

Conventional and modern therapeutic approaches in topical medication of onychosis

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ABSTRACT

Onychosis therapy is an ongoing challenge considering the diversity of nail pathology and the barrier function of the nail plate. Among the nail diseases, we identify the primary onychodystrophies, caused by tics or mental disorders, as well as severe onychoses, caused by bacterial and/or fungal infections, manifested by the degradation of the matrix and the nail bed. Onychosis treatment is complex, lasting 6-8 months, and is often frustrating for both patients and healthcare professionals. In this article we have described a series of common onychoses from the etiopathological point of view, briefly presenting the general therapeutic approach. We also highlighted the classic and modern pharmaceutical formulations used in local nail medication. From the perspective of recent approaches, there is the development of therapeutic systems for transungual administration that ensure the prolonged and controlled drug release to optimize the pharmacotechnical performance of medication used in local therapy of onychosis.

Keywords: onychodystrophies, topical nail medication, medicated varnish

INTRODUCTION

The treatment of nail diseases is difficult, considering the barrier function and the anatomical features of the nail unit. The complexity of nail pathology varies from simple onychodystrophies to severe onychoses caused by bacterial and/or fungal infections that can cause degradation of the matrix, plaque and even of the nail bed. The treatment is complex, long-lasting, from a few months to a year, and often involves combining systemic medication with topical or local medication. It is well known that oral therapy, especially antifungal medication, has many side effects and variable bioavailability. As for topical medication, it is defined by low permeability caused

by the barrier of the nail plate. Therefore, pharmaceutical research is currently focused on the development of new pharmaceuticals with topical administration at the level of the nail unit that can, through various mechanisms, ensure optimal bioavailability of the active ingredients. Basically, today we identify transungual therapeutic systems that generate an optimal permeability of drug substances on various segments of the nail unit. The aim of this paper is to highlight the advantages and limitations of conventional pharmaceutical forms from the perspective of modern formulations with their major objective the optimization of local therapy of nail diseases.

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Article History:
Received: 15 November 2021
Accepted: 5 December 2021

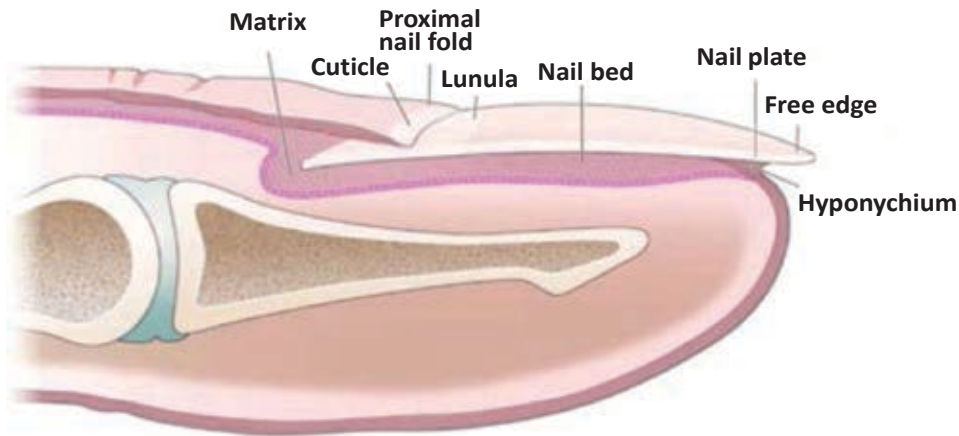


FIGURE 1. Normal nail – schematic representation

NAIL – ANATOMICAL FEATURES

The nail unit or nail apparatus consists of the *nail plate* and *four specialized epithelia* that form the proximal nail fold, known as the *cuticle*, *nail matrix*, *nail bed* and *hyponychium* (Figure 1) [1].

The *nail plate*, the corneous component, is hard, slightly flexible, made of keratin arranged in three layers. The outer layer consists of keratinized cells that provide the barrier function, while the inner layer includes many desmosomes and other structures responsible for the cellular adhesion of the nail plate to the nail bed.

The *nail matrix* or generating area, called the nail root, is derived from the surface epidermis. It is located under the skin behind the nail and is protected by the nail. The germinal matrix is strongly vascularized and innervated, and through the onychokeratinization process it forms the nail plate. The shape and thickness of the nail plate are determined by the matrix. The growth of the nail takes place continuously, throughout life with a rate of 0.5-1 mm per week, and the keratinization process occurs simultaneously from the matrix through the nail bed to the free edge, lasting about 6-8 months.

The *nail bed* is made up of a thin, soft epithelium that extends its entire length under the nail. It acts as a support for the nail plate. It is pink, being strongly vascularized with blood and lymph vessels. The nail bed is made up of two types of tissue: the internal dermis and the superficial epidermis. The dermis is attached to the bone, while the epidermis is present just below the nail plate. Both the dermis and the

epidermis are connected to each other by tiny longitudinal grooves known as matrix grooves.

The *cuticle* forms the distal part of the proximal nail fold, which protects the nail from pathogens and environmental irritants [2,3,4].

FREQUENT PATHOLOGIES OF THE NAIL UNIT

The pathology of the nail unit is diverse, being represented both by primary nail diseases and by secondary diseases that damage the nail in the context of other pathologies.

Paronychia is an inflammatory condition located in the proximal and lateral nail folds. It is usually caused by a mechanical or chemical aggression as result of which the cuticle loses its barrier function, and the area is contaminated with bacterial agents. Paronychia is known in 2 forms: acute and chronic. *Chronic paronychia*, also called *total perionyx*, is a chronic dermatitis of the proximal nail fold and nail matrix. There is chronic inflammation, cuticle degradation and separation of the nail plate from the proximal nail fold. The fold is edematous, creating favorable conditions for the proliferation of saprophytic flora or colonization with pathogenic microorganisms. It is usually located on the first 2-3 toes of the hand or foot (Figure 2a.) [1].

The first step in the therapeutic approach to total perionyx is to avoid humid environments and contact with irritants or allergens that have triggered the disease. If perionyx is diagnosed as a secondary



FIGURE 2. Paronychia:
a. chronic, b. acute

condition of another pathology, such as atopic dermatitis or psoriasis, these conditions must be subject to their own medication. After testing the sensitivity of the pathogenic microflora to antibiotics and antifungals, appropriate medication will be prescribed, usually in the form of local therapy. *Acute paronychia* or *partial perionyx* is caused by impairment of the integrity of the lateral or proximal fold and subsequently of the epidermis. It usually occurs as result of mechanical fold trauma followed by staphylococcal infections. Paronychia and ingrown toenail are the best-known forms of partial perionyx (Figure 2b.).

Therapeutic management of partial perionyx requires the drainage of the abscess in specialized medical offices, followed by the application of local antiseptics to reduce the microbial load and alleviate inflammation. At the same time, systemic and/or local antibiotic therapy is instituted [5].

Onychomycosis is a chronic progressive fungal infection of the nail unit, most commonly caused by dermatophytes and, less frequently, by *Candida spp.* Onychomycosis caused by dermatophytes represents up to 80% of nail pathology. Depending on the anatomical area affected, we distinguish distal and lateral subungual onychomycosis, superficial white

onychomycosis and proximal subungual onychomycosis [6].

Distal and lateral subungual onychomycosis begins in the hyponychium and extends subungually, and may even lead to onycholysis (Figure 3a.) [7,8]. Superficial white onychomycosis is manifested on the dorsal surface of the nail invaded by *Trichophyton spp.* (Figure 3b.). Superficial onychomycosis is manifested mainly in the toenails. The nail plate has some white spots or dots, and becomes brittle and floury in texture. Proximal subungual onychomycosis is manifested by whitening of the proximal portion of the nail and progression to the distal portion. This form of onychomycosis is specific to patients with low immunity (Figure 3c.).

The treatment of onychomycosis requires time due to the slow growth of the nail plate. There are many factors to consider when prescribing medication, such as: age and health of the patient; the nature of the pathogen; the clinical type of onychomycosis; the number of nails affected; severity of nail damage.

To assess clinical cure, patients should be monitored for at least 6 months after stopping treatment, as recurrences and reinfections are common. The most effective therapeutic approach is based on the



FIGURE 3. Onychomycosis: *a. subungual, b. white, c. proximal subungual*

combination of oral antifungal therapies with topical antifungal therapies [9,10].

Nail psoriasis is often seen as a secondary form of onychosis. Statistics show that up to 50% of patients with psoriasis develop a form of nail psoriasis in their lifetime, but patients diagnosed exclusively with nail psoriasis should not be omitted, as the only manifestation of this pathology. The impact on the patient's quality of life is major. As clinical signs we distinguish large longitudinal ridges, punctiform depressions, thickening of the nail plate and even onycholysis with erythematous hemorrhages (Figure 4).

Nail psoriasis progresses positively to the systemic therapy currently prescribed in psoriasis, including biologic medication. Topical application of emollient or keratolytic substances does not represent a therapeutic option in nail psoriasis. As a personalized therapy, doctors prescribe immunomodulators and even locally administered anti-inflammatory drugs, which are more effective under occlusive dressing. It should be noted that this approach is reserved for mild forms of nail psoriasis with hyperkeratosis [11].

CONVENTIONAL AND MODERN THERAPEUTIC SYSTEMS USED IN TOPICAL MEDICATION OF THE NAIL UNIT

Systemic therapy combined with local therapy is the most effective therapeutic approach for nail diseases. Although the low permeability of the nail plate is the major limiting factor of the local bioavailability of topical medication, this method of administration still offers many advantages, among which we mention: avoidance of the first hepatic passage; targeted and even controlled release of the drug substance; optimal compliance and adherence.

The reality of the last years has highlighted the development of therapeutic systems for transungual administration of medicinal substances intended for the local therapy of onychosis.

In topical transungual therapy we identify both conventional pharmaceutical forms, but especially modern pharmaceutical ones, such as medicinal varnishes. Conventional pharmaceutical forms, such as gels, creams, ointments or solutions, have the following main disadvantages: reduced nail residence



FIGURE 4. Nail psoriasis

time; the need for repeated administration; uneven release of drugs [12].

Nowadays, medicinal varnishes are considered the optimal pharmaceutical form in topical transungual medication. After application, the varnishes form a thin film resistant to water and abrasion, which acts as a reservoir, thus ensuring the controlled and prolonged release of the drug substance. After applying a drug varnish, the volatile solvents evaporate, and the drug substance is spread on the nail plate in the residual film or film. In addition, this film creates a local occlusive effect, favorable both to the diffusion of the drug substance through the nail plate and to the germination of fungal hyphae that thus become sensitive to the antifungal agent [13,14].

Currently, most drug varnish formulations are based on water-insoluble polymers derived from cellulose, methacrylic acid derivatives, vinyl resins that require mechanical removal, or with organic solvents over a certain period. This feature can adversely affect the condition of the nail when repeated. Water-soluble films, such as hydroxypropyl chitosan-based films, have good adhesion to the nail plate and generate both a uniform distribution and release of the drug molecule at the site of application. In addition, hydroxypropyl chitosan has been shown to accelerate nail growth, shortening the duration of treatment. However, water-soluble films are easy to remove by washing, so manufacturers recommend a well-defined time interval between application and first washing of the treated area, being used in the evening, before bedtime [15,16].

Transungual permeability is greatly enhanced by the combination of conventional topical medication with physical methods such as iontophoresis, microneedles, low-frequency ultrasound etc. as an alternative to injection [17,18,19].

CONCLUSIONS

The nail unit not only has a protective role, but can be considered a way of topical administration of medicinal

substances. As nail diseases are difficult to treat, the therapy should be aimed at the matrix and the nail bed to promote the correct and healthy growth of the new nail plate. New formulations such as medicated varnishes are the optimal pharmaceutical forms. Currently, new perspectives are opening in medical and pharmaceutical research for the introduction of other transungual vectors and even the association of topical medication with physical methods of optimizing transungual permeation.

Conflict of interest: none declared
Financial support: none declared

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