

# Diagnosis and Treatment of Onychomycosis and Other Fungal Infections Including Safety and Efficacy

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Onychomycosis is not just a cosmetic concern to patients, it can bring forth multiples problems and complications such as precipitating recurrent thrombophlebitis and cellulitis of lower extremities, causing pain and mobility problems in elderly patients. Safer and effective medications treating onychomycosis are therefore justifiable.

Diagnosis must be confirmed and if possible, organisms identified prior to commencement of any systemic treatment. It is because only about half of the abnormal nails are due to fungal infection and other condition such as psoriatic nails can sometimes be indistinguishable from onychomycosis clinically. The more popular and effective medications discussed were fluconazole, itraconazole and terbinafine. All three drugs work by interfering with the synthesis of ergosterol in fungal cell membrane. Terbinafine interferes with the conversion from squalene to squalene epoxide. The accumulation of squalene is toxic to the fungal cell membrane. The other two agents, itraconazole and fluconazole belong to the azole group. They interfere with the conversion of lanosterol to 14-demethyl lanosterol, another step of ergosterol synthesis.

One should also beware of the possible drug interactions especially in elderly, those on multiple drugs, impaired renal or hepatic functions, acute or unstable illnesses and AIDS patients. A detailed drug history should be taken before commencing therapy.

## Fluconazole

Fluconazole is a triazole. It is the only new antifungal agent being hydrophilic and therefore carries

a low protein binding and weak tissue affinity. Sixty-five percent of the drug is excreted through kidneys. The half-life ( $T_{1/2}$ ) in plasma is 22-30 hours. In treating onychomycosis, a dose of 150mg to 300mg can be administered once a week for 5-9 months. In a study using 150mg weekly for 5-12 months, the nail concentration was detected to rise up monthly and reached a concentration of 2 mcg/g at sixth month. Fluconazole can raise the serum levels of oral hypoglycemics, anticoagulants, phenytoin, cyclosporine and theophylline. It also inhibits the metabolism of oral contraceptives. On the other hand, rifampicin can increase serum level of fluconazole. Apart from these, caution should be exerted with cytochrome P450 metabolized drugs, for example, cisapride, terfenadine and astemizole.

## Itraconazole

Itraconazole is a lipophilic triazole with high protein binding and strong tissue affinity. The plasma  $T_{1/2}$  is 17-25 hours. It can be administered in pulse therapy regimen at a dosage of 200mg bd during the first week of the month, 2 pulses for fingernails and 3-4 pulses for toenails. When administered daily at 200mg, a period of 2 months is required for fingernails and 3 months for toenails. Studies showed that the drug stayed in nails for another 8 months after 4 pulses. The drug should be taken with food. It has the longest activity among the three antifungal agents. Moreover, it possesses a broad-spectrum antifungal activity and it is also active against moulds such as aspergillosis.

Concerning the drug interaction, Cimetidine ( $H_2$  blockers) and anticholinergics can reduce the efficacy of itraconazole; Cyclosporine and phenytoin levels are reduced whereas digoxin and coumarin levels are increased. Besides, the metabolism of rifampicin and isoniazid can be interfered. Co-administration with terfenadine, astemizole, lovastatin, simvastatin, midazolam, triazolam, and cisapride are contraindicated: Venticular arrhythmia are reported in patients with concomitant administration of terfenadine

or astemizole with azole drugs. For anti-lipid agents, there is an isolated report of acute rhabdomyolysis in patient on lovastatin when additionally treated with itraconazole. In midazolam and triazolam, itraconazole can markedly increase the serum level of these drugs, thereby increase their sedative and amnesic effect and prolonged the duration of hypnotic action. For cisapride, itraconazole can cause a marked rise in serum level of cisapride which can cause serious life-threatening ventricular arrhythmia. However, pulse/intermittent therapy can much reduce the possibility of drug interaction.

### Terbinafine

Terbinafine is an allylamine. It is also lipophilic with high protein binding and strong tissue affinity. It is mainly excreted through kidneys. Plasma  $T_{1/2}$  is 17-24 hours but there is a significant subpopulation of patients wherein the drug would remain in blood for 100 hours. Therefore, it is not a good choice for pulse/intermittent therapy. It is administered continuously at a dosage of 250mg qd, 2 months for fingernails and 3 months for toenails. For drug interaction, terbinafine can decrease caffeine clearance by 19% and increase cyclosporine clearance by 15%. Terfenadine can reduce terbinafine clearance by 16%. It is important to note that cimetidine reduces its clearance by 33% and rifampicin can increase its clearance by 100%.

### Adverse reactions of new antifungal agents

The adverse reactions with these new antifungal agents are mild and infrequent (10-12%) including gastrointestinal upsets (cramps and diarrhoea), headache, urticaria and drug eruption. Terbinafine can cause a reversible taste disturbance. Regarding hepatotoxicity, some authorities concluded that new antifungal agents appear to be implicated in only a rare incidence of hepatic injury, appropriate patient screening and instruction regarding the reporting of adverse events should allow the safe use of these agents.

### Why new antifungals are better?

The new antifungal agents can reach the distal nail plate in 7-21 days whereas griseofulvin needs 6 months to reach fingernail and 9-12 months for toenails. Secondly, the new antifungal agents persist in nails for months after therapy whereas griseofulvin leaves the nails shortly after 1-2 weeks. Because of these properties

of the new antifungals, short-term and pulse/intermittent therapy is feasible. However, each of them has its own pros and cons. Fluconazole acts against dermatophytes and yeasts, it does not require gastrointestinal acidity but there is increasing emergence of *Candida* resistant species; itraconazole has the broadest spectrum of activity (against dermatophytes, yeasts and moulds) but it needs gastrointestinal acidity for absorption (to be taken with food). Terbinafine carries the strongest anti-dermatophytic activity but being less effective against yeast and there is no data concerning activity against mould. Moreover, it can cause taste disturbance.

### Special considerations

In children, oral antifungal agents can be given if the infection is severe. These three agents are safe in children but itraconazole and fluconazole are the drugs of choice because oral suspension is available. For childbearing age and lactating women, treatment should be deferred. Onychomycosis in immunocompromised patients should be aggressively treated. One third of diabetic patients have onychomycosis. Since nail bed rests directly on underlying distal phalanx, onychomycosis may lead to osteomyelitis and 7% of the amputation in diabetics may be associated with onychomycosis. Therefore, onychomycosis should be addressed seriously in diabetic. They should be given a full course of antifungal therapy with combined local physical and mechanical measures; and education on footcare should be given as well. When necessary, maintenance or re-treatment may be required.

### Choosing antifungal

Several points should be considered when making a suitable choice of antifungal drug for patients. They include the past medical history (hepatic and renal diseases, AIDS), drug history, organisms cultured, prior treatment response, pregnancy status and preference of patient (pulse/intermittent/daily).

### Discussion

The speaker was asked to comment on the result of L.I.O.N. (Lamisil vs Itraconazole on onychomycosis) study which showed superiority of terbinafine to itraconazole. Dr. Scher frankly admitted that he could not fully explain the wide discrepancy of efficacy between the two drugs as demonstrated by the study. It could be partially explained by the fact that intestinal

absorption of itraconazole is much dependent on concurrent food intake. During his clinical practice, he actually found the drugs with similar efficacy.

The role of topical treatment in onychomycosis was inquired. Topical treatment may worth a trial if the affected nail area is less than 25% and the thickness of the subungual hyperkeratosis is less than 2 mm. The nail debris should be trimmed away at time intervals during treatment. Finally, the treatment of dermatophytoma was discussed. Dermatophytoma represents a fungal 'abscess' in the nail, consisting of tremendous number of fungal hyphae and clinically manifested as an area of dense yellow streaks. Dr. Scher recommended a partial avulsion of the affected nail together with a course of terbinafine. 15-20% of cases may show no response, when another antifungal agent can be tried. But if it is still ineffective, total nail avulsion can be proceeded.

***Learning points:***

***Co-administration of itraconazole with terfenadine, astemizole, lovastatin, simvastatin, midazolam, triazolam and cisapride are contraindicated.***