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Safety and tolerability of oral antifungal agents in the treatment of fungal nail disease: a proven reality

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Abstract: Clinicians now have five oral antifungal therapeutic agents to choose from when assessing the risk–benefits associated with a particular treatment for onychomycosis (OM): griseofulvin, itraconazole, terbinafine, ketoconazole, and fluconazole. Only the first three are approved by the FDA for this indication. Griseofulvin is fungistatic and inhibits nucleic acid synthesis, arresting cell division at metaphase, and impairing fungal wall synthesis. Due to its low cure rates and high relapse, it is rarely used for treatment of onychomycosis. Itraconazole is a broad spectrum drug and is effective against dermatophytes, candida, and some non-dermatophytic molds. Itraconazole works by inhibiting ergosterol synthesis via cytochrome P-450 (CYP450)-dependent demethylation step. This azole antifungal agent is metabolized in the liver by cytochrome P-450 3A4 (CYP3A4), and therefore has the potential to interact with drugs metabolized through this pathway. Terbinafine, an allylamine, is fungicidal and remains at therapeutic levels in keratinized tissues, but with a short plasma half-life of 36 hours. Terbinafine has the advantage in that it does not inhibit CYP3A4 isoenzyme during its metabolism where some 50% of all commonly prescribed drugs are metabolized. The only potentially significant drug interaction with terbinafine is with the cytochrome P-450 2D6 (CYP2D6) isoenzyme. The lack of widely reported or published clinically relevant drug interactions, and extensive experience from a large prospective, surveillance study conducted in "real world" setting with no patient exclusions, suggest that this is not a major issue. The high cure rates of terbinafine against dermatophytes, as shown in many studies since its launch in the 1990s, together with lack of clinically significant drug interactions and well established safety record, indicate the use of continuous oral terbinafine as the top choice for the treatment of onychomycosis in most patients.

Keywords: antifungal, safety, drug interactions, onychomycosis

Introduction

Onychomycosis is relatively common, with a prevalence of 6.5%–6.8% in the general population in Canada (Gupta et al 1997), 8.5% in the general male population in Finland (Heikkila and Stubb 1995), and up to 18.5% in the US (Ghannoum et al 2004). Some studies suggest that as much as 48% of the population may be affected by the age of 70 (Drake et al 1998; Scher 1999).

Balancing patient safety with therapeutic benefit is a prime directive when treating onychomycosis. There are several oral antifungal agents to choose from when assessing the risk–benefits associated with a particular treatment for onychomycosis; griseofulvin, ketoconazole, fluconazole, itraconazole, and terbinafine, although only three have been approved by the Food and Drug Administration (FDA). Fluconazole, an azole much like itraconazole, can be used, but it is not approved for onychomycosis. Ketoconazole is rarely used due to poor tolerability, low efficacy, and the availability

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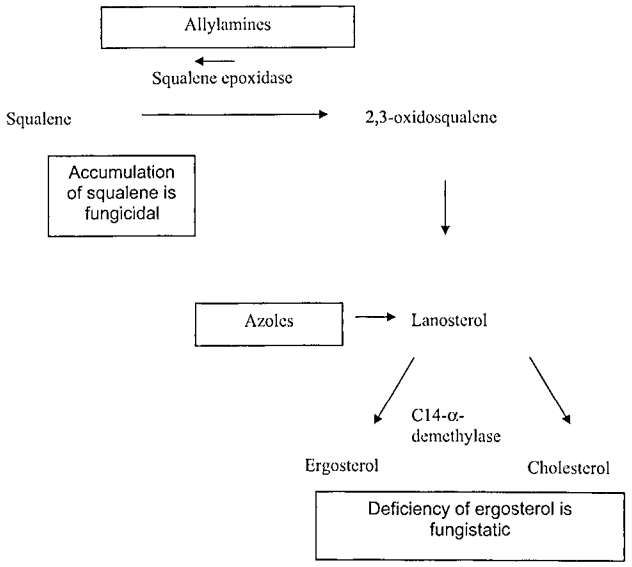

Figure 1 Mode of action of allylamine and azole antifungal agents.

of new antifungal agents. In this review, we compare the mode of action, pharmacokinetics, and potential for drug interactions for various oral antifungal agents. However, the focus is on the mode of action, pharmokinetics, tolerability, and safety of the three FDA approved oral drugs griseofulvin, itraconazole, and terbinafine. An increased understanding of the metabolism of all the oral antifungal agents allows a better appreciation of potential drug–drug interactions, impact on safety, and appropriate choice of therapy. This is particularly relevant as the number of patients on polypharmacy is increasing due to an aging population and increased comorbidities. Moreover, the widespread use of cholesterol-lowering statins and antihypertensive drugs in otherwise healthy individuals may put many patients at risk for drug interactions.

Pharmacokinetics

Mode of action

Griseofulvin acts by disrupting the fungal mitotic spindle, inhibiting cell wall synthesis, whereas azoles act to block ergosterol synthesis, required for assembly of the fungal cell wall, by inhibiting C14α-demethylase, a member of the cytochrome P-450 (CYP450) family. Terbinafine works much like azoles, with the exception that it blocks ergosterol synthesis further upstream by inhibiting squalene epoxidase. This results in cells becoming deficient in ergosterol and causes accumulation of toxic squalene, which, in turn, results in fungal death. This activity makes terbinafine a fungicidal drug compared with azoles which are fungistatic. This step does not involve CYP450 enzymes, therefore drug interactions are not typically an issue (Figure 1).

Absorption

Griseofulvin is poorly absorbed, unless micronized, or coated with polyethylene glycol, or given with fatty meals (Lin et al 1982). Its absorption decreases with repeated administration, possibly due to damage to the mucosal wall by unabsorbed griseofulvin (Debruyne and Coquerel 2001). This agent has therefore largely been superceded by compounds with better pharmacokinetics. The bioavailability of the most effective azole antifungal, itraconazole, is increased by coadministration of food, and decreased in the presence of agents that reduce gastric acidity, eg, antacids, H2 blocker antihistamines, proton pump inhibitors, and the anti-HIV agent, oral didanosine. The efficacy of itraconazole may therefore be compromised by drug coadministration. The bioavailability of terbinafine is good, with 70%–80% of the ingested dose being absorbed,

Table 1 Characteristics of oral antifungal agents

	Metabolic effect	Route of incorporation into nails	Oral absorption	Spectrum of activity	Efficacy
Allylamines (terbinafine)	Accumulation of squalene (fungicidal); depletion of ergosterol (fungistatic)	Via diffusion from nail plate and nail matrix	Good absorption unaffected by food or drug coadministration	Broad	Very high
Triazoles (itraconazole, fluconazole)	Depletion of ergosterol (fungistatic)	Via diffusion from nail bed and nail matrix	Absorption improved if administered with food; absorption decreased if coadministered with agents that decrease gastric acidity	Broad	Intraconazole more effective than fluconazole
Antibiotics (griseofulvin)	Disruption of fungal mitotic spindle (fungicidal)	Deposited in keratin matrix precursor cells	Poorly absorbed but improved if administered with food	Narrow	Low

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