Review

THE PHARMACOKINETIC PROPERTIES OF CURRENT SYSTEMIC ANTIFUNGAL AGENTS

L. Korošec

SUMMARY

Human fungal infections have increased dramatically and are difficult to treat. The spread of HIV/AIDS infection, the use of immunosuppressive drugs and broad-spectrum antibiotics have contributed to the spread of fungal infections. Spontaneous remissions are rare, and recurrence after treatment is common. The pharmacotherapy of the fungal diseases has been revolutionized by the introduction of the relatively non-toxic oral azoles. The systemic treatment with the new antifungal agents - fluconazole, itraconazole, and terbinafine - and the knowledge of their pharmacological and pharmacokinetic properties make possible the pulse therapy in the treatment of the fungal infections. This will be of great benefit for patients from pharmacological as well as pharmacoeconomic aspects.

KEY WORDS

dermatomycosis, onychomycosis, systemic treatment, azoles, ketoconazole, fluconazole, itraconazole, pulse therapy, terbinafine

INTRODUCTION

The incidence and severity of human fungal infections have dramatically increased in recent years, mainly due to advances in surgery, cancer treatment, and critical care accompanied by increases in the use of broad-spectrum antimicrobials and the HIV epidemic.

Pharmacotherapy of fungal diseases has been revolutionized by the introduction of the relatively non-toxical oral azole and allylamine drugs.

The antifungal drugs available belong to several categories: systemic drugs for systemic infections, oral and topical drugs for mucocutaneous infections.

The need for new antifungal agents with better therapeutic profiles arose from the requirement for intravenous and peroral systemic administration and the toxicity of the older antifungal agents. The relatively non-toxic oral azoles represented the first major advance in this direction. These medications have played an increasingly important role in the systemic therapy of fungal diseases, since they were introduced in 1980s.

Table 1. The pharmacokinetic properties of the commonly used systemic azole drugs.

Drug	Water Solubility	Absorption	CSF:Serum Conc. Ratio	t½ (h)	Elimination	Formulation
fluconazole	high	high	> 0.7	22 - 31	renal	oral, i.v.
itraconazole	low	variable	< 0.01	24 - 42	hepatic	oral
ketoconazole	low	variable	< 0.1	2 - 8	hepatic	oral

CLASSIFICATION

Azoles are synthetic compounds. They can be classified as imidazoles or triazoles according to the number of nitrogen atoms in the five-membered azole ring (1) (Fig 1). The imidazoles are represented by ketoconazole, miconazole, and clotrimazole. The triazoles include itraconazole and fluconazole. They are both in common use for systemic treatment of fungal diseases (2).

Each of the azole's pharmacology is unique and accounts for some variations in clinical use. Table 1 and table 2 summarize the pharmacological properties of some commonly prescribed antifungal agents.

The systemic antifungal agents are generally divided to:

1. Allylamines: terbinafine (Lamisil® tbl., Novartis)
2. Azoles: ketoconazole (Oronazol® tbl., Krka), and miconazole (Daktarin® amp., Krka)
3. Triazoles: fluconazole (Diflucan® caps., amp., Pfizer, Dimycon® caps., amp. Alkaloid), itraconazole (Sporanox® caps., Janssen)

The most important pharmacological characteristics of these new oral antifungal systemic drugs are good absorption from the gastrointestinal tract, pronounced keratophilic properties, slow elimination rate from keratinic tissues, prolonged therapeutic effects even after discontinuation of therapy, and higher selectivity and specificity against fungal cytochrome P-450 than mammalian cytochrome P-450.

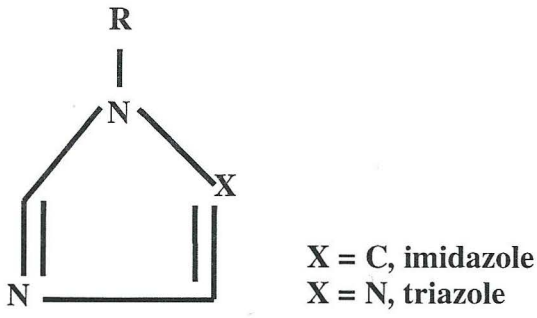

Figure 1. Azole nucleus.

The most common fungal skin infections are: dermatophytoses, pityriasis versicolor and candidiasis. Nail infections - onychomycoses - are notoriously difficult to treat (3,4,5). Infections of the fingernails take up to 6 months to respond to oral griseofulvin and those of the toenails a year or longer. About 60% of nail infections fail to respond or relapse after initial treatment course. The combined therapy with oral griseofulvin and a topical azole may produce a better response (6). The oral use of ketoconazole for nail infections is limited by its potential hepatotoxicity. Itraconazole is reported to be an effective alternative over a shorter treatment period (7,8,9), and also terbinafine may be effective over the same treatment period (10-14). Although topical treatment is generally ineffective in nail infections amorolfine applied as a lacquer has produced encouraging results (15,16). Another approach was the dissolution of the nail plate with 40% urea paste, usually in combination with bifonazole (17,18). Table 3 shows the main antifungal drugs used in the treatment of fungal infections (19-21).

THE "OLD" THERAPY OF ONYCHOMYCOSIS

Onychomycosis is very difficult to treat; the cure rates are low and relapse frequent. Topical antifungals cannot penetrate the nail plate and eradicate the infection in the nail bed; they are useful only in milder forms of disease. The older oral antifungal medications - griseofulvin and ketoconazole - penetrate the nail plate via the nail matrix, but both necessitate prolonged treatment courses (4 to 6 months for fingernails, 10 to 18 months for toenails). Mycological cure rates have been as low as 3% for toenails and 40% for fingernails (4).

Table 2. The antifungal drugs for systemic (p.o.) treatment.

Antifungal agent	FDA approval for p.o	Absorption	Bioavailab.(%)	Peak (h)	Protein binding (%)	Metabolism & Elimination
fluconazole	1990	fast	>90	1 - 2	11 - 12	renal 60-80%
flucytosine	1971	fast	>90	2.5 - 6	2 - 4	renal
griseofulvin	1959	variable	<80	4 - 8	84	renal/hepatic
itraconazole	1992	fast	90-100	4	> 99	hepatic 82-97%
ketoconazole	1981	fast	84-90	2 - 8	> 90	hepatic/renal 63 - 80%
terbinafine	1996	fast	>90	2	99	hepatic 70%

NEW ORAL ANTIFUNGAL AGENTS

The treatment of onychomycosis was changed by the introduction of the triazole and allylamine classes of antifungal agents. Three new drugs - fluconazole, itraconazole and terbinafine - have the advantage of shorter treatment courses, fewer side effects (the most common are gastrointestinal upset, headache, and allergic skin eruptions), and higher cure rates. They also exhibit the "reservoir effect"; which means that therapeutic concentration of the medication remains in the distal nail plate over weeks to months after treatment has been stopped.

TRIAZOLES

Itraconazole and fluconazole are synthetic triazole antifungals that interfere with the 14-α demethylase system, a cytochrome P-450 enzyme that is necessary for the conversion of lanosterol to ergosterol, an essential component of fungal cytoplasmic cell membranes. They have a greater affinity for fungal, as opposed to mammalian, cytochrome P-450. Inhibition of ergosterol synthesis results in increased cellular permeability, which causes leakage of cellular contents. Other antifungal effects of azole compounds have been reported: inhibition of endogenous respiration, interaction with membrane phospholipids, inhibition of yeast transformation to mycelial forms, inhibition of purine uptake and impairment of trigliceride and/or phospholipid biosynthesis (22).

Itraconazole shows maximal oral bioavailability when taken with a full meal. Absorption is impaired if it is taken on an empty stomach or with drugs that alter gastric pH (e.g., antacids, histamine H_2 blockers, or proton pump inhibitors - PPI). Itraconazole undergoes extensive hepatic metabolism. Pharmacokinetic studies showed that itraconazole penetrates the nail plate via the nail matrix and the nail bed. The drug was detected in nails as early as 1 week after oral administration.

Itraconazole reaches the MIC for dermatophytes and most Candida species within 7 to 21 days. Inhibitory concentrations were maintained for up to 6 months in fingernails and for up to 9 months in toenails. Itraconazole can be given by pulse dosing because it remains in the nails but is rapidly eliminated from the plasma. Mycological cure rates with two pulses have ranged from 78%± 10% to 87%± 8% for fingernails and with three pulses up to 77% for toenail onychomycosis (n=1389) (20,23,24).

Recommended dosing regimens are 200 mg per day continuously for 12 weeks for toenail onychomycosis or 200 mg twice daily, for the first week of each month for 2 months for fingernail onychomycosis (19). Pulse dosing for toenail onychomycosis is used frequently, usually three pulses are applied. Table 4. De Doncker (24) recommends for itraconazole in dermatomycoses the 1-2-3 concept: 1-cycle for superficial skin infection, 2-cycles for fingernail infections and 3-cycles for toenail infections.

Fluconazole is a bis-triazole, which, like itraconazole, blocks the enzyme 14-α demethylase. Fluconazole is more resistant to first-pass metabolism and has low protein-binding capacity. Thus it distributes quickly into tissues, and it is rapidly cleared from plasma. Its oral absorption is not affected by the absence of stomach acid. Peak serum concentration and AUC increase in proportion to the dose. Steady-state fluconazole plasma concentrations are achieved within 5-10 days. Therapeutic levels remain in the nails up to 6 months (25), possibly contributing to the increasing cure rates after treatment is discontinued. Fluconazole is well suited to intermittent (i.e., once weekly) dosing. Recent studies indicate that the optimum regimen is 150 to 300 mg once

Table 3. Main drugs for the treatment of fungal infections.

Fungal infections	Drugs
Aspergillosis	amphotericin
Blastomycosis	amphotericin, azoles
Candidiasis	
mucocutaneous	amphotericin, azoles, nystatin, terbinafine
deep or disseminated	amphotericin + flucytosine, azoles
Chromoblastomycosis	flucytosine, itraconazole, thiabendazole, terbinafine
Coccidioidomycosis	amphotericin, azoles
Cryptococcosis	amphotericin, azoles
Hystoplasmosis	amphotericin, azoles
Mycetoma	ketoconazole
Paracoccidioidomycosis	amphotericin, ketoconazole
Pneumocystis carinii pneumonia	co-trimoxazole, pentamidine, amphotericin
Protothecosis	amphotericin
Skin infections	
Dermatophytoses	
superficial	azoles, terbinafine, ciclopirox olamine, tolnaftate, griseofulvin
extensive or disseminated	azoles, griseofulvin, terbinafine, itraconazole, fluconazole
Onychomycosis	azoles, terbinafine, itraconazole, fluconazole, griseofulvin
Pityriasis versicolor	azoles, selenium sulphide, terbinafine (topically), itraconazole, sulfur 10%
Sporotrichosis	
cutaneous	terbinafine, potassium chloride
extracutaneous	amphotericin

weekly until the fungal infection clears – approximately 3 months for fingernails and 6 months for toenails.

ALLYLAMINES

Terbinafine is a synthetic allylamine antifungal agent that is administered either orally or topically. It is pharmacologically similar to naftifine. Oral terbinafine is highly effective for treating onychomycosis due to fungicidal activity and ability to become concentrated within the nail and has been found to be superior to griseofulvin for treatment of onychomycosis. The relapse rate was higher with griseofulvin than terbinafine (26,27). The mechanism of its action is the inhibition of the enzyme squalene epoxidase (monooxygenase), thereby preventing ergosterol synthesis. It also causes an accumulation of squalene, which has a fungicidal activity against dermatophytes. Oral terbinafine is well absorbed from the gut, reaching peak plasma concentrations within 2 hours. Although terbinafine is to 99% protein-bound it is widely distributed, including the central nervous system. Terbinafine rapidly distributes into the nail plate via the nail bed and the nail matrix, reaching minimum inhibitory concentration (MIC) quickly, and remains in the nail plate for up to 10 months (28). Most of the oral dose (70%) is metabolized through oxidation and hydrolysis to the dihydrodiol, and excreted in the urine. There are no significant active metabolites. Mycological cure rates of 70% for toenails and 79% for fingernails are reported (26,27). 2-year mycological cure rates for infections caused by Candida species are more variable and have been reported as 52% for toenails and 65% for fingernail (29). Relapse is unlikely after terbinafine treatment.

Pulse dosing regimens (typically, 1 week on therapy, 3 weeks off therapy) are reported to be as effective as continuous dosing (30). Pulse therapy is possible because terbinafine remains in the nail plate for extended periods. Pulse dosing may also reduce side effects. Although terbinafine does not have many side effects, its pharmacokinetic profile does not readily suggest that it should be dosed this way (it may remain longer in the blood than the triazoles do (20,24,25). Dosage adjustment is not needed in elderly patients since the pharmacokinetics in elderly patients have been shown to be comparable to healthy volunteers (31).

Table 4. New antifungal agents for systemic treatment of onychomycoses: dosage, activity, and contraindications.

Drug	Dosage	Activity	Contraindications
terbinafine	*Toenails*:250 mg/d x 12 consecutive weeks *Fingernails*: 250 mg/d x 6 consecutive weeks	*Fungicidal* against dermatophytes, some Candida species, and some moulds *Fungistatic* against C. albicans and some moulds	Hypersensitivity to terbinafine
itraconazole	*Toenails*: 200 mg/d x 12 consecutive weeks; or 200 mg twice daily 7 days, and 3 weeks pause, 3 pulses *Fingernails*: 200 mg twice daily 7 days, and 3 weeks pause, 2 pulses	*Fungistatic* against dermatophytes, yeasts, some nondermatophytic fungi	Hypersensitivity to itraconazole or other azoles Concurrent use of cisapride, lovastatin, terfenadine or triazolam
fluconazole	*Toenails*: 150-300 mg once weekly, until infection clears *Fingernails*: 150-300 mg once weekly, until infections clears	*Fungistatic* against dermatophytes, most Candida species, some nondermatophytic fungi	Hypersensitivity to fluconazole or other azoles Caution with oral hypoglycemics, cumarin-type anticoagulants, phenytoin, cyclosporine, rifampicin, theophylline, hydrochlorothiazide, cimetidine, terfenadine, cisapride and astemizole

CONCLUSIONS

The new generation of oral antifungal agents is basically safe for treatment of onychomycosis. We can say that new systemic drugs, because of their pharmacokinetic properties and their biphasic penetration, can be a key to rational therapy, presupposing a rational dosing strategy. The reduction from previous long-term therapies to a three-month therapy and now the pulse therapy represents a great advance.

Pharmacokinetic studies showed that the optimal treatment regimens for superficial fungal infections of the skin and of onychomycosis of the fingernails and toenails differ. Thus, the total amount of antifungal agent required depends on the site of infection. The concept with pulse therapy provides a global and unique strategy in dermatomycoses, and offers several advantages, most notably:

- reduction in the total drug dosage and hence reduced potential of drug's side effects
- improved patient compliance
- increased flexibility and
- reduced total therapeutic costs.

REFERENCES

1. Martindale The Extra Pharmacopoeia 31st ed. Ed. Reynolds JEF, The Royal Pharmaceutical Society, London 1996: 393-417.

2. Sheppard D, Lampris HW. Antifungal Agents. In: Katzung BG. Basic and Clinical Pharmacology, 7th ed, Appleton and Lange, Stamford, Connecticut, 1998:780-7.

3. Anonymous. Onychomycosis and terbinafine. Lancet 1990; 335:636

4. Korting HC, Schaefer-Korting M. Is tinea unguium still widely incurable? A review three decades after introducing of griseofulvin. Arch Dermatol 1992; 128:243-8.

5. Goodfield MJD et al. Treatment of dermatophyte infection of the finger- and toe-nails with terbinafine (SF 86-327, Lamisil), an orally active fungicidal agent. Br J Dermatol 1989; 121:753-7.

6. Hay RJ et al. A comparison of tioconazole 28% nail solution versus base as and adjunct to oral griseofulvin in patients with onychomycosis. Clin Exp Dermatol 1987; 12:175-7.

7. Degreef H. The treatment of superficial skin infections caused by dermatophytes. Curr Top Med Mycol 1992; 4:189-206.

8. Hay RJ et al. An evaluation of itraconazole in the management of onychomycosis. Br J Dermatol 1988; 119:359-66.

9. Piepponen T et al. Efficacy and safety of itraconazole in the long-term treatment of onychomycosis. Antimicrob Chemother 1992; 29:195-205.

10. Arikian SR et al. A multinational pharmacoeconomic analysis of oral therapies for onychomycosis. Br J Dermatol 1994; 130(suppl 43):35-44.

11. Hay RJ et al. A comparison of 2 weeks of terbinafine 250 mg/day with 4 weeks of itraconazole 100 mg/day in plantar-type tinea pedis. Br J Dermatol 1995;132:604-8.

12. Anonymous. Terbinafine for dermatophytes in skin and nail. Drug Ther Bull 1992;12:47-8.

13. Goodfield MJD et al. Short term treatment of dermatophyte onychomycosis with terbinafine. Br Med J 1992;304:1151-4.

14. Shuster S, Munro SC. Single dose treatment of fungal nail disease. Lancet 1992;339:1066.

15. Reinel D. Topical treatment of onychomycosis with amorolfine 5% nail lacquer: comparative efficacy and tolerability of once and twice weekly use. Dermatology 1992;184:21-4.

16. Anonymous. Amorolfine - putting a gloss on infected nails. Drug Ther Bull 1992;30:19.

17. Nolting S. Non-traumatic removal of the nail and simultaneous treatment of onychomycosis. Dermatologica 1984;169:117-20.

18. Roberts DT et al. Topical treatment of onychomycosis using bifonazole 1% urea/40% paste. Ann NY Acad Sci 1988;544:586-7.

19. Denning DW et al. Fungal nail disease: a guide to good practice (report of a working group of the British Society for Medical Mycology). Br Med J 1995;311:1277-81.

20. Scher RK, Coppa LM. Advances in the diagnosis and treatment of onychomycosis. Hosp Med 1998;34:11-20.

21. Veller Fornasa C, Carrozzo V, Forte I, Peserico A. Cutaneous lymphatic sporotrichosis treated with terbinafine. Acta Dermven APA 1994;3:161-3.

22. Borgers M. Mechanism of action of antifungal drugs, with special references to the imidazole derivatives. Rev Inf Dis 1980;2:520-34.

23. De Doncker P et al. Antifungal pulse therapy for onychomycosis. A pharmacokinetic and pharmacodynamic investigation of monthly cycles of 1-week pulse therapy with itraconazole. Arch Dermatol 1996;132:34-41.

24. De Doncker P, Gupta AK, Marynissen G, Stoffels P, Heremans A. Itraconazole pulse therapy for onychomycosis and dermatomycosis: an overview. J Am Acad Dermatol 1997; 37(6): 969-74.

25. Fergemann N, Laufen H. Levels of fluconazole in normal and diseased nails during and after treatment of onychomycosis in toe-nails with fluconazole 150 mg once weekly. Ac Derm Venerol 1996;76:219-25.

26. Hofmann H et al. Treatment of toenail onychomycosis: a randomized double-blind study with terbinafine and griseofulvin. Arch Dermatol 1995, 131:919-22.

27. Hankeke E et al. Short treatment of fingernail dermatomycosis: a randomized, double-blind study with terbinafine and griseofulvin. J Am Acad Dermatol 1995; 32:72-7.

28. Schatz F et al. Nail incorporation kinetics of terbinafine in onychomycosis patients. Clin Exp Dermatol 1995; 20:377-83.

29. Nolting S, Brautigam M, Weidinger G. Terbinafine in onychomycosis with involvement by non-dermatophytic fungi. Br J Dermatol 1994;130(S43):16-21.

30. Alpsoy E, Yilmaz E, Basaran E. Intermittent therapy with terbinafine for dermatophyte toe-onychomycosis: new approach. J Dermatol 1996; 23(4): 259-62.

31. Reents S, Seymour J. Terbinafine. In: Clinical Pharmacology, GSM Inc., Tampa, FL 1997:1-2.

AUTHOR'S ADDRESS

Ladko Korošec MD, MSc, pharmacologist, Dpt. Pharmacology, Medical Faculty, University of Ljubljana, Korytkova 2, SI-1000 Ljubljana, Slovenia.