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Onychomycosis: Therapy Directed by Morphology and Mycology

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ABSTRACT

Onychomycosis is one of the most common nail disorders. Despite recent therapeutic advances with the introduction of effective systemic agents and transungual drug delivery systems, the incidence of onychomycosis is increasing. This is of concern, as the morbidity related to this infection also increases as our population ages with associated conditions, such as diabetes and immunosuppression from illness and medical therapy. Rational and effective treatment plans are needed.

Keywords: itraconazole; morphology; mycology; onychomycosis; nail disorders; terbinafine

In a multicenter survey about the incidence of onychomycosis in 15,000 consecutive patients, Gupta et al.[1] reported that this condition affects 6.5% of Canadian adults. These patients visited their clinical physicians for any reason and consented to an examination of their fingernails and toenails, and to fungal cultures of any nail plates that appeared abnormal. The nail plate cultures were positive in 1,199 (8%) patients, and 1,137 (7.6%) of them had only pedal onychomycosis. This confirmed the work of other investigators by showing that the most common organisms responsible for >90% of onychomycosis involving the toenails are the dermatophytes *Trichophyton rubrum* and *Trichophyton mentagrophytes*.

Baran et al.[2] proposed a morphological classification based on the portal of entry, which has proven very useful in the clinical setting. Clinical presentations may combine features of basic morphologic patterns. Three basic clinical presentations include:

Clinical Presentations	Portal of Entry
Distal/lateral subungual onychomycosis (DLSO)	through the distal subungual area and the lateral nail groove
Superficial white onychomycosis (SWO)	directly into the dorsal surface of the nail plate
Proximal subungual onychomycosis (PSO)	through the under-surface of the proximal nail fold

A fourth clinical presentation is total dystrophic onychomycosis (TDO), which may be considered secondary to severe DLSO, SWO, PSO, or primary when associated with severe immunodeficiency.

Gupta et al.[1] noted in their review that the relative frequency of presentation was 360:59:1 for DLSO:SWO:PSO when the toenails were involved. They also noted that in the DLSO group, the percentage of the nail plate involvement could be categorized as mild (<25%), moderate (26%-74%) and severe (>75%) with relative incidences of 27.6%, 39.9%, and 32.5%, respectively.

The morphological presentation of the infection within the nail plate aids in the choice of treatment agents and in determining prognosis and the need for adjunctive therapy. The involvement of the lunula appears to be the critical morphologic criteria that establishes the need to consider systemic therapy in the management of onychomycosis. Therefore, in most clinical settings, when <75% of the nail plate surface area is involved and the lunula is spared, topical therapy may be considered as monotherapy. The number of nails involved may also contribute to this decision. Most authorities recognize that they should consider the addition of systemic therapy when a patient presents with the involvement of more than 5 infected nails.

The morphology of the nail plate infection at the time of presentation may also help determine the need for adjunctive therapy. These presentations are:

- Dermatophytoma/longitudinal streaking with nail plate changes that are produced by keratin debris and filled with dermatophytes, which produce a relatively inaccessible foci of infection.
- Lateral nail plate involvement/onycholysis, whereby seperation of the nail plate from the nail bed reduces the vascular access to the plate and limits the penetration of systemic therapy.

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- Thick nail (>2mm), which may indicate matrix involvement, and keratinaceous debris can limit drug diffusion regardless of the delivery system.

These presentations all limit the access of pharmaceutical agents to the site of the dermatophyte infection and all require adjunctive therapy that is directed to the physical removal of the keratinaceous debris. Mechanical or chemical debridement is essential for effective therapy.

Scher et al.[4] discuss the difficulties in assessing the results of randomized controlled trials (RCTs) to aid in the selection of specific treatment modalities. The trials are not consistent in their design or in their use of criteria to determine the relative effectiveness of treatment modalities. Scher proposes definitions for clinical cure in RCTs, which are either 100% morphologic cure, or mycological cure of <10% of the nail plate with morphologic disturbance or thickening of the plate related to comorbidity. Mycological cure rates, however, appear to be the most consistent criteria as they can be objectively determined and compared. Gupta[5] provided a meta-analysis of published studies from 1966 through 1999, which recorded mycological cure rates for terbinafine (3 months continuous), itraconazole (3 pulses) and griseofulvin (daily) as 77%, 70%, and 41% respectively. Topical therapy with 8% ciclopirox, when used in mild-to-moderate onychomycosis without lunular involvement, produced a mycologic cure of 52.6%.

Chang et al.,[6] using a meta-analysis of 122 studies with 20,000 patients, reviewed the safety of oral anti-fungal treatments in immunocompetent patients. The risk of treatment discontinuation as a result of an adverse event was 3.4% for continuous terbinafine (250mg/day for 3 months) and 2.58% for pulse itraconazole (400mg/day for 1 week). Transaminase elevations requiring treatment termination occurred in 0.34% of patients receiving continuous terbinafine and 0.39% of patients on pulse itraconazole. Transaminase elevations not requiring treatment termination occurred in 0.70% and 1.04% of patients, respectively. These treatment regimens did not reveal the risk of an adverse event to be any greater than the placebo groups in those studies that were placebo controlled.

Baran et al.[7,8] proposed a severity index for assessing the responses to treatment of onychomycosis. The index assigns a numerical value to the morphological presentation, to the mycology, and to host factors, which would influence the outcome of treatment. The values are added together to assign a prognosis that could then be discussed with patients. This index would provide an indication of which patients would be likely to fail therapy, so that a rational treatment program could be developed that might also include mechanical or chemical intervention. The concept of a booster dose, which is another cycle of systemic therapy delivered for 1 month at approximately 6 to 9 months from the start of therapy, is also supported for patients who are likely to fail therapy.

The recurrence of onychomycosis (relapse or reinfection) is a significant challenge in the management of patients with this infection. The LION study group[9] documented mycological cure at 72 weeks in 75%-80% of terbinafine treated patients and 38%-49% of itraconazole treated patients. However, a 5 year follow-up study of 151 of these patients revealed that only 46% of terbinafine- and 13% of itraconazole-treated patients were disease free. These patients were treated with systemic monotherapy. There is a discussion in the literature suggesting that topical therapy, both concomitantly and intermittently, may improve these results by providing a longer treatment period for slow growing nails, and offering treatment for individuals prone to reinfection due to genetics or comorbidities.

Conclusion

The goal of treatment is to completely eradicate the infection and return the nail plate to its normal appearance. Unfortunately, the eradication of the dermatophyte does not routinely result in a normal nail plate. The changes related to chronic infection, repeated trauma, and other disease processes, such as psoriasis, may all predispose the patient to a dermatophyte infection and not allow for a return to a normal nail plate. Reviewing the information that is presented in this paper with the patient will help to develop a rational treatment, manage expectations, and encourage compliance.

References

1. Gupta AK, Jain HC, Lynde CW, et al. Prevelance and epidemiology of onychomycosis in patients visiting physicians' offices: a multicentre Canadian survey of 15,000 patients. *J Am Acad Dermatol* 43(2 Pt 1):244-8 (2000 Aug).
2. Baran R, Hay RJ, Haneke E, et al. *Onychomycosis: the current approach to diagnosis and therapy.* 2nd edition (2006).
3. Gupta AK, Cooper EA. A simple alogrithm for the treatment of dermatophyte toenail onychomycosis. *Skin Therapy Lett Family Practice Ed.* 4(3):1-3 (2008 Jun).
4. Scher RK, Tavakkol AT, Sigurgeirsson B, et al. Onychomycosis: diagnosis and definition of cure. *J Am Acad Dermatol* 56(6):939-944 (2007 Jun).
5. Gupta AK. Pharmacoeconomic analysis of ciclopirox nail lacquer 8% and the new oral antifungal agents used to treat dermatophyte to onychomycosis in the United States. *J Am Acad Dermatol* 43(4 Suppl):S81-95 (2000 Oct).
6. Chang CH, Young-Xu Y, Kurth T, et al. The safety of oral antifungal treatments for superficial dermatophytosis and onychomycosis: a meta-analysis. *Am J Med* 120(9):791-8 (2007 Sep).
7. Baran R, Hay RJ, Garduno JI. Review of antifungal therapy and the severity index for assessing onychomycosis: part I. *J Dermatolog Treat* 19(2):72-81 (2008).
8. Baran R, Hay RJ, Garduno JI. Review of antifungal therapy, part II: treatment rationale, including specific patient populations. *J Dermatolog Treat* 19(3):168-75 (2008).
9. Sigurgeirsson B, Olafsson JH, Steinsson JP, et al. Long-term effectiveness of treatment with terbinafine vs itraconazole in onychomycosis: a 5-year blinded prospective follow-up study. *Arch Dermatol* 138:353-7 (2002 Mar).

Many Common Drugs in Dermatology are Light, Temperature, or Moisture-Sensitive

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ABSTRACT

Photosensitivity is defined as responsiveness to light exposure. For many common dermatologic drugs, proper storage conditions are essential for maintaining drug activity. Degradation and loss of activity can occur with exposure to light, temperature, and/or moisture. For example, ketoconazole degrades after 24 hours of light exposure. In this article storage guidelines for common dermatology drugs are provided. We suspect that drug degradation is common due to improper storage and that improved patient instruction regarding storage will reduce degradation and alleviate some of the danger associated with improper storage and usage patterns.

Key Words: drug storage; drug degradation; light sensitive; moisture sensitive; temperature sensitive

Light can change the properties of different materials and products, and the number of drugs found to be photochemically unstable is steadily increasing. We define "photosensitivity" as the response that a compound shows to light exposure and includes not only degradation reactions, but also other processes, such as the formation of radicals, energy transfer, and luminescence.[1] Most are familiar with the traditional brown medicinal flask or the white pillbox; these offer adequate protection for most drug products during storage and distribution. Indeed, proper storage conditions are essential for the efficacy of many common dermatologic drugs. In modern hospital pharmacies, drugs are often stored in unit-dose containers on an open shelf. In many cases, the protective market pack is removed; the inner container can be made of transparent plastic materials that offer little protection toward UV and visible radiation. The unprotected drug can then be exposed to fluorescent tubes and/or filtered daylight for several weeks or months before it is finally administered to the patient.

Drug efficacy depends on its stability, pH, correct chemical composition, and potency. Preservation of these characteristics require that many commonly used dermatologic drugs be kept in light-, temperature-, or moisture-free storage conditions. Indeed, itraconazole and erythromycin base are sensitive to all 3 conditions. The most common consequence of drug photodecomposition is loss of potency with concomitant loss of therapeutic activity. Although less common, even less severe degradation can lead to problems. Adverse effects due to the formation of minor degradation products during storage and administration have been reported.[2]

In general, 2 aspects of drug photostability must be considered: *in vitro* and *in vivo* stability.[1] Even if a drug product is shown to be photochemically inert, in the sense that it does not decompose during exposure to light, it can still act as a source of free radicals or form phototoxic metabolites *in vivo*.[1] Epstein and Wintroub suggested that patients who take certain dermatologic drugs and subsequently become exposed to light may develop phototoxic drug metabolites.[3]

Call for Renewed Vigilance in the Proper Storage of Drugs

Table 1 lists some commonly used dermatologic drugs that have special storage requirements; the general storage guidelines that follow provide an easy way to remember which drugs require special attention. The table was generated using *The Pharmacopeia of the United States of America,* 31st revision,[4] *Physicians' Desk Reference* at www.pdr.net,[5] *European Pharmacopeia*,[6] and *British Pharmacopoeia 2007*.[7] An in-depth treatise on the effects of temperature, light, and moisture is provided by Rubinstein.[8] Actual rates of degradation are not listed in these references, however, as this information is difficult to obtain because studies have not been done to determine degradation rates; most available information about degradation comes from studies that analyze the activity of the medicine.

Rates of Degradation

Studies with ketoconazole have shown that photodegradation occurs after 24 hours of UV light exposure.[9] Following this, ketoconazole degradation products will peak at 4 minutes with high-resolution gas chromatography, while ketoconazole alone normally peaks at 6 minutes without the 4-minute degradation product peak. Acyclovir activity decreases after exposure to moisture, but the resulting rate of decline is unknown. Likewise, while terbinafine is light-sensitive, we only know that light exposure reduces its activity, although the activity loss-rate is also unknown.

Finally, expiration dates are used because the more time that passes from the initial issuance of the drug to the time when the drug is used will lead to degradation, not only because of its inherent activity, but also because of light exposure. In one Sudanese study, there was a 55% usage rate of old, unfinished drugs.[10] Patients need clear instructions about the fact that old medications should be discarded or replaced

once the expiration date passes. They should understand that it is not a cost-savings to use expired drugs, because they may not be effective and may even be harmful if degradation leads to the formation of toxic metabolites. Likewise, patients should receive clear storage instructions to avoid exposure to light, moisture, and temperature. While overworked doctors, nurses and pharmacists sometimes give hurried instructions, it is most important that patients be given clear directions.

For example, when patients are prescribed antibiotics, they should always be advised to complete the entire course of treatment. Despite these instructions, patients may not comply, assuming that the drug is no longer needed when they feel better and they may save any remaining medication for another time. This practice has led to the growth of drug-resistant strains of bacteria.[11-14] In other cases, unknowingly taking antibiotics previously associated with allergic symptoms can cause an allergic reaction.[15]

General Storage Guidelines

1. Clarithromycin extended-release tablets: preserve in well-closed containers, protected from light. Store at 25°C, excursions permitted between 15°C, and 30°C.
2. All erythromycin preparations should be packaged and stored in tight containers.
3. Tetracycline hydrochloride should be packaged and stored in tight, light-sensitive containers.
4. Ketoconazole should be packaged and stored in well-closed containers.
5. Acyclovir should be packaged and stored in tight containers at room temperature, protected from light and moisture.
6. Isotretinoin capsules should be packaged and stored in tight containers, protected from light, and stored at room temperature in a dry place.

Conclusion

The pharmacist receives training on appropriate drug labeling with respect to temperature, light, and humidity. Unfortunately, little literature exists that covers patient-stored drug stability in well-lit, humid, non-air-conditioned areas. We suspect that drug degradation may be routine. Improved patient instruction may alleviate some of the danger associated with improper storage and usage patterns.

References

1. Tønnesen HH. *Photostability of drugs and drug formulations*, 2nd ed. Boca Raton, FL:CRC Press (2004).
2. de Vries H, Beijersbergen van Henegouwen GMJ, Huf FA. Photochemical decomposition of chloramphenicol in a 0.25% eyedrop and in a therapeutic intraocular concentration. *Int J Pharm* 20:265-71 (1984).
3. Epstein JH, Wintroub BU. Photosensitivity due to drugs. *Drugs* 30(1):42-57 (1985 Jul).

Generic Name	Brand Name	Light-Sensitive	Moisture-Sensitive	Temperature-Sensitive
Acyclovir	Zovirax® (GlaxoSmithKline)	+	+	+
Clarithromycin	Biaxin® 250mg tabs (Abbott)	+		
Clarithromycin	Biaxin® XL (Abbott)	+		+
Clarithromycin	Biaxin® granules (Abbott)			+
Erythromycin base	PCE Dispertab	+	+	+
Erythromycin base	Ery-Tab	+		+
Erythromycin base	Eryc	+		+
Griseofulvin ultramicrosize	Gris-PEG® (Pedinol Pharmacal)	+		
Isotretinoin	Accutane® (Roche), Amnesteem® (Mylan), Claravis® (Barr), Sotret® (Ranbaxy) and others	+		+
Itraconazole	Sporanox® (Janssen-Ortho)	+	+	+
Ketoconazole	Nizoral® (Johnson & Johnson)	+	+	
Terbinafine	Lamisil® (Novartis)	+		
Tetracycline HCl	Sumycin	+		+

Table 1: Common dermatologic drugs with sensitivities. + = sensitivity to exposure

4. *United States Pharmacopeia and National Formulary* (USP 31-NF 26). Vol 2,3. Rockville, MD: United States *Pharmacopeia Convention*, pp. 1303, 1786-9, 2084-98, 2301-5, 2479-80, 2488-90, 3359-65 (2008).
5. *Physicians' Desk Reference*. 62nd ed. Montvale, NJ: Thomson PDR (2008).
6. European Pharmacopoeia Commission. *European Pharmacopoeia*. 6th ed. Strasbourg, France: Council of Europe (2007).
7. *British Pharmacopoeia*. London, UK: The Stationery Office (2007).
8. Duchene D, Vaution C, Glomot F. Cyclodextrins, their value in pharmaceutical technology. In: Rubinstein MH, editor. *Pharmaceutical Technology - Drug Stability*. Chichester, NY: Halsted Press;Ellis Horwood, pp. 9-23 (1989).
9. Staub I, Cruz AS, Pinto T, et al. Determinação da segurança biológica do xampu de cetoconazol: Teste de irritação ocular e avaliação do potencial de citotoxicidade in vitro. *Revista Brasileira de Ciencias Farmaceuticas* 43:301 (2007).
10. Yousif MA. In-home drug storage and utilization habits: a sudanese study. *East Mediterr Health J* 8(2-3):422-31 (2002 Mar-May).
11. *World Health Organization: WHO model prescribing information*. Geneva: World Health Organization (2001).
12. MayoClinic.com. Antibiotics: Use them wisely. At: http://www.mayoclinic.com/health/antibiotics/FL00075. Last accessed Dec 2008.
13. MD Consult. Antibiotic Resistance. At: http://www.mdconsult.com/das/patient/body/110084196-2/0/10062/15492.html. Last accessed Dec 2008.
14. American College of Physicians. Antibiotic Resistance. At: http://www.acponline.org/patients_families/disease_conditions/antibiotic_resistance. Last accessed Dec 2008.
15. Karch AM, Karch FE. When it's time to clean out the medicine cabinet. *Am J Nurs* 102(2):23 (2002 Feb).

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Update on Drugs

Name/Company	Approval Dates/Comments
Ceftobiprole *Zeftera*® Johnson & Johnson/ Basilea Pharmaceuticals	The US FDA rejected the New Drug Application for this antibiotic in November 2008. The FDA asked that additional audit work of clinical investigator sites be conducted and that specific questions related to site monitoring be addressed. This formulation has been approved in Canada and Switzerland to treat complicated skin and soft-tissue infections.
IV Iclaprim Arpida Ltd.	The Therapeutic Products Directorate of Health Canada received, in September 2008, a New Drug Submission for this hospital antibiotic drug candidate for the treatment of complicated skin and skin structure infections. This dihydrofolate reductase inbitor has potent bactericidal activity against MRSA and an extended range of pathogens.
HPV Vaccine *Gardasil*® Merck & Co.	The US FDA approved additional indications for this HPV vaccine in September 2008 to include the prevention of vaginal and vulvar cancer caused by HPV types 16 and 18 in girls and women aged 9 to 26 years. The vaccine's label has been revised to note that presently available information is insufficient to support use beyond age 26.
Alitretinoin *Toctino*® Basilea Pharmaceuticals	The Danish Medicines Agency (DKMA) approved this once-daily oral treatment in September 2008 for the treatment of adults with severe chronic hand eczema that is unresponsive to potent topical corticosteroids. Marketing applications for this product are also under review in Canada and Switzerland.
Atazanavir sulfate *REYATAZ*® Bristol-Myers Squibb	The US FDA approved the use of this 300mg once daily product in October 2008 to be boosted with ritonavir 100mg once daily as part of a combination therapy in treatment naïve HIV-1 infected adult patients.

Drug News

In October 2008, Genentech issued a Dear Healthcare Provider letter to inform potential prescribers of a case of progressive multifocal leukoencephalopathy (PML) in a 70-year old patient who had received Raptiva® (efalizumab) for more than 4 years for treatment of chronic plaque psoriasis. The case was recently reported to the company in late September as part of Genentech's ongoing safety monitoring and surveillance program. There are no other cases of confirmed PML in patients treated with this humanized therapeutic antibody, which is approved by the US FDA for the treatment of chronic moderate-to-severe plaque psoriasis in adults 18 years of age or older who are candidates for systemic therapy or phototherapy. The company will work with the US FDA to update the prescribing information for Raptiva® and determine if further action is needed. The Dear Healthcare Provider letter has been posted to the Genentech web site along with the current package insert that includes Raptiva® safety information and is available by clicking the Raptiva® link at http://www.gene.com/gene/products.

The US FDA notified healthcare professionals in November 2008 that it is investigating new preliminary data regarding a potential increase in the risk of serious skin reactions, incoluding Stevens-Johnson syndrome and toxic epidermal necrolysis from phenytoin therapy in Asian patients who are positivie for the human leukocyte antigen allele HLA-B*1502. This allele occurs almost exclusively in Asian patients with ancestry from areas such as China, the Philipines, Malaysia, India, and Thailand. This concern also applies to fosphenytoin because it is a prodrug that is converted to phenytoin after administration. Because this new data suggests a possible association between HLA-B*1502 and phenytoin or fosphenytoin-induced SJS/TEN, and because of the known association between phenytoin and SJS/TEN, healthcare providers should consider avoiding phenytoin and fosphenytoin as alternatives for carbamazepine in patients who test positive for HLA-B*1502.

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Articles are indexed by drug names, trade names and disease terms. Bold entries refer to major references.