CHAPTER 49

ORAL TREATMENT OF ONYCHOMYCOSIS

Joe T. Southerland, D.P.M.

Onychomycosis, or tinea unguium, is a common presentation in the podiatric physician's office. Until recently, however, it has been extremely difficult to treat. Fortunately, due to clinical trials and subsequent FDA approval, several oral agents are proving to be quite effective in the treatment of onychomycosis. The available oral agents which will be reviewed include griseofulvin, ketaconazole, itraconazole, fluconazole, and terbinafine. Although terbinafine is not available as of this writing, it is anticipated that it will be released early in 1996.

GRISEOFULVIN

Griseofulvin, available in various forms and brand names, was introduced in the late 1950s as the first oral antifungal. Its efficacy against lower extremity onychomycosis is much lower than the other available oral drugs, offering a cure rate of 10% to 30%. This low percentage is probably due to the low penetration rate of the agent into the nail keratin.

The normal dosage of griseofulvin for nail infection is 500 mg to 1000 mg daily in adults, and 10 mg/kg to 15 mg/kg in children. The absorption of griseofulvin varies from person to person, but can be increased if taken in micro-sized or ultramicro-sized particles on a full stomach. The duration of treatment is continued until chemical resolution of the onychomycosis is achieved. There are few reported side effects with griseofulvin, with the most common being headache and gastrointestinal distress.

KETACONAZOLE

Ketaconazole, sold under the trade name Nizoral (Janssen Pharmaceutica, Inc., Titusville, N.J.), is in the antifungal category of the imidazoles, and is the first one that is orally-active. Ketaconazole works by blocking the formation of ergosterol in the cell membrane. Dosed at 200 mg daily, ketaconazole has a greater history of hepatic side-effects when compared to the other oral antifungals. Although it has shown to be more efficacious than griseofulvin, ketaconazole still lags behind in effectiveness when compared to the newer agents, itraconazole and fluconazole.

ITRACONAZOLE

Itraconazole, marketed under the trade name Sporanox (Janssen Pharmaceutica, Inc., Titusville, N.J.), is a synthetic triazole antifungal agent that works by inhibiting the cytochrome P-450 dependant synthesis of ergosterol, a vital component of fungal cell membranes. Traditionally, itraconazole has been used in the treatment of histoplasmosis, blastomycosis, and aspergillosis in both immuno-compromised and non-immunocompromised patients. It was approved for the treatment of tinea unguium in 1995.

Because of itraconazole's effect on the cytochrome P-450 enzyme system, it is prone to interactions with other drugs dependant on this system for metabolism. The concomitant use of itraconazole and terfenadine, astemizole, cisapride, or triazolam can result in elevated plasma levels of these particular agents. Therefore, the use of itraconazole and these agents is contraindicated. The use of itraconazole is also contraindicated in pregnant women due to teratogenicity, and it is also excreted in human milk. Due to the effects of itraconazole on the liver, the manufacturer recommends pre-therapy baseline and monthly liver enzyme profiles during treatment.

The recommended dosage of itraconazole for the treatment of onychomycosis is 200 mg daily (on a full stomach), for a period of three months (Figs. 1, 2). However, a pulsed therapy of 400 mg daily for seven days, then discontinue for three weeks, repeated for three to four months may prove to be more effective, if tolerated. Although it takes a new nail approximately six to eight months to grow, the course of drug therapy is only three to four months long. This is due to the fact that itraconazole levels can persist in the tissues 180 to 270 days after the completion of therapy.

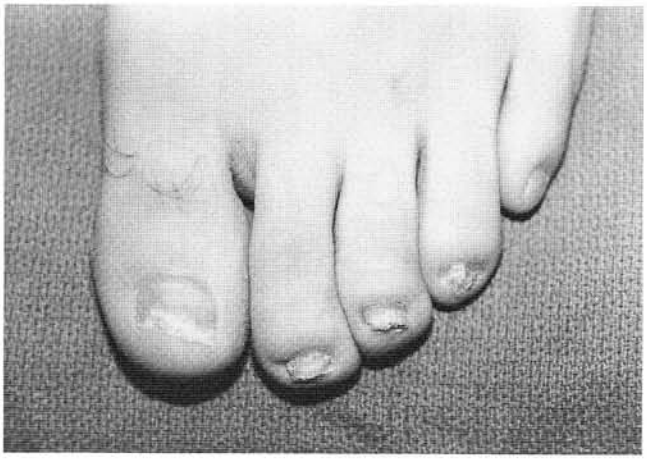

Figure 1. Onychomycosis due to *Mycelia sterilia* and *Trichophyton rubrum* prior to therapy of 200 mg/day itraconazole. The right foot was unaffected.

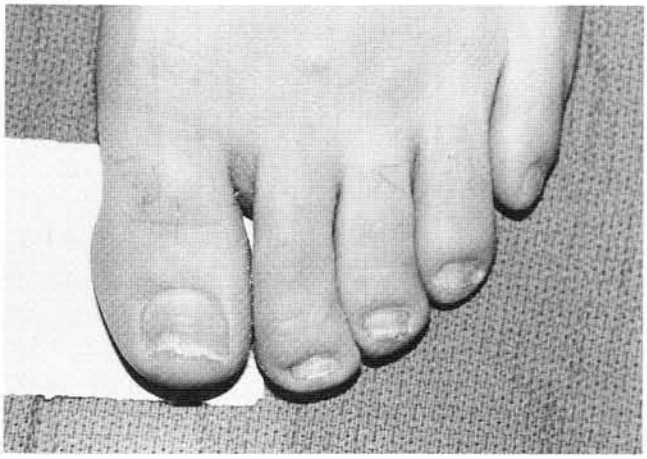

Figure 2. The patient after 8 weeks of daily itraconazole. Note the nail changes, especially in the lesser nails.

FLUCONAZOLE

Fluconazole, marketed as Diflucan (Pfizer-Roerig, A Division of Pfizer, Inc., New York, N.Y.) but not yet approved for onychomycosis, is an azole that works by interfering with ergosterol synthesis. Like itraconazole, it has a history of use in systemic fungal patients. The drug is rapidly absorbed due to its water solubility. However, unlike itraconazole, it does not persist for a long period of time in the tissues after treatment is terminated. Therefore, fluconazole therapy must be continued for a longer period of time than itraconazole. Fluconazole possesses a high cure rate, approaching 80% - 90%.

The dosage of fluconazole has been varied since its introduction, ranging from 100 mg to 200 mg weekly, to 100 mg to 200 mg every-other day. The most effective treatment of onychomycosis appears to be at the higher doses. One study recommended 150 mg every-other day for eight months, to achieve an adequate cure rate.

TERBINAFINE

One of the newer antifungals, that has proven to be very effective topically for skin infection (or tinea pedis), is also available in an oral form. The oral form, as of the writing of this paper, is not yet available in the United States. It is currently undergoing FDA trials, and is projected to be released in 1996. However, it has been available in Europe and has shown very promising results.

Terbinafine, marketed topically as Lamisil (Sandoz Pharmaceuticals Corporation, East Hanover, N.J.), is in a new class of antifungal agents called the allylamines. Unlike any other of the antifungal agents, it is fungicidal not fungistatic. Terbinafine works by inhibiting the fungal enzyme squalene epoxidase.

Terbinafine is generally well-tolerated when given orally, with the main side effects being gastrointestinal distress, headache, and skin rashes. Unlike the imidazoles, terbinafine does not interfere with the cytochrome P-450 enzyme system which could be of benefit in patients who are taking other medications. In one trial, patients with lower extremity onychomycosis responded in a mean time of 28 weeks with a cure rate approaching 80%.

CONCLUSION

The availability of the new oral agents has greatly advanced the treatment of onychomycosis. The addition of itraconazole and the promised addition of terbinafine will allow a wide range of patients to be helped. Before prescribing, however, it is important to be aware of any underlying medical conditions, and any current prescriptions being taken by the patient. These precautions will help make the use of these agents safer.

Table 1

COMPARATIVE DATA ON THE ORAL ANTIFUNGALS

AGENTS	CURE RATE TOE NAILS	RELAPSE RATE	ASYMPTOMATIC LFT* CHANGES	HEPATITIS
GRISEOFULVIN	10-30%	>40%	RARE	VERY RARE
KETACONAZOLE	50%	HIGH	2-10%	.01%
ITRACONAZOLE	70-90%	8-11%	0.3-5%	FEW CASES
FLUCONAZOLE	80-90%	NO DATA	<1%	FEW CASES
TERBINAFINE	70-80%	10-20%	<1%	FEW CASES

*LFT = Liver Function Tests

BIBLIOGRAPHY

Coldron B: Racalcitrant onychomycosis of the toenails successfully treated with fluconazole *Arch Derm* 128(7):909, 1992.

Goodfield MJD, et al: Short Term Treatment of Dermatophyte Onychomycosis with Terbinafine *Br Med J* 304:1151, 1992.

Kraus SJ, Rosen T, Smith EB: Recalcitrant nail fungal infections: onychomycosis update, Program and Abstracts, Presented in Atlanta, GA,June 1995.

Roberts DT: Oral therapeutic agents in fungal nail disease *J Am Acad Derm* 31(3):S78, 1994.

Savin RC: Oral terbinafine versus griseofulvin in the treatment of moccassin-type tinea pedis *J Am Acad Derm* 23(4):807, 1990.

Smith TJ: Onychomycosis: Update and practical management protocol. In Camasta CA, Vickers NS, Carter S:*Reconstructive Surgery of the Foot & Leg*, Update 95 Tucker, GA: Podiatry Institute Publishing; 1995: 301-306.

Wenig JA: The systemic treatment of onychomycosis *Clin Pod Med & Surg* 12(2):263, 1995.