Exp Dermatol 1992;17(suppl 1):26–28.
[13] Franz TJ. Absorption of amorolfine through human nail. Dermatology 1992;184(suppl 1):18–20.
[14] Mensing H, Polak-Weiss A, Splanemann V. Determination of the subungual antifungal activity of amorolfine after 1 month's treatment in patients with onychomycosis: comparison of two nail lacquer formulations. Clin Exp Dermatol 1992;17(suppl 1):29–32.