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Itraconazole
A Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Use in Superficial and Systemic Mycoses

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Synopsis

Itraconazole is an orally active triazole antifungal drug which has demonstrated a broad spectrum of activity and a favourable pharmacokinetic profile. It is a potent inhibitor of most human fungal pathogens including Aspergillus *sp.*

In non-comparative clinical trials itraconazole was shown to be extremely effective in a wide range of superficial and more serious 'deep' fungal infections when administered once or twice daily. Generally, greater than 80% of patients with superficial dermatophyte or yeast infections are cured by itraconazole. Similarly, good to excellent response rates (clinical cure or marked improvement) are achieved in paracoccidioidomycosis, histoplasmosis, sporotrichosis, blastomycosis, systemic candidiasis, coccidioidomycosis, chromomycosis, aspergillosis and cryptococcosis. Understandably, given the rare nature of some of these diseases, clinical experience is relatively limited and further evaluation, preferably controlled trials with amphotericin B and ketoconazole, would help clarify the ultimate role itraconazole will have in their management. Preliminary findings also indicate that itraconazole may hold promise for the prophylaxis of opportunistic fungal infections in patients at risk, for example women with chronic recurrent vaginal candidiasis, immunodeficient patients with chronic mucocutaneous candidiasis, AIDS patients and patients receiving immunosuppressant drugs. In studies to date itraconazole has been very well tolerated. Transient changes in indices of liver function occurred in 1 to 2% of patients; however, symptomatic liver dysfunction (as occurs infrequently with ketoconazole) has not been reported. Wider clinical experience is needed to permit clear conclusions as to whether liver dysfunction can result from itraconazole administration.

Thus, while several aspects of the drug's profile require further investigation, itraconazole is a promising new oral treatment of fungal disease. The extent to which itraconazole will be employed in preference to ketoconazole will be clarified by wider clinical experience.

Pharmacodynamic Studies

Itraconazole was active *in vitro* against a wide variety of fungi with a spectrum of activity which qualitatively resembles that of ketoconazole, the first oral azole to gain widespread acceptance. This spectrum includes dermatophytes (e.g. *Microsporum*, *Trichophyton* and *Epidermophyton* species), yeasts (e.g. *Candida* spp., *Pityrosporum* spp. and *Cryptococcus neoformans*), dimorphic fungi (e.g. *Histoplasma*, *Paracoccidioides brasiliensis*, *Blastomyces dermatitidis* and *Sporothrix schenckii*), various organisms which cause chromomycosis, and other fungi including *Aspergillus fumigatus*. Quantitatively itraconazole was more potent than ketoconazole, although *in vitro* results vary considerably depending on culture medium, inoculum size, conditions of incubation, etc. Because of the variability of *in vitro* results these tests may not necessarily reflect *in vivo* efficacy.

In *in vivo* models of superficial mycoses itraconazole was effective orally and topically in treating dermatophytic infections. Cutaneous candidiasis in guinea-pigs and vaginal candidiasis in the pseudoestrus rat were cured by itraconazole. In guinea-pigs injected intravenously with *Candida albicans*, itraconazole improved the survival rate at a dosage of 0.63 mg/kg/day and prevented systemic disease at 5 mg/kg/day administered for 21 days. While all control animals infected with *Aspergillus fumigatus* died, > 80% of guinea-

pigs, including immunocompromised animals, treated with itraconazole 5 mg/kg/day survived and most were culture negative and free of organ necrosis. Itraconazole 200mg daily sterilised the cardiac vegetations of rabbits infected with *A. fumigatus* and improved the survival rate of these animals in comparison to those treated with amphotericin B and/or 5-fluorocytosine. In *in vivo* models of cryptococcal meningitis itraconazole sterilised CSF cultures in the majority of animals. Higher doses of itraconazole (40 mg/kg/day) cured guinea-pigs with a disseminated infection of *Sporothrix schenckii* and *Histoplasma capsulatum* var. *duboisii*. Itraconazole 200 mg/kg/day administered for 7 weeks effected parasitological cure in mice infected with a virulent inoculum of *Trypanosoma cruzi*.

The mechanism of action of itraconazole relates to its binding of fungal cytochrome P-450 isozymes with resultant inhibition of ergosterol synthesis and perturbation of membrane-bound enzyme function and membrane permeability. Itraconazole binds more avidly to fungal cytochrome P-450 than does ketoconazole and, unlike ketoconazole, has little effect on mammalian cytochrome P-450 enzyme systems. There is some preliminary evidence that fungal killing by host defence cells is facilitated by the antifungal activity of itraconazole, although the clinical significance of this is not yet clear.

Pharmacokinetic Studies

Following oral administration of itraconazole peak plasma concentrations are reached within 1.5 to 4 hours. Absorption varies between individuals but is improved when the drug is administered with a meal and this schedule is recommended to maximise therapeutic effect. Steady-state plasma concentrations are achieved after 14 days' administration and the concentrations attained with 100mg daily (peak and trough concentrations of 0.6 and 0.2 mg/L, respectively) should be effective against most common fungal pathogens.

Itraconazole is widely distributed in the body, achieving concentrations in some tissues up to 10 times higher than corresponding plasma concentrations. Itraconazole can be detected in stratum corneum up to 4 weeks after discontinuing therapy, which probably reflects the drug's affinity for sebum and for keratinocytes. Low to negligible concentrations of itraconazole are found in cerebrospinal fluid. The drug is 95% protein bound, primarily to albumin. Only 0.2% of itraconazole in plasma is present as free drug, the remainder being bound to blood cells.

Itraconazole undergoes extensive hepatic metabolism prior to being excreted in inactive form in urine and bile. Itraconazole biotransformation may be a saturable process at clinically useful dosages leading to disproportionate increases in AUC for a given dosage increment. The elimination half-life in healthy volunteers is about 20 hours after a single oral dose of 100mg and approximately 30 hours following 2 to 4 weeks' treatment with itraconazole 100mg once daily. In patients with renal impairment, the disposition of itraconazole does not differ significantly from that of healthy subjects. Haemo- and peritoneal dialysis have a negligible effect on itraconazole clearance, hence dosage supplements are not necessary. Preliminary evidence suggests that dosage adjustment is not required in patients with liver dysfunction; however, further studies are needed to confirm these findings.

Therapeutic Use

Most clinical experience with itraconazole in superficial mycoses has been gained from non-comparative studies, particularly a few large multicentre trials and some dose-finding clinical trials. Overall, itraconazole 100mg once daily has proven to be the optimal dosage in dermatophytoses, producing $\geq$ 80% clinical and mycological response (cure or marked improvement) against tinea corporis, tinea cruris, tinea pedis and tinea manuum. Itraconazole 50mg once daily elicited less consistent results, while there is some evidence that a higher dosage (200mg once daily) may permit shorter courses of treatment. In very limited experience with the treatment of tinea capitis, itraconazole 100mg once daily produced an excellent therapeutic response, although therapy was more prolonged (3 to 7 weeks). Compared with griseofulvin 500mg (ultramicronised) once daily itraconazole 100mg once daily was superior in terms of mycological clearance in patients

with various tinea infections, and it also produced a significantly better clinical response in patients with tinea corporis and tinea cruris. Studies in patients with pityriasis versicolor showed that, provided the total dosage was ≥ 1000mg, itraconazole cured more than 90% of patients and helped reduce the number of early relapses. Itraconazole 200mg daily for 5 days was found to be as effective as selenium sulphide 2.5% shampoo but tended to be better tolerated. Reduction in *P. orbiculare* colonisation during treatment with itraconazole 50 to 100mg daily was associated with clearing or marked improvement of lesions in a small number of patients with sebopsoriasis. In women with acute vaginal candidiasis itraconazole maintained initial mycological clearance during a follow-up period of 4 weeks in at least 80% of patients provided a minimum total dosage of 400mg had been administered. For recalcitrant vaginal candidiasis itraconazole 200mg once daily for 3 days produced the best results; symptoms such as leucorrhoea, pruritus, dysuria and dyspareunia were relieved in > 90% of cases. Preliminary data indicate that one day's treatment with itraconazole (400mg in 2 divided doses) produced mycological cure in > 80% of women with acute infection and that a single 200mg dose on the first day of menses may provide effective prophylaxis in patients with chronic recurrent disease.

Itraconazole 100mg once daily has also proven useful in fungal diseases such as chronic mucocutaneous candidiasis and chromomycoses although, as expected, much longer durations of treatment have been necessary. Further study is needed to determine whether itraconazole can maintain a remission in these problematic conditions, particularly in chronic mucocutaneous candidiasis patients.

As expected, far fewer patients with systemic mycoses have been treated with itraconazole, and it is probably too early to clearly define how useful it will prove in these diseases. However, preliminary experience is extremely encouraging and clinical cure or significant improvement has been documented in > 80% of patients with paracoccidioidomycosis, sporotrichosis, histoplasmosis and blastomycosis. Itraconazole has also proven very useful in the treatment of systemic candidiasis, chromomycosis, coccidioidomycosis, aspergillosis and cryptococcosis (including meningeal cryptococcosis). In most cases itraconazole dosage was initiated at 200mg daily and titrated up to 400mg in 1 or 2 divided doses if the patient failed to respond. Preliminary findings suggest that itraconazole may hold promise for the prophylaxis of invasive opportunistic fungal infections in patients at risk, for example AIDS patients and those receiving immunosuppressant drugs. Indeed, in small pilot studies itraconazole 200mg twice daily was significantly superior to ketoconazole 200mg twice daily in protecting patients undergoing immunosuppressive therapy from fatal *Aspergillus* infections.

Adverse Effects

Itraconazole is well tolerated by most patients, the most common side effects relating to gastrointestinal disturbances. The incidence of side effects increases with duration of treatment; administration for ≥ 1 month results in an incidence of adverse effects of 17.7%, with a resulting dropout rate of 4.7%. Itraconazole appears to be devoid of effects on the pituitary-testicular-adrenal axis at the dosages used to date. Rarely, transient increases in liver enzymes have occurred; however, no cases of symptomatic liver dysfunction have been reported. Seven instances of hypokalaemia have been described.

Dosage and Administration

The recommended itraconazole dosage for superficial fungal infections is 100mg once daily at mealtime for: 15 days in patients with tinea corporis/cruris; 30 days, tinea pedis/manuum; 4 to 8 weeks, tinea capitis, and a minimum of 3 to 6 months, onychomycoses. In pityriasis versicolor, vaginal candidiasis and fungal keratitis the recommended dosage is 200mg once daily for 5 days, 3 days, and 3 weeks, respectively. The initial dose in systemic mycoses is 200mg daily increased to 400mg daily in 1 or 2 divided doses when oral absorption is questionable and/or response is inadequate. Treatment length in systemic disease should be individualised by clinical and mycological response. It is recommended that treatment continue beyond an apparent mycological cure, although the length of this additional treatment has not been well defined. In children the recommended dose is 3 to 5 mg/kg/day. Itraconazole is contraindicated in pregnancy.

1. Pharmacodynamic Studies

Itraconazole is an azole derivative, more specifically a triazole analogue (fig. 1), which has been found to be very active following oral administration. *In vitro* and *in vivo* assessments of antifungal activity have demonstrated that itraconazole possesses excellent activity against most human fungal pathogens. Indeed, preliminary evidence suggests that it may be more potent and have a broader spectrum of activity than ketoconazole, which was the first orally active azole derivative to gain widespread acceptance.

1.1 Antimicrobial Activity *In Vitro*

Results from quantitative tests of antifungal potency can vary significantly depending on test protocol. The MICs of the azole derivatives are affected in particular by culture medium, pH and inoculum size (Odds et al. 1984; Saag & Dismukes 1988; Van Cutsem et al. 1986). Indeed, in some test media, the low solubility of itraconazole becomes problematic (Van Cutsem et al. 1987a). Consequently, *in vitro* results must be considered a poor guide to antimicrobial usefulness. *In vivo* results may reflect therapeutic efficacy more accurately, sometimes demonstrating significant activity where *in vitro* results were disappointing (see section 1.2).

Tables I and II summarise the *in vitro* activity of itraconazole and, where data are available, compare it with MIC values for ketoconazole reported within the same studies. Although these results cannot necessarily be extrapolated to fungal isolates at different institutions, they suggest that itraconazole is a very potent antifungal agent and is generally more active than ketoconazole under identical test conditions.

The dermatophytes, *Microsporum*, *Trichophyton*, and *Epidermophyton* species, are all very sensitive to itraconazole, including *T. schoenleinii*, the favus fungus. Two isolates of *Trichophyton* spp., one each of *T. mentagrophytes* and *T. tonsurans*, required 10 mg/L for complete growth inhibition; 95% of isolates were sensitive to 0.1 mg/L (Van Cutsem et al. 1987a). Similarly, the range of MICs

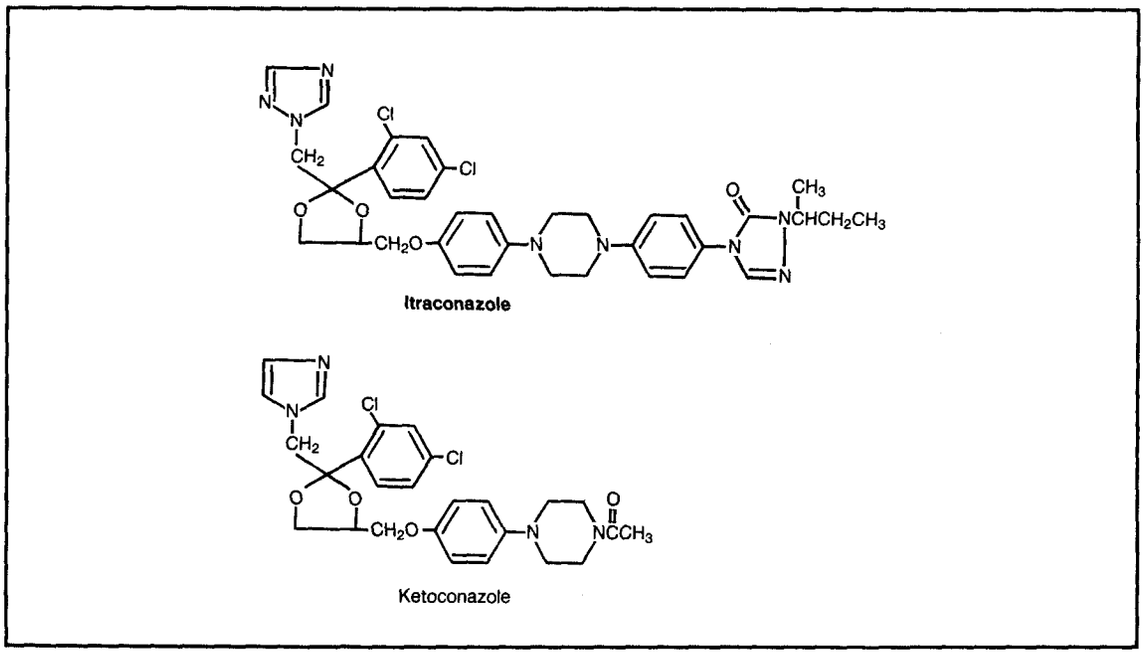

Fig. 1. Structural formulae of itraconazole and ketoconazole.

Table I. *In vitro* studies comparing the activity of itraconazole and ketoconazole as determined on Kimmig agar (from Espinel-Ingroff et al. 1984)

Organism	No. of isolates	MIC_{90} (mg/L)	
		itraconazole	keto-conazole
Dermatophytes			
Trichophyton sp.	15	4	2
Microsporum sp.	10	0.25	2
Epidermophyton floccosum	5	0.063	0.25
Yeasts			
Candida albicans	11	128	16
C. parapsilosis	6	> 128	4
C. tropicalis	7	> 128	64
Torulopsis glabrata	4	128	4
Cryptococcus neoformans	10	0.063	0.25
Dimorphic fungi (mycelial phase)			
Blastomyces dermatitidis	10	0.13	1
Histoplasma capsulatum	10	0.063	0.25
Sporothrix schenckii	10	4	2
Zygomycetes			
Rhizopus sp.	5	> 128	> 128
Mucor sp.	3		
Other Eumycetes			
Aspergillus fumigatus	10	0.13	8
A. flavus	9	0.13	1
Fonsecaea pedrosoi	3	> 128	> 128
Phialophora verrucosa	3		
Exophiala jeanselmei	4	0.13	0.5
Wangiella dermatitidis	5		
Cladosporium bantianum	4		

for *Trichophyton* spp. in the study by Espinel-Ingroff et al. (1984) was very large (0.063 to 64 mg/L) and the resulting MIC_{90} (4 mg/L) was considerably higher than the values noted for other dermatophyte species.

The range of MICs for yeast species was quite large, the majority of isolates requiring 0.001 to 10 mg/L for complete growth inhibition (table II). Two of 1076 isolates of *Candida albicans*, 1 of 43 isolates of *C. krusei* and 1 of 159 isolates of *Torulopsis glabrata* required 100 mg/L for complete inhibition of growth (Van Cutsem et al. 1987a). In this study, comparison of ketoconazole and itraconazole activity against a number of *Candida* spp. and *Cryptococcus* spp. suggests that, in brain-heart infusion broth, these drugs have similar activity against yeasts. Conversely, in the agar dilution study of Espinel-Ingroff et al. (1984), *Candida* spp. (28 isolates tested) were resistant to itraconazole, while *C. neoformans* remained very sensitive (table I).

A further study has been published which addresses the perceived pathogenic process in *Candida* infections by using the inhibition of yeast-mycelial transformation as the end-point of antifungal activity (Schaude et al. 1987). In this study yeast-mycelial transformation MICs were determined for various antifungal drugs against 19 isolates of *C. albicans* grown in broth which contained a chitin precursor to induce hyphal growth (table III). The results correlated well with the observed therapeutic efficacy of currently available antifungals and indicate that itraconazole is at least as active as other azole derivatives. A similar approach was used by Strippoli et al. (1988) who determined the concentration of itraconazole which inhibited germ tube formation by 10 strains of *C. albicans*, 6 strains of *Aspergillus* spp. and a mixture of 10 strains of Hyphomycetes (*A. fumigatus, A. niger, A. nidulans, M. canis, T. rubrum, Mucor* sp. and *Penicillium* sp.). Itraconazole completely inhibited spore germination in all strains of *Aspergillus* spp. at concentrations of 6.25 to 12.5 mg/L. Simultaneous tests with ketoconazole revealed a marked difference in potency; 60 to 100 mg/L of ketoconazole was required to achieve the same effect. Similar activity against germ tube formation by non-*Aspergillus* hyphomycetes was observed for both azoles but itraconazole was the more active agent against *C. albicans* germination.

Of the dimorphic fungi tested, *Blastomyces dermatitidis* (blastomycosis), *Paracoccidioides brasi-*

Table II. The *in vitro* activity of itraconazole (I) as determined in brain-heart infusion broth. Same-study comparison with ketoconazole (K) included where data available (Van Cutsem et al. 1987a,b)

	Range of MIC (mg/L)							No. of strains tested
	0.001	0.01	0.1	1	10	100	> 100	
Dermatophytes								
Microsporum canis		I	I					43
M. audouini		I	I					4
M. gypseum		I	I					2
Trichophyton rubrum	I	I	I					127
T. mentagrophytes	I	I	I	I	I			47
T. schoenleinii		I	I					2
T. verrucosum		I	I	I				8
T. violaceum		I	I					9
T. tonsurans			I	I	I			3
Epidermophyton floccosum	I	I	I					10
Dermatophyte spp.		I	I	I				NA[c]
			K	K				NA
Yeasts								
Candida albicans	I	I	I	I	I	I		1,076
C. stellatoidea	I	I	I	I				4
C. tropicalis	I	I	I	I				68
C. parapsilosis		I	I	I	I			65
C. krusei	I	I	I	I	I	I		43
Torulopsis glabrata	I	I	I	I	I	I		159
Cryptococcus neoformans		I	I					27
Pityrosporum ovale[a]			I	I				22
Candida sp. + *Cryptococcus* sp.		I	I					NA
		K	K	K				NA
Dimorphic fungi								
Blastomyces dermatitidis	I	I	I					3
Paracoccidioides brasiliensis	I	I	I					5
Histoplasma spp.	I	I						2
Sporothrix schenckii			I	I				12
Zygomycetes								
Mucor sp.				I	I			2
Rhizopus sp.						I		1
Other eumycetes								
Aspergillus fumigatus		I	I	I				NA
				K	K	K		NA
A. nidulans		I	I					17
				K				9
A. niger					I	I		5
A. flavus			I					1
Cladosporium spp.	I	I	I					2
				K				2
Fonsecaea pedrosoi	I	I	I	I				13
			K	K	K			11
Phialophora verrucosa		I						1
				K				1

Table II. Contd

	Range of MIC (mg/L)							No. of strains tested
	0.001	0.01	0.1	1	10	100	> 100	
Trichosporon beigelii		⊢	—	—	—	—		7
Fusarium sp.			⊢	—	—	—	—	5
				K	—	—	K	5
Hendersonula toruloidea					⊢	—		3
Scopulariopsis brevicaulis						⊢	—	14
Madurella spp.	⊢	—	—					2
			K	—	—	K		2
Actinomycetales[b]					⊢	—	—	5
				K	—	—	K	7

a In Dixon broth.

b 1 species each of *Nocardia brasiliensis, N. asteroides, Streptomyces pelletieri, S. somaliensis, Actinomyces Israeli* (in fluid thioglycollate).

c NA = not available.

liensis (South American blastomycosis), and *Histoplasma* sp. (histoplasmosis) were all very sensitive to itraconazole (MICs ≤ 0.13 mg/L). *Sporothrix schenckii*, a dimorphic fungus responsible for the subcutaneous mycosis sporotrichosis, required an itraconazole concentration of ≥ 1 mg/L for complete growth inhibition.

With the exception of *Madurella* spp., the majority of mycetoma fungi were resistant *in vitro* to all but the highest concentrations of itraconazole. As well, *zygomycetes*, most *Fusarium* spp., and *actinomycetales* were generally resistant to clinically achievable plasma concentrations of itraconazole.

Cladosporium sp., *Fonsecaea pedrosoi* and *Phialophora verrucosa*, all causative organisms of chromomycosis, were highly sensitive to itraconazole when tested in brain-heart infusion broth (table II). The MICs of itraconazole for these fungi were lower than the MICs of ketoconazole by 10- to 1000-fold. This pattern of sensitivity was not duplicated in the agar dilution tests (table I) where *F. pedrosoi* and *P. verrucosa* were resistant (MICs > 128) to both drugs.

Significantly more sensitive to itraconazole than to ketoconazole in both brain heart infusion broth and Kimmig agar was *Aspergillus fumigatus*. Indeed, itraconazole was the most potent systemic agent tested against 8 clinical isolates of *Aspergillus* sp. in the study by Odds et al. (1984). This study expressed antifungal potency in relative inhibition factors (RIF) which were determined by measuring the area under a sector of the dose-response curve (drug concentration *vs* fungal biomass) relative to a theoretical curve where 100% is non-inhibitory and 0% is totally inhibitory (table IV). These RIF data correlated well with *in vivo* results for established non-azole antifungals and appeared to be more reliable than conventional MIC determination methods for predicting the antifungal efficacy of azole compounds. This method predicts that

Table III. Minimum inhibitory concentrations of various antifungals to the yeast-mycelial (Y-M) transformation of *C. albicans* isolates (from Schaüde et al. 1987)

Drug	Y-M transformation	
	MIC_{90} (mg/L)	MIC range (mg/L)
Itraconazole	**0.195**	**0.003-0.195**
Ketoconazole	0.012	0.012-0.025
Clotrimazole	0.00076	0.00019-0.0015
Econazole	0.049	0.025-0.049
Miconazole	0.049	0.025-0.049
5-Fluorocytosine	0.098	0.006-0.098
Amphotericin B	0.78	0.195-0.78
Griseofulvin	6.25	1.56-6.25
Tolnaftate	100.00	50.00-100.00

Table IV. Relative inhibition factors of several antifungals tested *in vitro* against 8 clinical isolates of *Aspergillus* sp. (after Odds et al. 1984)

Drug	Relative inhibition factor [mean % (range)][a]
Itraconazole	**25 (19-30)**
Ketoconazole	54 (43-71)
Clotrimazole	47 (37-58)
Miconazole	67 (54-81)
5-Fluorocytosine	92 (79-100)
Amphotericin B	36 (26-49)
Griseofulvin	97 (91-100)

a Value approaches 0% for a drug to which the fungus is highly sensitive, and approaches 100% for a drug which is non-inhibitory.

itraconazole would be effective clinically against aspergillosis.

With the notable exception of 5-fluorocytosine, antifungal drugs are not commonly associated with the development of resistant organisms even though treatment of fungal infections is often very lengthy. Iwata et al. (1987) attempted to induce resistance to itraconazole in 6 clinical isolates of *C. neoformans* sensitive to $\leq$ 1.25 mg/L of the drug; however, following 10 passages in the presence of increasing itraconazole concentrations, the MICs of all 6 strains were not significantly changed. Mutagenesis with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine produced 1 resistant mutant which displayed gross morphological and ultrastructural changes and which had lost all virulence in mice.

Azole resistance has been documented in *Candida* isolates from 4 patients with chronic mucocutaneous candidiasis treated with ketoconazole for a protracted period (Smith et al. 1986). These isolates are resistant to itraconazole and all other azoles investigated both *in vitro* and *in vivo* although they are less virulent pathogens than azole-sensitive strains in animal models.

1.2 Antimicrobial Activity *In Vivo*

In guinea-pig models, dermatophytoses responded well to both topical and oral treatment with itraconazole (for reviews see Van Cutsem et al. 1987a,c). A good response against *T. mentagrophytes* and *M. canis* infections was obtained with topical itraconazole 0.063% and 0.125%, respectively. Both infections were eliminated by the higher concentration of itraconazole. Oral treatment of *M. canis* dermatophytosis with 2.5 mg/kg/day for 7 days cured 92% of animals. A 3-day treatment interval was ineffective, while treatment for 14 days with half the daily dosage produced equivalent rates of cure. Furthermore, the outcome of treatment was the same whether these therapies were begun on the day of infection or 3 days after inoculation. Oral treatment of *T. mentagrophytes* dermatophytosis was similarly successful, including one strain which had required 10 mg/L for complete growth inhibition during *in vitro* testing. In guinea-pigs infected with *T. mentagrophytes*, itraconazole 1.25 mg/kg/day was superior to both griseofulvin and ketoconazole 10 mg/kg/day in the number of animals cured or markedly improved.

Superficial candidiasis also responded well to oral and topical administration of itraconazole; alloxan-diabetic guinea-pigs were cured of skin candidiasis by 5 mg/kg/day orally for 14 days (Van Cutsem et al. 1987a,c). In the pseudoestrus rat model of vaginal candidiasis, short courses of oral itraconazole (2.5 mg/kg/day for 3 days) cured 90% of animals. Compared with ketoconazole, itraconazole was 4 times more potent, requiring only 1 mg/kg/day for 3 days to cure 50% of rats *versus* 4.8 mg/kg/day ketoconazole (Sobel & Muller 1984). In a rat model of vaginal candidiasis, a single oral dose of itraconazole 10 mg/kg cured 67% of animals and improved another 25%, and 1 day's treatment with itraconazole 2% cream cured all animals (Van Cutsem et al. 1987a).

During *in vivo* studies of systemic infection, all control animals were severely infected and remained culture positive throughout the study period (for a summary of results see table V). Systemic candidiasis, as studied in immune competent guinea-pigs, rats and rabbits, responded well to itraconazole therapy. Guinea-pigs, injected intravenously with 8×10^3 blastospores of *C. albicans* per gram bodyweight, were treated with 0.63 to 10 mg/kg/day for 14 days starting the day of infection,

Table V. *In vivo* activity of oral itraconazole in experimental systemic mycoses

Infection	Animal	Delay/ duration[a] (days)	% of animals responding at dosage indicated (mg/kg/day)								Response	Reference
			1.25	2.5	5	10	20	40	80	160		
Candidiasis	Guinea-pig	0/14	27		96						Negative kidney culture	Van Cutsem et al. (1987c)
	Rat	0/3		100							Survived 21 days	Yozwiak & Galgiani (1987)
	Rabbit	+ 1/7							86[b]		Negative kidney culture	Perfect et al. (1986)
Aspergillosis	Guinea-pig	0/14			83	75					Survived 28 days	Van Cutsem et al. (1987c)
	Guinea-pig	+ 1/14			50	83					Survived 28 days	Van Cutsem et al. (1987c)
	IC[d] guinea-pig	0/28			100						Survived 28 days	Van Cutsem & Janssen (1988)
	IC[d] guinea-pig	+ 1/28			80						Survived 28 days	Van Cutsem & Janssen (1988)
	Mouse	0/5							47		Negative kidney culture	Van Cutsem et al. (1987a)
	Rabbit[c]	+ 3/14			100						Cured	Longman & Martin (1987)
Cryptococcosis	Guinea-pig	+ 3/35				88	100				Negative culture (CSF excluded)	Van Cutsem & Van Gerven (1986)
	Mouse	0/14								53	Negative CSF culture	Van Cutsem & Van Gerven (1986)
	Rabbit	+ 4/14							73[b]		Negative CSF culture	Perfect et al. (1986)
Sporotrichosis	Guinea-pig	0/28					80	100			Cured	Van Cutsem et al. (1987a)
Histoplasmosis	Guinea-pig	0/14				63		100			Cured	Van Cutsem et al. (1987a)
Coccidioidomycosis	Rat	− 3/14					100[e]				Negative lung culture	Finquelievich et al. (1988)
	Rat	+ 7/14					80[e]				Negative lung culture	Finquelievich et al. (1987)
Paracoccidioido-mycosis	Mouse	0/28				100					Survived 28 days	McEwen et al. (1985)

a Delay in start of treatment relative to time of infection/duration of treatment.
b 200mg given to each animal, roughly equivalent to 80 mg/kg/day.
c Itraconazole administered intravenously.
d IC = immunocompromised by cyclophosphamide, corticosteroids or mechlorethamine.
e Actual dosage 16 mg/kg/day.

and followed for folliculitis and positive kidney cultures (Van Cutsem et al. 1987c). The lowest dose (0.63 mg/kg/day) improved survival (2.5% of treated animals died *vs* 30% of control animals) and decreased folliculitis (27.5% of treated animals had negative skin cultures *vs* 0% of control animals). At an itraconazole dosage of 5 mg/kg/day half the animals had negative kidney cultures at 14 days, and after a further 7 days' treatment all animals were culture negative.

A dose-dependent response was also observed in rats injected with 5×10^6 colony-forming units (cfu) of *C. albicans* (Yozwiak & Galgiani 1987). At a dosage of 0.63 mg/kg/day itraconazole did not increase survival compared with a control group, whereas a dosage of 2.5 mg/kg/day resulted in 100% survival compared with 0% in the control group.

In an animal model of *Candida* pyelonephritis, rabbits were infected with 10^6 to 10^7 cfu of *C. albicans* and treated with itraconazole 200mg daily (approximately 80 mg/kg/day) for 7 days, beginning 24 hours after inoculation. After 1 week of treatment the number of positive urine and renal tissue cultures was significantly less in treated animals; 4 of 29 rabbits given itraconazole had positive cultures from renal pelvis swabs *versus* 13 of 15 control animals (Perfect et al. 1986).

Experimental infection with *Aspergillus fumigatus* resulted in the deaths of all control animals (Longman & Martin 1987; Van Cutsem & Janssen 1988; Van Cutsem et al. 1987a,c). Itraconazole 2.5 mg/kg/day starting on the day of infection prolonged survival in guinea-pigs infected with *A. fumigatus* and 83% of animals given 5 mg/kg/day survived a 28-day study period (Van Cutsem et al. 1987c). Survivors characteristically were culture negative in most of 9 organs sampled, and were free of organ necrosis. A beneficial effect was also noted when itraconazole 5 mg/kg/day was delayed for 24 hours. Similarly, 50% of itraconazole-treated mice surviving 42 days after inoculation with *A. fumigatus* were culture negative (Van Cutsem et al. 1987a). In guinea-pigs immunocompromised by pretreatment with cyclophosphamide, corticosteroids or mechlorethamine, oral itraconazole 5 mg/kg/day initiated on the day of infection resulted in the survival of all animals injected with 2.5×10^4 spores per gram bodyweight of *A. fumigatus*. A 24-hour delay in initiating treatment reduced the survival rate to 80% after 28 days. In both cases, surviving animals were in good condition and exhibited fewer lesions and fewer positive organ cultures at necropsy (Van Cutsem & Janssen 1988).

Rabbits with induced cardiac vegetations were used as a model of *A. fumigatus* endocarditis. Intravenous itraconazole 5 mg/kg/day sterilised the endocardial vegetations, while lower concentrations did not improve the outcome of infection compared with controls (Longman & Martin 1987). In this study, only 1 rabbit treated with the combination of amphotericin B (3 mg/kg/day) and 5-fluorocytosine (35 mg/kg/day) survived the study period, whereas all rabbits receiving itraconazole 5 mg/kg/day survived.

In animal models of *C. neoformans* meningitis, itraconazole was effective in sterilising CSF cultures in 29 of 55 mice (Van Cutsem & Van Gerven 1986) and 11 of 15 rabbits (Perfect et al. 1986) treated for 14 days with itraconazole 160 mg/kg/day and 200mg daily, respectively. Similar benefit was obtained in guinea-pigs intravenously infected with *C. neoformans* which were treated with itraconazole 10 to 20 mg/kg/day for 35 days (Van Cutsem & Van Gerven 1986). These animals were free of the skin and organ lesions of disseminated cryptococcosis and had significantly fewer organisms isolated from their CSF than did control animals.

Itraconazole was found to completely protect mice against a lethal inoculum of *Paracoccidioides brasiliensis* (McEwen et al. 1985). Surviving control animals had residual lung disease and most had lesions of the spleen and liver. Following 4 weeks of itraconazole 10 mg/kg/day all but one animal were free of spleen and liver disease; however, only 3 of 30 treated animals had no lung lesions.

Two treatment schedules of oral itraconazole 16 mg/kg/day for 14 days were employed in Wistar rats inoculated intracardiacally with 200 arthrospores of *C. immitis*. In the first instance, itraconazole was begun 3 days before infection and suc-

cessfully prevented lung granulomas in 27 of 30 rats. Lung cultures were negative in all animals. In the second instance, 9 of 10 rats treated with itraconazole beginning 7 days after inoculation developed pulmonary granulomas with very small sporangia and no endospores. Lung cultures from this group were positive in 2 cases but the cfu per gram of lung tissue were significantly ($p < 0.001$) fewer than in control animals (Finquelievich et al. 1988).

All liver and testicle cultures were negative in guinea-pigs treated with itraconazole 40 mg/kg/day for 28 days following intratesticular injection with 9.8×10^4 cfu of *Sporothrix schenckii*. Likewise, the same dosage for 14 days protected all guinea-pigs infected intratesticularly with 1.3×10^5 cfu of *Histoplasma capsulatum* var. *duboisii* (Van Cutsem et al. 1987a).

In an *in vivo* study of *Trypanosoma cruzi* (Chagas' disease), itraconazole proved to be active against this intracellular protozoan (McCabe et al. 1986). Mice infected with an inoculum of the virulent blood form of the trypanosome were completely protected against death by itraconazole 15 mg/kg/day. A dosage of 200 mg/kg/day for 7 to 9 weeks produced a parasitological cure which was still evident 13 months post-treatment.

1.3 Mechanism of Action

The mechanism by which azole derivatives inhibit fungal growth has been well described (for reviews see Janssen 1987; Vanden Bossche & Janssen 1986). The addition of the triazole ring to the azole nucleus appears to confer on itraconazole increased specificity for fungal enzyme systems and may be responsible for its apparent increased potency and spectrum of activity.

Azole derivatives impair ergosterol synthesis which causes a cascade of abnormalities in membrane permeability, membrane-bound enzyme activity, and coordination of chitin synthesis (Janssen 1987; Marichal et al. 1985; Vanden Bossche & Janssen 1986). At higher concentrations azoles may increase the amount of saturation in fatty acids of the phospholipid bilayer. Such saturated membrane lipids impair membrane fluidity and, thus, contribute to membrane-bound enzyme dysfunction and altered membrane permeability (Borgers & Vanden Bossche 1982).

Cytochrome P-450 is required for ergosterol biosynthesis and itraconazole interacts with the substrate-binding site of this enzyme (Yoshida & Aoyama 1987). The azole nitrogen interacts with the haem iron of yeast cytochrome and the large hydrophobic portion of itraconazole binds to the apoprotein portion of the enzyme. As a result, the site of 14α-demethylation of ergosterol precursors is blocked and lanosterol and various 14α-methyl sterols accumulate. 50% inhibition of ergosterol biosynthesis is achieved with 10 times less itraconazole than ketoconazole in intact *C. albicans* and *Pityrosporum ovale* cells (Janssen 1987). This difference is even more pronounced for *A. fumigatus*; a 100-fold smaller concentration of itraconazole is required to achieve 50% inhibition of ergosterol synthesis. Protonation of the imidazole nitrogen of ketoconazole, as occurs in the intracellular environment of *A. fumigatus*, prevents the drug from interacting with cytochrome P-450 and this effect may account for the marked difference in sensitivity of *A. fumigatus* observed for the 2 azoles (Vanden Bossche et al. 1988a).

Studies with different cytochrome P-450 species suggest that the binding of itraconazole is highly specific to the apoprotein of fungal lanosterol 14α-demethylase. While ketoconazole 5×10^{-6} mol/L inhibits androstenediol and testosterone synthesis in mammalian cytochrome P-450, itraconazole is devoid of activity up to the limit of its solubility (10^{-5} mol/L) [Vanden Bossche et al. 1988b]. This lack of activity is borne out in limited studies of human volunteers and patients where itraconazole elicits no effect on pituitary-testicular-adrenal function (De Coster et al. 1987; Phillips et al. 1987b). At concentrations 100 times greater than those required for the total inhibition of ergosterol biosynthesis, itraconazole partially inhibits cholesterol synthesis in human lymphocytes (Vanden Bossche et al. 1986). The significance of this effect is probably small, since mammalian cells can utilise dietary cholesterol and thus are not dependent on *de novo* cholesterol synthesis.

Morphological studies have revealed consistent ultrastructural changes in various pathogenic fungi when exposed to itraconazole 10^{-10} to $> 10^{-6}$ mol/L (for reviews see Borgers 1987; Borgers & Van de Ven 1987). Transmission electron micrographs of *C. neoformans, C. albicans, P. brasiliensis, T. rubrum*, and *A. fumigatus* revealed enlargement of the central vacuole, discontinuities in the cell membrane, and accumulation of lipid-like vesicles. *P. ovale* cells suffered disorganisation of the internal organelles without changes at the cell periphery. Thus, completely necrotic cells presented a 'mummified' external appearance on microscopic examination (Borgers 1987; Del Palacio-Hernanz et al. 1986; Galimberti et al. 1987).

When *C. albicans* was grown in a mycelium-promoting medium, hyphal branching was inhibited by low concentrations of itraconazole although initial germ tube formation was not prevented (Odds et al. 1985). Importantly, when itraconazole was added to cultures of human leucocytes plus *C. albicans* blastospores, the leucocytes were able to kill ingested blastospores despite germination. Drug-free cultures, on the other hand, showed abundant viable mycelia with few intact phagocytic cells after 24 hours' incubation (Johnson et al. 1986). Macrophages, too, may have enhanced fungicidal capability in the presence of itraconazole (Perfect et al. 1985). Binding of itraconazole to the effector cells with resultant increased delivery of the drug to the fungal cells may be partially responsible for the increased antifungal effect noted with the combination *in vitro*.

Studies investigating potential toxicity of itraconazole on host immune cells have found adverse effects only at concentrations in excess of 10^{-6} mol/L (Abruzzo et al. 1987; Aerts et al. 1986).

2. *Pharmacokinetic Studies*

Although a relatively large number of azole antifungal drugs have been developed, poor absorption or rapid elimination have prevented almost all from being used orally. Ketoconazole represented a turning point in this respect, being the first orally active azole derivative to gain widespread acceptance. Itraconazole also appears to be well absorbed orally; clinically useful plasma concentrations were attained when the drug was administered with food. Indeed, food has a statistically and clinically significant effect on the bioavailability of itraconazole and, unless otherwise stated, itraconazole was administered at mealtime in all of the pharmacokinetic studies reviewed in this section. As might be expected for a recently developed drug, further studies are needed to fully evaluate the metabolic pathways involved in the elimination of itraconazole and to fully assess its pharmacokinetics in patients with renal and hepatic diseases.

2.1 Absorption

Itraconazole 100mg administered in capsule form to 6 healthy fasting volunteers achieved peak plasma concentrations within 1.5 to 4 hours. Relative to a reference solution of itraconazole which attained maximal concentrations within 1.5 to 2 hours, the capsule formulation was, as expected, more slowly absorbed and yielded a bioavailability of only 40%. Administration of itraconazole capsules after a meal normalised the bioavailability relative to the reference solution and increased the area under the concentration-time curve (AUC) from 0.7 mg/L·h (fasting) to 1.9 mg/L·h (with food) [Heykants et al. 1987]. Despite mealtime administration, Hardin et al. (1988) observed wide intersubject variation in the plasma concentration-time curves of itraconazole in healthy volunteers.

Administration of itraconazole at mealtime may influence clinical outcome. Mean approximate peak concentrations of 0.02 mg/L were measured when itraconazole 100mg was taken while fasting, and these low plasma concentrations were associated with reduced efficacy and treatment failures in patients with dermatophytoses, superficial candidiasis or pityriasis versicolor. Patients who took the drug after breakfast recorded much better treatment responses, which were ascribed to much higher plasma itraconazole concentrations (mean approximate peak 0.18 mg/L) [Wishart 1987].

In 2 trials of neutropenic patients receiving itra-

conazole for longer term prophylaxis, the incidence of fatal fungal infections was dramatically reduced among patients maintaining adequate plasma levels (> 0.25 mg/L). In these studies inadequate plasma concentrations were frequently found in patients whose antineoplastic therapy predisposed them to very poor oral intake and frequent vomiting (Boogaerts et al. 1988; Tricot et al. 1987).

Following single oral doses of itraconazole 50, 100 and 200mg, increases in AUC were more than proportional to increases in dose (Heykants et al. 1987). Steady-state kinetics were determined following administration of itraconazole 100mg once daily for 2 to 4 weeks to a total of 16 healthy volunteers. At 14 days steady-state plasma concentrations were achieved, with mean peak concentrations of 0.4 and 0.6 mg/L and 24-hour AUCs of 5 and 9 mg/L • h in the studies by Hardin et al. 1988) and Heykants et al. (1987), respectively. Hardin et al. (1988) also studied steady-state pharmacokinetics of itraconazole 200mg once daily and twice daily in 6 healthy volunteers. The maximum plasma concentration and AUC observed for the once daily dosage was 1.1 mg/L and 15.4 mg/L • h, respectively, and for the twice daily dosage 2.0 mg/L and 39.3 mg/L • h, respectively. Thus, dosage increases between 100, 200 and 400mg daily produced non-linear increases in the AUC, suggesting the possibility of saturable metabolic processes.

Steady-state plasma concentrations of itraconazole in some patient groups, especially neutropenic patients, were generally lower than those of healthy volunteers (fig. 2). As noted above, poor oral intake and frequent vomiting associated with antineoplastic therapy may predispose neutropenic patients to lower than expected plasma itraconazole concentrations. Differences in age, underlying disease and nutritional status are a few of the variables which may contribute to altered itraconazole disposition in non-neutropenic patients (Ganer et al. 1987). What factors account for the reduced steady-state concentrations of itraconazole have not been ascertained; however, low plasma levels are associated with the failure of prophylaxis and treatment.

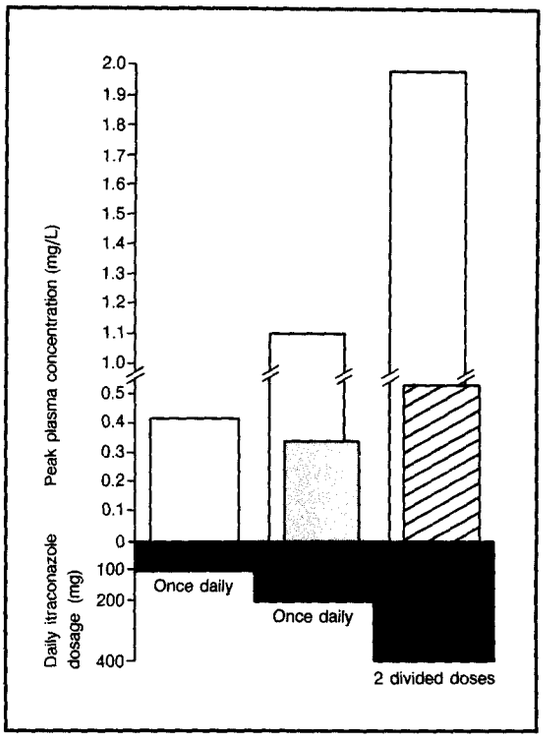

Fig. 2. Peak plasma concentrations achieved at steady-state on different daily dosages of itraconazole in healthy volunteers (□), non-neutropenic patients (▨), and neutropenic patients (▨) [after Hardin et al. 1988; Heykants et al. 1987].

2.2 Distribution

Itraconazole is highly protein-bound. *In vitro* studies using equilibrium dialysis and human whole blood show itraconazole to be 99.8% bound; 94.9% to plasma proteins, primarily albumin, and 4.9% to blood cells leaving only 0.2% as free drug.

Itraconazole is highly lipophilic and is extensively distributed to the tissues in humans following single and repeated administration of 100 or 200mg orally (table VI). Fluids equivalent to body water such as CSF, eye fluid and saliva contain low to negligible amounts of itraconazole, whereas exudates like pus have up to 3.5 times the simultaneous plasma concentration. Most tissues which are prone to fungal invasion such as skin and female genital tract tissues have several times the plasma concentration of itraconazole.

Table VI. Ratio of fluid or tissue concentration of itraconazole to the simultaneous plasma concentration in patients treated with the drug for fungal disease and in 20 women administered a single dose of itraconazole before elective hysterectomy (after Heykants et al. 1987; Viviani et al. 1987b)

Fluid or tissue under examination	Itraconazole dosage	Ratio of fluid or tissue conc. : plasma conc.
Cerebrospinal fluid	200mg od	⩽ 0.002
Eye fluid	200mg od	⩽ 0.007[a]
Saliva	100mg od	⩽ 0.002[a]
Sputum	200mg od	0.07-0.38
Pus	200mg od	1.3-3.4
Vaginal fluid	200mg sd	0.12-0.48
Vagina	200mg sd	2.9-7.5
Cervical mucus	200mg sd	3.2-11.4
Endometrium	200mg sd	5.8-13.9
Skin	100mg od	0.5-2.0
Skin	200mg od or bid	3.1-10.5
Lung	200mg od or bid	0.9-2.4
Kidney	200mg od or bid	1.5[a]
Liver	200mg od or bid	3.5[a]
Bone	200mg od or bid	4.7[a]
Omentum	200mg od	19.1[a]
Fat (adipose)	200mg od	16.9[a]
Spleen	200mg od	1.9[a]
Muscle	200mg od	1.8[a]

a Data from 1 patient.
Abbreviations: od = once daily; sd = single dose; bid = twice daily.

The pharmacokinetics of itraconazole in the skin differ from those in other tissues (Cauwenbergh et al. 1988a). The major route of itraconazole delivery to the skin appears to be via the sebum. Sebum levels of itraconazole are 5 to 10 times higher than corresponding plasma levels within 4 days of starting the drug, and detectable amounts persist for up to 14 days after the drug is stopped. Itraconazole is detectable in sweat 24 hours after the first dose; however, the kinetics of itraconazole in this fluid parallel those in plasma. After 7 days itraconazole can be detected in the distal part of the fingernail, probably through a combination of diffusion into the nail plate and incorporation into the nail matrix. Itraconazole binds avidly to keratinocytes in the basal layer of the epidermis, such that drug concentrations in skin and hair do not decline until 1 to 2 weeks after cessation of therapy and may still be detected up to 4 weeks later (Cauwenbergh et al. 1988a; Heykants et al. 1987). Thus, itraconazole does not distribute back to plasma but is eliminated in the stratum corneum and hair as they are shed through normal growth.

The apparent volume of distribution measured in the beagle dog was 17 L/kg (Heykants et al. 1987). In many organs itraconazole tissue concentrations exceeded the corresponding plasma levels by 2 to 10 times (Cauwenbergh & Degreef 1987). This trend was in contrast to ketoconazole, where plasma concentrations generally exceeded tissue concentrations (Heykants et al. 1987). In addition, administration of ^{3}H-labelled itraconazole and ketoconazole to male Wistar rats revealed differences in the pattern of tissue binding between the 2 azoles (fig. 3). ^{3}H-Itraconazole studies in the pregnant Wistar rat (18th day of gestation) indicated limited transfer of the drug through the placenta; only 0.4% of the maternal dose could be recovered from the fetuses (Heykants et al. 1987). Tissue concentrations in dogs following a 12-month chronic toxicity study demonstrated no significant accumulation, despite prolonged administration of itraconazole in doses up to 80 mg/kg/day (Heykants et al. 1987).

2.3 Elimination

After administration of a single oral dose of itraconazole 100 or 200mg to healthy volunteers, itraconazole plasma concentrations declined biexponentially with a terminal half-life of approximately 20 hours. Repeated administration of itraconazole 100 to 400mg daily produced an increase in terminal half-life to approximately 30 hours at steady-state (Hardin et al. 1988; Heykants et al. 1987). During daily administration of itraconazole 100 and 200mg and twice daily administration of itraconazole 200mg, Hardin et al. (1988) observed reductions of 43 to 61% in the elimination rate constant and 69 to 80% in the oral clearance of itraconazole over a 15-day period. Together with the non-linear increases in bioavailability (section 2.1), these find-

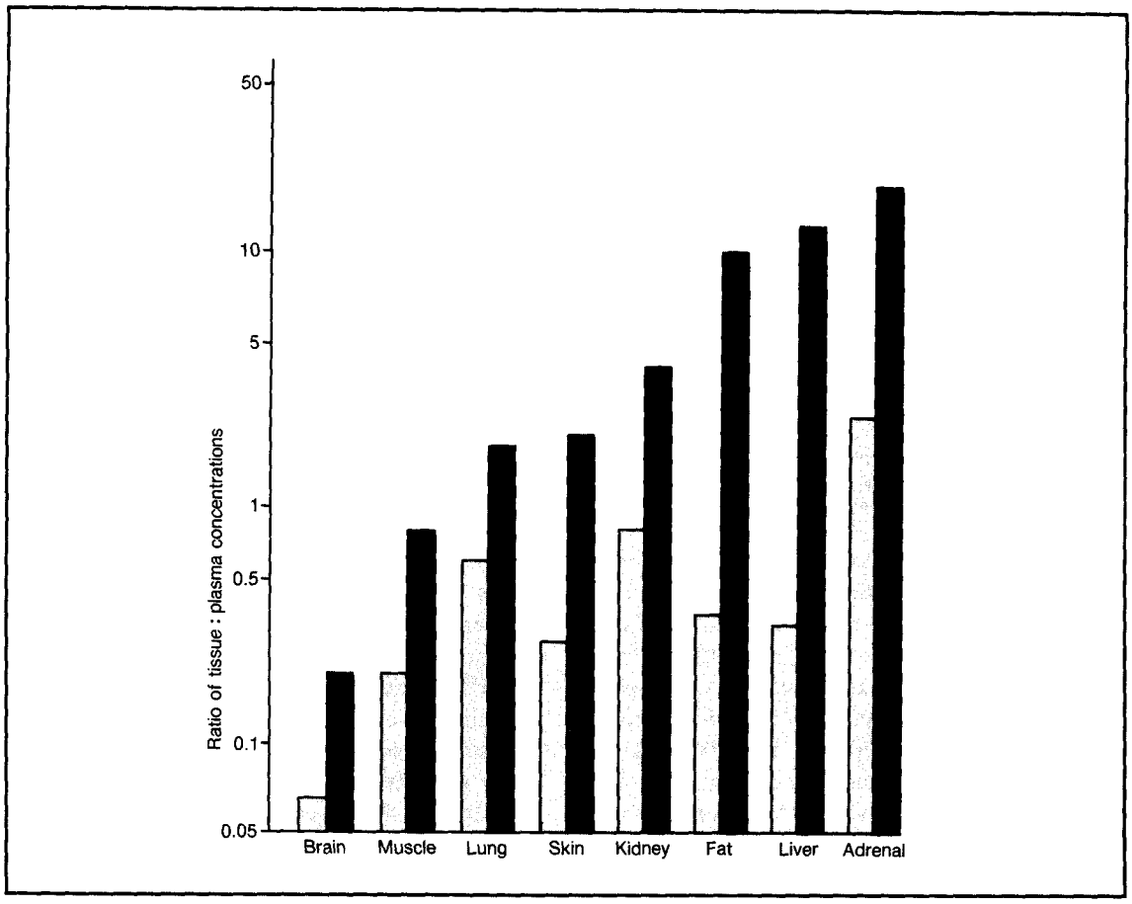

Fig. 3. Ratio of peak tissue to peak plasma concentration in different tissues following administration of ^{3}H-labelled itraconazole 10 mg/kg (■) and ketoconazole 20 mg/kg (□) to male Wistar rats (after Heykants et al. 1987).

ings suggest that itraconazole elimination is a saturable process which is overcome at clinically useful dosages.

Itraconazole undergoes extensive hepatic metabolism with more than 30 metabolites identified in humans and animals. The primary routes of excretion are, as metabolites, via bile and urine. After administration of a single oral dose of ^{3}H-itraconazole to healthy volunteers, 54.1% of the radioactivity was recovered in the faeces and 35.2% in the urine within 7 days of administration. Enterohepatic circulation of biliary metabolites has been demonstrated in rats. None of the metabolites isolated from human urine or rat bile exhibit antifungal activity (Heykants et al. 1987).

2.4 Pharmacokinetics in Patients with Renal or Hepatic Impairment

Some preliminary information is available on the disposition of itraconazole in patients with end-stage renal disease (table VII). A single-dose study was conducted in 7 elderly uraemic patients (mean creatinine clearance 13 ml/min/1.73m^2; mean age 66 years) not yet on maintenance dialysis, 7 patients (mean age 62 years) with end-stage renal disease undergoing thrice weekly haemodialysis and 5

Table VII. Pharmacokinetic parameters (mean) after a single 200mg dose of itraconazole in healthy volunteers and in 3 groups of patients with renal insufficiency managed (a) without dialysis, (b) with thrice weekly haemodialysis or (c) with chronic ambulatory peritoneal dialysis (after Boelaert et al. 1988)

	Young, healthy volunteers	Non-dialysis patients	Haemo-dialysis patients[a]	Peritoneal dialysis patients
t_{max} (h)	3.0	4.0	4.7	4.4
C_{max} (mg/L)	0.27	0.21	0.14	0.08
$AUC_{0-\infty}$ (mg/L · h)	4.2	3.5		
AUC_{0-8h} (mg/L · h)		1.0	0.63	0.33
$t_{1/2\beta}$ (h)	21	25		
Protein binding (%)	99.8	99.8		

a Parameters measured on a non-dialysis day.

patients (mean age 66 years) with chronic uraemia treated with chronic ambulatory peritoneal dialysis (CAPD) [Boelaert et al. 1988]. The pharmacokinetics of itraconazole were not significantly different between non-dialysis and haemodialysis patients; nor were the kinetic variables determined for these patients significantly different than those determined in healthy volunteers. The clearance of itraconazole was not influenced by haemodialysis and no drug was detected in dialysate. In CAPD patients the maximum plasma concentration of itraconazole was half the value obtained in the other 2 patient groups. The elimination half-life was not altered and no itraconazole could be detected in the peritoneal dialysate effluent, hence decreased oral bioavailability may account for the difference observed. This preliminary evidence suggests that patients with renal failure do not require a dosage reduction and that supplementation after dialysis is not necessary. Further study is required to clarify the cause of reduced itraconazole plasma concentrations in CAPD patients and to confirm the disposition of itraconazole in uraemic patients after multiple dosing.

Information on the disposition and safety of itraconazole in patients with hepatic dysfunction is extremely limited. Heykants et al. (1987) report that 3 patients with cirrhosis given a single dose of itraconazole 100mg had pharmacokinetic variables similar to those reported in healthy volunteers (peak plasma concentration 0.08 mg/L, AUC 1.2 mg/L · h and terminal half-life 29.5h *vs* 0.13 mg/L, 1.9 mg/L · h and 17 hours, respectively, in healthy subjects). Because hepatic biotransformation is required for the elimination of itraconazole, further pharmacokinetic study in patients with hepatic dysfunction is clearly warranted. In particular, the safety of itraconazole treatment in patients with pre-existing hepatic injury needs to be clarified.

3. *Therapeutic Use*

Itraconazole has been investigated for use in a variety of superficial and systemic mycoses, the majority of reported clinical experience resulting from non-comparative trials involving small numbers of patients and following common study protocols (see Cauwenbergh & DeDoncker 1986; Cauwenbergh et al. 1987a). In a large proportion of patients both the initial diagnosis and the evaluation of itraconazole treatment were based on clinical presentation confirmed by mycological and serological evidence. Included in these studies were many patients who had resistant disease or who had relapsed from previous successful therapy and thus could be considered to represent particularly difficult cases.

In non-comparative studies involving patients with superficial mycoses, itraconazole cured or markedly improved most patients treated for dermatophytosis, superficial candidiasis, onychomycosis, and pityriasis versicolor. In chronic mucocutaneous candidiasis the results were excellent, although long durations of treatment were required to clear all lesions.

Clinical experience with itraconazole in the treatment of systemic mycoses is too limited to form conclusions on its efficacy in these infections. Nonetheless, among the patients treated to date, excellent responses have been recorded for sporotrichosis, paracoccidioidomycosis, and histoplasmosis. Aspergillosis also responded well to oral itraconazole. Good responses were reported in systemic candidiasis, blastomycosis, coccidioidomycosis and chromomycosis. In cryptococcal men-

ingitis the response rate was lower relative to that of other 'deep' mycoses, but considering the difficulty in treating this infection and the increasing number of patients presenting with this disease further evaluation is clearly worthwhile. As well, itraconazole showed promise as a prophylactic agent against fungal invasion of immunocompromised patients.

Only very limited information is available comparing itraconazole with other antifungal drugs. Clearly, a small number of well-designed comparative trials are needed to clarify the relative efficacy of itraconazole, particularly in comparison with topical preparations in superficial mycoses, and with ketoconazole and amphotericin B in 'deep' mycoses.

3.1 Superficial Fungal Infections

3.1.1 Dermatophytoses

Non-Comparative and Placebo-Controlled Studies

An initial double-blind placebo-controlled study with itraconazole 50mg demonstrated a significantly superior cure rate for itraconazole over placebo (59 *vs* 32%; p = 0.02) [Cauwenbergh & DeDoncker 1987]. Subsequently, the drug was evaluated for optimal dose and duration of therapy in patients with mycologically proven *Trichophyton* sp., *M. canis* and *E. floccosum* infections. Comparison of 50 and 100mg administered once daily until clinical cure in 173 patients with 185 sites of infection (91 cases of tinea corporis/cruris, 94 cases of tinea pedis/manuum) showed both regimens were effective with ≥ 80% response in all treatment groups, although patients receiving 100mg daily manifested improvement earlier than the 50mg group (DeGreef et al. 1987b). Saúl et al. (1987) found itraconazole 50mg once daily to be disappointing in 29 cases of dermatophytosis, and subsequently recommended a dosage of 100mg be employed.

In a study involving 18 patients with tinea corporis, comparison of 4 and 6 weeks' treatment with itraconazole 100mg once daily revealed no difference between the 2 treatment groups. Indeed, at 2 weeks 50% of all patients were culture negative (Nuijten & Schuller 1987). In a similar study, a 2-week course of 100mg once daily produced both mycological and clinical cure in all tinea cruris patients (n = 15) and mycological cure in all tinea corporis patients (n = 10). In the latter group, at a 2-week post-treatment follow-up all residual clinical signs had disappeared (Panconesi & Difonzo 1987). Tinea cruris infections have also responded very well to a shortened treatment regimen of 200mg daily for 5 days (DeGreef et al. 1987a). These excellent preliminary results have been confirmed in a multicentre study comprising 2912 patients treated with either 100mg daily for 15 days for infections localised to body areas, groin, feet and hands, or 100mg daily for 30 days for infections on palms and soles (Alcántara & Garibay 1988).

Very limited data are available on the efficacy of itraconazole in tinea capitis. Of 15 patients treated with 100mg once daily, all had responded within 3 to 7 weeks of initiating therapy (Cauwenbergh & DeDoncker 1987).

Comparative Studies

The efficacy of oral itraconazole 100mg once daily was compared with griseofulvin 500mg (ultramicronised) once daily in a double-blind randomised clinical trial in patients with various tinea infections (fig. 4; Cauwenbergh & DeDoncker 1987). The clinical response in patients with tinea corporis/cruris (15 days' treatment) was significantly better with itraconazole (p = 0.015), while both drugs were similarly effective in patients with tinea pedis/manuum (30 days' treatment). Furthermore, itraconazole was superior to griseofulvin in achieving mycological cure in both patient groups (p = 0.009 and 0.04 in tinea corporis/cruris and tinea pedis/manuum, respectively).

Topical applications of itraconazole 1% cream and ketoconazole 2% cream were compared in single-blind studies involving patients with tinea corporis, cruris and pedis (unpublished data on file). The patients with tinea corporis and tinea cruris infections responded well to daily application of

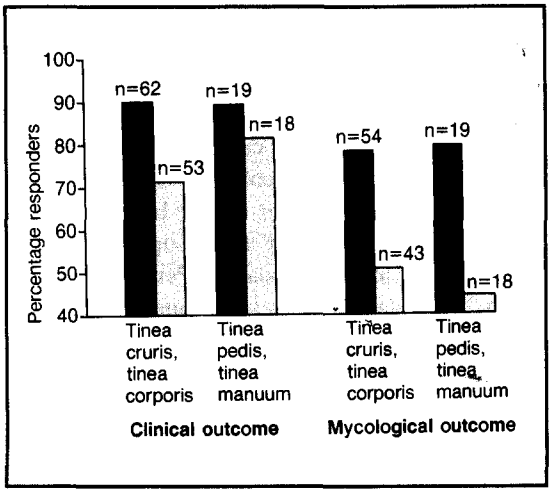

Fig. 4. Results of a randomised double-blind study of itraconazole 100mg once daily (■) and griseofulvin 500mg (ultramicronised) once daily (□) for 15 days in patients with tinea cruris/corporis and for 30 days in patients with tinea pedis/manuum (after Cauwenbergh & DeDoncker 1987).

either agent. Itraconazole produced mycological cure in 100% of patients, whereas ketoconazole cured 76.5%. Similarly, 77% and 61% of tinea pedis infections were mycologically cleared by itraconazole and ketoconazole, respectively. Two patients complained of irritation due to ketoconazole cream. There were no side effects among itraconazole treated patients.

3.1.2 Pityriasis Versicolor

Non-Comparative Studies

Several hundred patients with pityriasis versicolor have been treated with oral itraconazole in non-comparative studies (Biggio et al. 1986; Cauwenbergh et al. 1987b; Delescluse et al. 1986; Del Palacio-Hernanz et al. 1986; Estrada 1987; Galimberti et al. 1987; Morales-Doria 1987; Panconesi & Difonzo 1987; Robertson 1987). All patients had clinical and microscopic evidence of infection and most investigators demonstrated positive Wood's light fluorescence in their patients prior to treatment. A variety of treatment protocols were employed, and the results can be divided into those patients treated with a total dosage of < 1000mg (usually 100mg once daily for 5 to 7 days) and those treated with ≥ 1000mg (usually 100mg once daily for 10 to 15 days or 200mg daily as single or 2 divided doses for 5 to 7 days) [fig. 5].

Treatment with itraconazole 200mg once daily or 100mg twice daily for 5 days cured more than 90% of patients when assessed 3 weeks after therapy (Biggio et al. 1986; Del Palacio-Hernanz et al. 1986; Estrada 1987). Clinical and mycological recovery continued in patients for several weeks after completion of therapy, perhaps due to the persistence of itraconazole in the skin (see section 2.1).

Repigmentation of affected skin lagged behind the relief of other symptoms as is normally observed during recovery, but by 2 months most responders had normal skin colour. Hyperpigmented lesions normalised faster than hypopigmented lesions (Del Palacio-Hernanz et al. 1986; Galimberti et al. 1987; Morales-Doria 1987).

Post-treatment surveillance of responding patients suggests that a minimum total dosage of 1000mg is required to prevent early relapses (Cauwenbergh et al. 1988b). Indeed, relapse of pityriasis versicolor is so common that some authors have suggested that itraconazole may be worthy of a trial as maintenance therapy in these patients (Galimberti et al. 1987; Robertson 1987).

Comparative Studies

Oral itraconazole 200mg once daily for 5 days was compared with selenium sulphide 2.5% shampoo applied for 10 minutes each night for 7 days in 40 patients with pityriasis versicolor (Del Palacio-Hernanz et al. 1987). When assessed at 3 weeks post-treatment, 17 of 20 and 16 of 20 patients in the itraconazole and selenium sulphide groups, respectively, were lesion free and the remainder had mild residual lesions.

The tolerability of itraconazole was described as excellent, whereas 5 patients experienced burning and irritation of the skin secondary to selenium sulphide; in 1 patient it was sufficiently severe to require discontinuation of therapy and treatment for the resulting exudation and pustules. On questioning, all itraconazole-treated and half the selen-

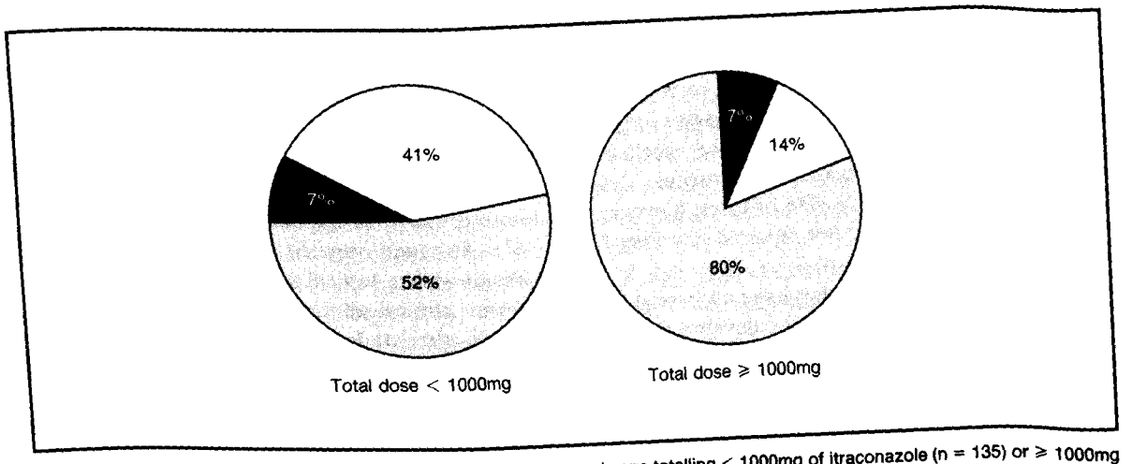

Fig. 5. Results of non-comparative studies using various dosing regimens totalling < 1000mg of itraconazole (n = 135) or ≥ 1000mg of itraconazole (n = 351) in patients with pityriasis versicolor (Biggio et al. 1986; Cauwanbergh et al. 1987b; Delescluse et al. 1986; Del Palacio-Hernanz et al. 1986; Estrada 1987; Galimberti et al. 1987; Morales-Doria 1987; Panconesi & Difonzo 1987; Robertson 1987). *Key:* □ = non-responders; ■ = responders; ⊡ = cured.

ium sulphide-treated patients expressed a preference for oral medication.

3.1.3 Sebopsoriasis

P. orbiculare has been implicated as a trigger for complement activity which results in sebopsoriatic lesions. In a small non-comparative trial, 10 patients with sebopsoriasis were treated with itraconazole 50 to 100mg daily for 6 weeks (Faergemann 1985). Based on quantitative *P. orbiculare* cultures and lesion area-severity scores one patient was considered cured of sebopsoriasis, 3 patients had complete clearing of scalp lesions and 5 patients had moderate improvement in non-scalp sebopsoriatic lesions.

Psoriasis probably has multiple aetiologies and characteristically remits and relapses, hence the results of a small uncontrolled study must be regarded with caution. Nonetheless, an effective non-steroidal oral treatment would be welcome, and, based on these results, itraconazole appears worthy of further investigation.

3.1.4 Vaginal Candidiasis

Oral itraconazole has been studied in patients with acute vaginal candidiasis and in patients with chronic or recurrent infection. In 2 open studies of acute vaginal candidiasis (n = 666) designed to evaluate various dosing schedules, it was concluded that the total dose rather than the duration of therapy was more important and that a minimum total dosage of 400mg was required to maintain a mycological cure in 80% of patients 1 month after treatment (Cauwenbergh 1987; Peeters et al. 1986). In 151 patients with acute vaginal candidiasis, 1 day's treatment with itraconazole (400mg in 2 divided doses) produced a mycological cure rate comparable with that of 200mg once daily for 3 days (81% and 84%, respectively) [Cauwenbergh 1987].

In a study of similar design involving 60 women with acute vaginal candidiasis, itraconazole 400 to 600mg over 1 to 3 days produced a clinical and mycological cure in 65 to 85% of patients after 1 week. Patients were designated carriers if cultures remained positive but clinical symptoms were absent and, among 8 women found to be carriers after 1 week, 5 had relapsed at follow-up examination 1 month later (Sanz Sanz & Del Palacio-Hernanz 1987).

Among women with a history of chronic or recurrent vaginal candidiasis, the best results have been obtained with itraconazole 200mg once daily

for 3 days (Cauwenbergh & DeDoncker 1987). In a multicentre trial involving 1,438 women with chronic or recurrent infections, the response to itraconazole 200mg once daily for 3 days was judged by patients and by investigators to be excellent. Itraconazole relieved leucorrhoea, pruritus, dysuria and dyspareunia in > 90% of cases; however, mycological response was not reported (Garibay & Alcántara 1988).

A limited number of studies have addressed the problem of relapse in women who develop chronic vaginal candidiasis. In one study 30 patients achieved remission with itraconazole 200mg daily for 3 days and were then instructed to take a single 200mg dose on the first day of menses for 6 consecutive cycles. Only 20% of patients experienced a relapse while on this prophylactic regimen. Once treatment was discontinued, infection began recurring 2 to 3 months later (Cauwenbergh & DeDoncker 1987). In a placebo-controlled study concomitant treatment of the sexual partner with itraconazole 100mg daily for 5 days did not provide any evidence of improved clinical or mycological response in 40 women with recurrent vaginal candidiasis treated with itraconazole 100mg once daily for 5 days (Calderón-Marquez 1987).

3.1.5 Other Superficial Candida *Infections*

In a double-blind comparison of itraconazole 100 and 200mg daily and placebo, both doses of itraconazole were significantly better than placebo in 100 patients with oral *Candida* infections secondary to predisposing disease or drug treatment (Cauwenbergh et al. 1988b). A randomised nonblind clinical trial comparing the efficacy of oral itraconazole and clotrimazole troches against oral candidiasis in the same predisposed patients showed that the 2 drugs produced virtually the same final cure rate, although patients treated with itraconazole experienced symptom improvement sooner than clotrimazole-treated patients. The authors felt an additional advantage of itraconazole therapy was its once daily administration *versus* the 5 times daily administration of clotrimazole (Cauwenbergh et al. 1988b).

Very limited data are available on itraconazole therapy for *Candida* infections of the skin. Itraconazole 50mg once daily failed to clear the lesions in 2 patients with intertriginous candidiasis and 2 patients with pedis candidiasis, despite 60 days of therapy. All patients did, however, experience improvement in their symptoms and 1 patient was culture negative at the end of therapy (Saúl et al. 1987). Although superficial candidiasis generally responds well to topical medication, some patients and some clinical settings may require oral therapy. Hence, further studies seem warranted utilising the higher itraconazole dosages employed in other dermatomycoses.

Patients with various cellular immunodeficiency states represent a special case of cutaneous candidiasis. Although relatively rare, chronic mucocutaneous candidiasis (CMC) represents a persistent and recalcitrant form of infection, often with multiple foci (Jorizzo 1982). An excellent response rate (79%) has been observed in CMC patients treated to date with oral itraconazole (Cauwenbergh & DeDoncker 1987).

Itraconazole 100mg daily for 3 to 6 weeks produced a remission in 7 CMC patients with oral candidiasis, all of whom had experienced at least 3 episodes of relapse or reinfection subsequent to ketoconazole therapy. As with the ketoconazole experience, however, 2 of the patients treated with itraconazole had relapsed by the 6-week follow-up evaluation (Hay & Clayton 1987). One patient with very extensive skin involvement experienced almost complete disappearance of lesions following 11 months of treatment with itraconazole 100 to 200mg daily (Phillips et al. 1987a). He had previously had incomplete results with prolonged ketoconazole therapy.

3.1.6 Onychomycosis

As in many other areas of use, most of the clinical experience with itraconazole in onychomycosis derives from small non-comparative studies (Ganer et al. 1987; Hay & Clayton 1987; Hay et al. 1988a,b; Koster & Botter 1987). Itraconazole 100 to 200mg once daily has cured both dermatophyte (*T. rubrum, T. mentagrophytes*) and yeast (*Candida albicans* and other *Candida* sp.) onycho-

mycoses. Hay et al. (1988b) observed treatment failure despite *in vitro* susceptibility to itraconazole in 2 patients with *T. violaceum* onychomycoses. Infections due to *Hendersonula toruloidea* do not appear to respond to itraconazole (Hay et al. 1988b). As expected, fingernail infection responds more readily than toenail infection, the latter requiring approximately twice the duration of treatment to achieve mycological cure (Botter & Middag-Broekman 1987; Cauwenbergh et al. 1988b). In patients with other contributory diseases (CMC, Cushing's syndrome, peripheral vascular disease, systemic lupus erythematosus), prolonged treatment, often in excess of 6 months, may be required for total clearing of fungal elements from all nails (Hay et al. 1988a,b; Koster & Botter 1987). Clinical improvement and regrowth are, however, evident much earlier.

Responders in the study by Hay et al. (1988b) were followed for 6 months after treatment. Clinical and mycological relapse occurred in 14% of infected fingernails and 16% of infected toenails.

Svejgaard et al. (1988) have presented in brief the results of a double-blind trial comparing itraconazole 100mg daily with griseofulvin 500mg daily for up to 8 months in 20 patients with onychomycosis due to *T. rubrum* or *T. mentagrophytes.* Clinical and mycological assessment revealed a cure or marked improvement in 1 of 2 and 1 of 9 patients treated with griseofulvin for fingernail and toenail infections, respectively. Two of 4 and 4 of 9 patients responded similarly to itraconazole treatment of fingernail and toenail infections, respectively, thus showing a non-significant trend to a better clinical outcome with itraconazole. Six patients in the griseofulvin group were subsequently treated with itraconazole 100mg once daily for 6 months with marked improvement in all patients.

3.2 Deep Fungal Infections

3.2.1 Systemic Candidiasis

The number of patients with systemic yeast infections who have been treated with oral itraconazole is small. The majority of infections have been due to *Candida* sp., most frequently *C. albicans*, but experience with *T. glabrata* has also been reported. In an overview of experience with 55 patients treated for systemic *Candida* mycoses, 69% were cured or markedly improved by itraconazole at a mean dosage of 200mg once daily administered for a mean of 1 month (Cauwenbergh et al. 1988b).

Results against specific infections have also been reported (Foreman et al. 1988; Palumbo et al. 1987; Phillips et al. 1987a; Van Cutsem et al. 1988). Itraconazole cured or improved 4 of 4 patients with *Candida* oesophagitis, 3 of 3 patients with candiduria, and a child who developed intracranial *Candida* abscesses subsequent to chemotherapy. Two patients with *T. glabrata* infections treated with itraconazole 200mg once and twice daily for 7 and 4 weeks, respectively, failed to respond to treatment; this yeast also responds poorly to ketoconazole (Clissold 1987).

3.2.2 Cryptococcal Infections

Preliminary results from non-comparative studies employing itraconazole against cryptococcal meningitis show some success against this disease provided treatment is initiated early (Cauwenbergh & DeDoncker 1987; Cauwenbergh et al. 1988b). Furthermore, itraconazole has proved useful against disseminated cryptococcosis, as evidenced by a number of case reports (Dambrosi et al. 1987; DeBeule et al. 1987; Viviani et al. 1987b, 1989).

In a study involving 14 patients (including 13 AIDS patients) with *C. neoformans* cultured from various sites, itraconazole only was administered as sole therapy to 6, and a further 8 patients received itraconazole following treatment with amphotericin B combined, in 5 cases, with 5-fluorocytosine (DeBeule et al. 1987). Clinical cure or marked improvement was achieved in 7 patients while receiving itraconazole, usually 200mg daily for 2 to 7 months. In only 2 patients receiving itraconazole as monotherapy did the drug fail to clear the organism from the CSF, and these patients also failed to improve clinically. One case was not evaluable. The last 4 patients were maintained on itraconazole 100 to 400mg daily for 3 to 8.5 months

following clinically successful treatment with amphotericin B and 5-fluorocytosine. Itraconazole cleared the CSF of 2 patients who were still positive for *Cryptococcus* on microscopic examination and maintained mycological cure in the remaining 2.

Viviani et al. (1989) report itraconazole treatment of a further 7 patients with cryptococcosis, 3 of whom had recurrent or persistent infection following a complete course of amphotericin B plus 5-fluorocytosine. Itraconazole 200 to 300mg once daily was employed as monotherapy in these 3 patients and the remaining 4 patients initially received a combination of itraconazole 200 to 400mg daily together with 5-fluorocytosine for 4 to 8 weeks followed by itraconazole alone. All patients were considered responders and, among the patients treated with the combination of itraconazole and 5-fluorocytosine, the time to clinical improvement and mycological clearing of biological samples was halved.

Because AIDS patients afflicted with *C. neoformans* meningitis commonly relapse after their initial response to treatment, maintenance therapy has been advocated (De Gans et al. 1988; Viviani et al. 1987a). In a maintenance dose study, 5 AIDS patients presenting with cryptococcal meningitis underwent 6 to 8 weeks' treatment with amphotericin B plus 5-fluorocytosine. Subsequently, 4 patients received oral itraconazole 100mg twice daily, while the fifth patient received 400mg daily to compensate for the effect of concomitant rifampicin intake. Two patients died of non-fungal infections (1 each due to *Mycobacterium avium intracellulare* and *Pseudomonas aeruginosa*); both had negative CSF cultures prior to death. A third patient died of severe AIDS-dementia complex without evidence of cryptococcal relapse, although he refused CSF re-examination. Finally, 2 patients remained alive at 10 and 12 months, without evidence of relapse (De Gans et al. 1988). 18 AIDS patients received itraconazole 200 to 400mg daily as maintenance therapy following successful treatment for cryptococcus meningitis for periods ranging from 14 days to 16 months (Viviani et al. 1988). Itraconazole alone (5 patients) or itraconazole plus 5-fluorocytosine (7 patients) had induced the initial response and amphotericin B plus 5-fluorocytosine had been used as initial treatment in the remaining 6 patients. 10 patients remained alive after 1.5 to 16 months of itraconazole maintenance treatment. Two patients relapsed, one while receiving rifampicin together with itraconazole 300mg and the other during the end-stage of the syndrome.

Although the small number of patients precludes meaningful conclusions about the efficacy of itraconazole in cryptococcosis, further studies appear worthwhile. In particular, the convenience of administering oral itraconazole makes it an attractive alternative to weekly intravenous amphotericin B in maintenance regimens. A larger clinical trial is necessary to fully evaluate the efficacy of oral itraconazole compared with amphotericin B and with fluconazole, a new triazole antifungal being evaluated in meningeal infection because of its *in vivo* efficacy and its penetration into the CSF (Dismukes 1988).

3.2.3 Aspergillus Infections

The good *in vitro* and *in vivo* activity of itraconazole against *Aspergillus* sp. (see sections 1.1 and 1.2) has prompted the trial of oral itraconazole in a small number of non-comparative studies in patients with deep infections caused by these organisms. Excellent responses (80% cured or markedly improved) have been observed in patients treated for *Aspergillus* keratitis (Thomas et al. 1988). Additionally, results have been promising in invasive aspergillosis and aspergilloma (Cauwenbergh et al. 1987a, 1988b).

In a report of 40 patients with fungal infections of the cornea, oral itraconazole 200mg once daily was administered until the epithelial defect had healed (median 17 days) and then tapered off over a further 10 days (Thomas et al. 1988). An excellent response (complete healing with good visual recovery and negative mycology) was achieved in 9 patients with *A. flavus* keratitis and 1 patient with *A. fumigatus* keratitis. Complete eradication of the organism but incomplete closure of the corneal ulcer (moderate response) was observed in 2

patients with keratitis due to *A. fumigatus*. Neither mycological nor clinical recovery was reported in 2 patients with *A. fumigatus* and 1 patient with *A. flavus* keratitis. Thus itraconazole induced a mycological cure in 80% of patients with *Aspergillus* keratitis, and this result was not influenced by the severity of infection at the time of presentation. Among the 10 patients completely cured by itraconazole, follow-up examination at 4 to 16 weeks detected no evidence of relapse.

A small number of aspergilloma patients have been treated with itraconazole (Dupont & Drouhet 1987; Phillips et al. 1987a; Viviani et al. 1987b). Evidence of drug-induced improvement was largely subjective and included decreased dyspnoea, expectoration and cough. In individual studies, weight gain and small decreases in the number of precipitin bands were also associated with subjective improvement. No radiological changes were reported. None of the authors obtained direct evidence of a cure; nonetheless, only 1 patient was stated to have failed to respond to itraconazole. Whether mycological cure can be achieved with itraconazole has not been clarified by the current studies and this question awaits long term trials.

In an overview of experience with itraconazole in systemic mycoses, 78% of patients (n = 60) diagnosed with invasive aspergillosis were improved by itraconazole treatment. 53% were cured or markedly improved, and a further 25% of patients experienced moderate improvement on a mean daily dose of 200mg for a mean duration of 4 months (Cauwenbergh et al. 1988b).

Individual case reports detailing treatment of invasive aspergillosis with itraconazole (usually 200mg daily) have been published by a number of investigators (Ganer et al. 1987; Pamphilon et al. 1987; Phillips et al. 1987a; Viviani et al. 1987b). Dupont and Drouhet (1987) also report treatment of a more indolent form of infection, chronic necrotising pulmonary aspergillosis, with itraconazole 200mg daily. In most instances, itraconazole was administered as monotherapy to patients not responding to amphotericin B and/or 5-fluorocytosine, or experiencing unacceptable toxicity from these drugs. The diagnosis of invasive aspergillosis was based on combinations of clinical signs, radiographic evidence of pulmonary infiltration, positive serology, and positive cultures from sputum, bronchial washings or biopsy. Responding patients exhibited progressive resolution in clinical signs (apyrexia, decreased cough and sputum production) and clearing of the radiographic picture. After several weeks of therapy, culture specimens became negative.

Of the patients who failed to improve, inadequate serum concentrations of itraconazole were demonstrated in some (Pamphilon et al. 1987; Phillips et al. 1987a). Because of the life-threatening nature of acute invasive aspergillosis, it would seem prudent to check plasma itraconazole concentrations in such patients to ensure therapeutic concentrations are achieved.

The role of itraconazole as an adjunct to amphotericin B and/or 5-fluorocytosine in the treatment of aspergillosis awaits study. Encouragingly, *in vitro* (Kerkering & Espinel-Ingroff 1987) and *in vivo* (Polak 1987) investigations suggest itraconazole and 5-fluorocytosine are synergistic against *Aspergillus* sp. In mice infected with *A. fumigatus*, the combination of itraconazole and amphotericin B was generally indifferent (Polak 1987; Van Cutsem & Janssen 1988) even though antagonism between azole and polyene antifungals might be anticipated based on their mechanisms of action. Clearly, a small number of well-designed studies are needed to clarify the role of itraconazole in treating systemic aspergillosis either alone or in combination with currently employed antifungal agents.

3.2.4 Dimorphic Fungal Infections

Paracoccidioidomycosis

A small number of patients with paracoccidioidomycosis (South American blastomycosis) received oral itraconazole 50 or 100mg daily for 6 to 12 months in non-comparative studies (Borelli 1987; Negroni et al. 1987; Restrepo et al. 1987). In all but 1 patient the diagnosis was confirmed by direct visualisation of *P. brasiliensis*. In 2 studies, positive serological tests were also diagnostic. The

majority of patients had disseminated disease with multiple lesions involving the mouth, lungs, lymph nodes, larynx and skin.

All patients responded to treatment within 2 weeks to 3 months. Typically the response included cicatrisation of visible ulcerated lesions and decreased dysphonia, dysphagia, cough, dyspnoea and sputum production. Chest roentgenograms revealed a more gradual improvement of pulmonary lesions. In 1 study, loose or confluent infiltrates were decreased from 75% at baseline to 7.6% after 6 months' treatment with itraconazole. The converse was true for fibrotic lesions, which became more apparent during treatment (Restrepo et al. 1987).

Some mycological clearance was noted within the first month of treatment and all cultures and microscopic examinations were negative after 3 and 6 months, respectively (Restrepo et al. 1987). Furthermore, decreased titres or seronegativity were demonstrated in > 65% of patients following treatment with itraconazole. In the study by Negroni et al. (1987) involving 25 patients with paracoccidioidomycosis, 13 of 17 previously anergic patients (54.5%) became skin test positive to specific antigens after 3 to 6 months' treatment with itraconazole 50mg once daily. In this study, 19 patients were considered to be cured by itraconazole and have been followed for up to 2 years; 2 patients relapsed and were successfully retreated with itraconazole 50mg once daily for 6 months. Thus, itraconazole appears to be effective in controlling active paracoccidioidomycosis. Early follow-up results are very encouraging but longer term observation is required before definitive conclusions on the true efficacy of itraconazole in this chronic disease can be formed.

Histoplasmosis

In a non-comparative study of 18 patients, histoplasmosis was diagnosed by direct visualisation of *H. capsulatum*, by culture, or by serological testing. Two of these patients had chronic cavitary pulmonary histoplasmosis; the remaining 16 patients presented with disseminated disease (Negroni et al. 1986). Itraconazole 100mg daily was administered until a clinical cure was established (60 to 90 days) and then reduced to 50mg daily for a total treatment course of 6 months. All patients were considered to have responded; 16 were cured and 2 patients exhibited marked improvement. Improvement in laboratory parameters paralleled clinical improvement. Specific serum titres decreased in 13 of 16 patients, and 5 of 6 previously anergic patients developed a positive skin test.

Cumulative patient data in 2 overviews of clinical experience with itraconazole likewise indicated that > 80% of patients with histoplasmosis are cured or markedly improved with treatment (Cauwenbergh & DeDoncker 1987; Cauwenbergh et al. 1988b). In addition, several authors have described individual successes with itraconazole in patients with relapsing histoplasmosis (Dupont & Drouhet 1987; Ganer et al. 1987).

Blastomycosis

Information on the efficacy of itraconazole in patients with blastomycosis is very limited. In an overview of clinical experience with this drug, 10 of 11 patients who were administered 200mg daily for 2 to 6 months were either cured or markedly improved by therapy (Cauwenbergh & DeDoncker 1987). In an ongoing multicentre trial, 38 patients with non-meningeal non-life-threatening blastomycosis have been treated with itraconazole 200 to 400mg daily (dose escalation study). 24 patients have successfully completed therapy (mean duration 6 months) and 9 are considered cured after 1 year of follow-up. One patient did not respond to itraconazole and 13 patients remain on therapy (Saag et al. 1988).

Coccidioidomycosis

A number of authors have reported their individual experience with itraconazole in treating coccidioidomycosis (Ganer et al. 1987; Gillespie 1986; Lavalle et al. 1987; Phillips et al. 1987a). Additionally, preliminary results from a multicentre trial have been reported (Graybill et al. 1986). In this trial 43 patients were entered into 3 treatment groups and received either 100mg daily (n = 5), 200mg daily (n = 5) or 400mg daily (n = 33). Pre-

treatment factors included underlying disease in 40% and prior relapse in 58% of patients. Coccidioidomycosis manifested as chronic pulmonary lesions and as lesions of the soft tissues and musculoskeletal system. Clinical response was evaluated by disease scores based on lesion size, symptoms, serology and cultures, and these had decreased by 25% in 20 evaluable patients after 3 months and by 54% in 7 evaluable patients after 7 months. One patient discontinued treatment due to progressive disease. In this study, 7 of 10 patients initially treated with itraconazole 100 or 200mg daily required a dosage increase to 400mg daily.

Preliminary results from a trial of 38 evaluable patients with lung, meningeal, skin, bone, nodal or urogenital coccidioidomycosis have been reported by Tucker et al. (1988). Based on serological, culture and clinical parameters, itraconazole 50mg daily to 200mg twice daily produced a response in 23 (61%) evaluable treatment courses after 6 months. A partial response was obtained in 6 patients, and 9 patients were unresponsive to itraconazole therapy. Patients who did not respond had a longer disease duration (mean 92 months) and a history of non-response to prior therapies. Itraconazole produced a response in 2 of 2 patients with refractory meningitis allowing ongoing intrathecal amphotericin B to be tapered and, in 1 patient, discontinued. Nine responding patients were followed after itraconazole was discontinued for a mean of 12 months; 2 patients have relapsed.

3.2.5 Subcutaneous Mycoses

Subcutaneous mycoses, although not common, represent a therapeutic challenge because of the long term damage they cause to the tissues involved and their resistance to therapy. As expected considering the rare nature of these diseases, only small numbers of patients have been treated with itraconazole to date. The greatest experience has been gained in patients with sporotrichosis (Restrepo et al. 1986) and chromomycosis (Borelli 1987) and preliminary results are very encouraging. Several authors have published the results of their experience with itraconazole in individual cases of sporotrichosis, chromomycosis, lymphangitic *T. rubrum* infection, rhinoentomophthoromycosis and mycetoma (Borelli 1987; Dupont & Drouhet 1987; Lavalle et al. 1987; Mayou et al. 1987; Notowicz 1987; Vuillecard et al. 1987; Viviani et al. 1987b).

Sporotrichosis

In a non-comparative study, 17 patients with cutaneous or lymphangitic sporotrichosis were treated with itraconazole 100mg once daily for a mean duration of 18 weeks. In 5 patients, prior treatment with iodides had been unsuccessful. Clinical and mycological cures were achieved in all patients. Indeed, after 90 days of treatment all but 3 patients were culture negative. The authors followed 14 patients for 13 to 38 weeks post-treatment, at which time none showed clinical signs of relapse (Restrepo et al. 1986).

Higher doses (150 to 200 mg/day) have been recommended by some authors based on their clinical experience with a further 6 patients (Borelli 1987; Lavalle et al. 1987).

Chromomycosis

Oral itraconazole 100 to 400mg daily was employed in a non-comparative study of 14 patients with longstanding chromomycosis. Although all patients were improved by itraconazole, the authors noted a striking difference in apparent cure rates according to the infecting organism (fig. 6). After 4 to 8 months of treatment 8 of 9 patients with chromomycosis due to *Cladosporium carrionii* were considered cured, whereas only 2 of 5 patients infected with *Fonsecaea pedrosoi* achieved sterilisation of cultures and then only after 5-fluorocytosine or thermotherapy had been added to their treatment regimen (Borelli 1987). Indeed, in a study of 10 patients with chromomycosis due to *F. pedrosoi*, symptomatic improvement was not apparent until after 6 months' treatment with itraconazole 100 to 200mg daily (Restrepo et al. 1988). Only patients suffering less severe disease experienced a clinical cure with itraconazole; however, after 12 to 24 months' therapy, minor to major improvement was achieved in all but 1 patient. Mycolog-

ical tests became negative in 6 patients although eradication of the fungus was confirmed in only 3.

Other Subcutaneous Mycoses

Table VIII summarises results from a small number of patients with 'miscellaneous' subcutaneous mycoses that have been treated with oral itraconazole. Although some encouraging improvement has been recorded, the numbers of patients studied are clearly too small to allow meaningful generalisations.

3.2.6 Other Infections

A small number of patients with other relatively rare 'mycoses' such as zygomycosis (mucormycosis), alternariosis and fungal keratitis have also been treated with itraconazole (Borelli 1987; Ganer et al. 1987; Marone et al. 1987; Thomas et al. 1988). Itraconazole has been used successfully in a controlled trial of 15 patients with cutaneous leishmaniasis (Dogra et al. 1988). With such limited data it is clearly not possible to make definitive statements regarding the efficacy of itraconazole. Nevertheless, in conditions such as cutaneous leishmaniasis and alternariosis results do appear encouraging.

3.3 Prophylaxis

A role for itraconazole has been suggested in the prophylactic management of patients who, because of predisposing host factors, suffer frequent recurrences of fungal infections. As discussed in previous sections, low-dose or intermittent itraconazole regimens have been suggested for AIDS-related cryptococcal meningitis (section 3.2.2), chronic vaginal candidiasis (section 3.1.3), and pityriasis versicolor (section 3.1.2). Only very preliminary information is available on the safety and efficacy of itraconazole in such regimens; however, the greater oral availability of itraconazole compared with other azoles, its wide tissue distribution and broad spectrum of antimicrobial activity recommend it for further investigation.

A second form of prophylaxis in which itraconazole has shown promise is against opportunistic mycoses in patients receiving immunosuppressive therapy. Ketoconazole 200mg twice daily and itraconazole 200mg twice daily were assessed in 2 sequential non-randomised studies in patients with prolonged granulocytopenia. Although the design of the study precludes direct comparison, the level of protection against fungal infections was significantly better with itraconazole than with keto-

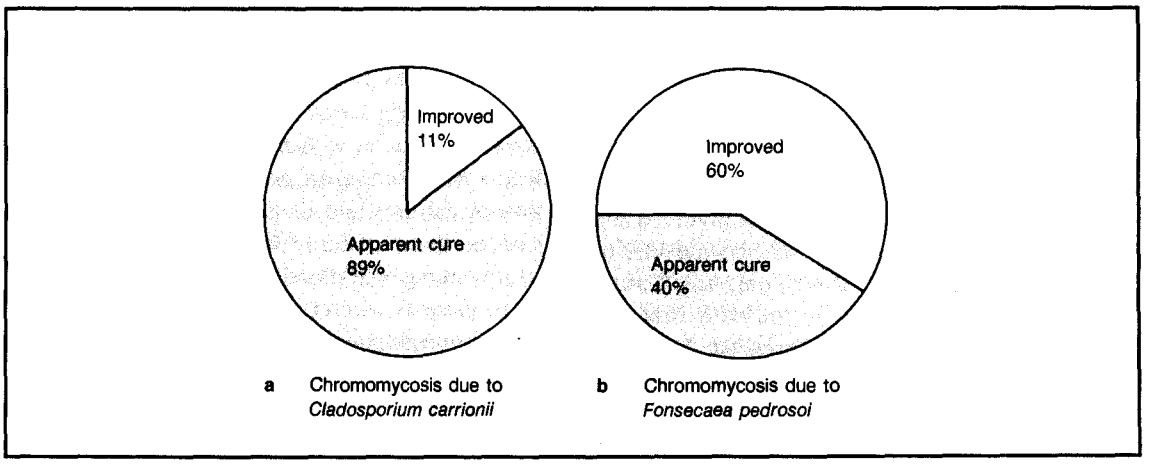

Fig. 6. Results of 4 to 8 months' treatment with oral itraconazole in patients with chromomycosis due to (a) *Cladosporium carrionii* (mean daily dose 277mg; n = 9) and (b) *Fonsecaea pedrosoi* (mean daily dose 360mg plus 5-fluorocytosine or thermotherapy; n = 5) [after Borelli 1987].

Table VIII. Response to treatment with orally administered itraconazole in patients with subcutaneous mycoses other than sporotrichosis and chromomycosis (Borelli 1987; Dupont & Drouhet 1987; Mayou et al. 1987; Vuillecard et al. 1987)

Diagnosis (no. of pts)	Dosage (mg/day) [duration of treatment (months)]	Median duration of disease (years)	Clinical result			Comments
			remission	marked improvement	moderate improvement	
Phialophora parasitica of the knee (1)	200 [4.5]	3			1	Initial clinical improvement and sterilisation of knee fluid; secondary failure associated with decreasing concentrations of itraconazole in knee fluid
Trichophyton rubrum of both feet with lymphangitic spread (1)	100 [12]	14		1		After 12 months all lesions cleared except 3 toenails
Rhinoentomophthoromycosis (3)	100-200 [0.5-3]	2	3			
Mycetoma (3)	200 [3-15]	22		1	2	In 2 patients the role of itraconazole in initial moderate improvement was equivocal

conazole (7 and 19 fatal fungal infections in itraconazole- and ketoconazole-treated patients, respectively; $p = 0.02$). The difference between itraconazole and ketoconazole was most marked among patients with prolonged (> 25 days) granulocytopenia (3 and 16 fatal fungal infections, respectively; $p < 0.0001$). Of particular importance, *Aspergillus* sp. was the pathogen in all fatal fungal infections in ketoconazole-treated patients, whereas it was the causative organism in the deaths of 5 itraconazole-treated patients ($p = 0.045$). The authors felt that failures of prophylaxis within the itraconazole group may have been due to inadequate plasma drug concentrations (< 0.25 mg/L), perhaps secondary to poor absorption (Tricot et al. 1987). Whether similar inadequate absorption of ketoconazole influenced treatment outcome was not evaluated in this study.

Similar clinical experience has been reported by Boogaerts et al. (1988). 72 patients undergoing intensive remission induction of haematological malignancies were treated prophylactically with itraconazole 200mg daily. The mean duration of neutropenia (< 500/mm^3) was 28 days and the incidence of invasive fungal infection was 18%; 12.5% were fatal. Plasma itraconazole concentrations measured 2 hours after administration revealed a significantly ($p < 0.001$) higher incidence of fungal infection in the group of patients with persistently low (< 0.25 mg/L) plasma levels. This group of patients underwent more intensive cytostatic treatment and, thus, may have developed malabsorption of itraconazole. The causative organisms isolated during itraconazole prophylaxis included *Aspergillus* and *Candida* but also included the relatively itraconazole-resistant organisms *Fusarium* and *Torulopsis*.

4. Adverse Effects

To date, more than 15,000 patients have been treated with itraconazole, and the drug appears to be very well tolerated. The incidence of adverse reactions ranges from about 7% in patients on short

courses of therapy to 17.7% in patients requiring itraconazole for longer than 1 month, with 4.7% of patients on long term treatment dropping out because of side effects. This latter group includes many patients with serious systemic mycoses. Most of the adverse reactions were transient and of mild to moderate severity; gastrointestinal disturbances, dizziness, pruritus and headache were most frequently reported (fig. 7; Cauwenbergh et al. 1988b).

In over 4,000 well-documented patients, there have been asymptomatic increases in liver enzymes in 1 to 2% of patients (Cauwenbergh et al. 1988b). These enzymes returned to pretreatment levels after discontinuing therapy or, as reported in 1 study, without a change in dosage (Restrepo et al. 1986). No cases of itraconazole-induced hepatitis have been reported. Indeed, itraconazole has been safely administered to a few patients with a history of hepatitis due to ketoconazole or amphotericin B (Cauwenbergh et al. 1988b; Viviani et al. 1987b). Since ketoconazole-induced hepatitis appears to be idiosyncratic, with an incidence of 1 in 10,000 to 15,000 (Clissold 1987), wider clinical experience with itraconazole is required to fully assess any potential for hepatic toxicity.

Among patients receiving itraconazole for short or long term treatment, no endocrine effects have been reported (Cauwenbergh et al. 1988b; Phillips et al. 1981b). A small number of patients (n = 6) have complained of impotence during therapy; however, those patients in whom serum testosterone levels were measured had values in the normal range (Cauwenbergh et al. 1988b).

There have been isolated instances of hypokalaemia developing during treatment with itraconazole 400mg daily for 4 months (n = 2; Borelli 1987; Ganer et al. 1987) and 600mg daily for a mean of 5 months (n = 5; Sharkey et al. 1988). At the higher dosage mild hypertension was reported in association with significant (p = 0.05) decreases in serum potassium.

Itraconazole produces embryotoxic and teratogenic effects (usually multiple skeletal malformations) in rats (Van Cauteren et al. 1987). Therefore, the drug is contraindicated during pregnancy and women of childbearing age should practise adequate birth control methods. There has been 1 report of itraconazole administration during the first 5 months of pregnancy. Examination of the infant at 3 months detected no abnormalities (Lavalle et al. 1987).

5. *Drug Interactions*

In vivo models suggest itraconazole is devoid of the ability to induce drug metabolising enzymes (Heykants et al. 1987; Lavrijsen et al. 1986). Nei-

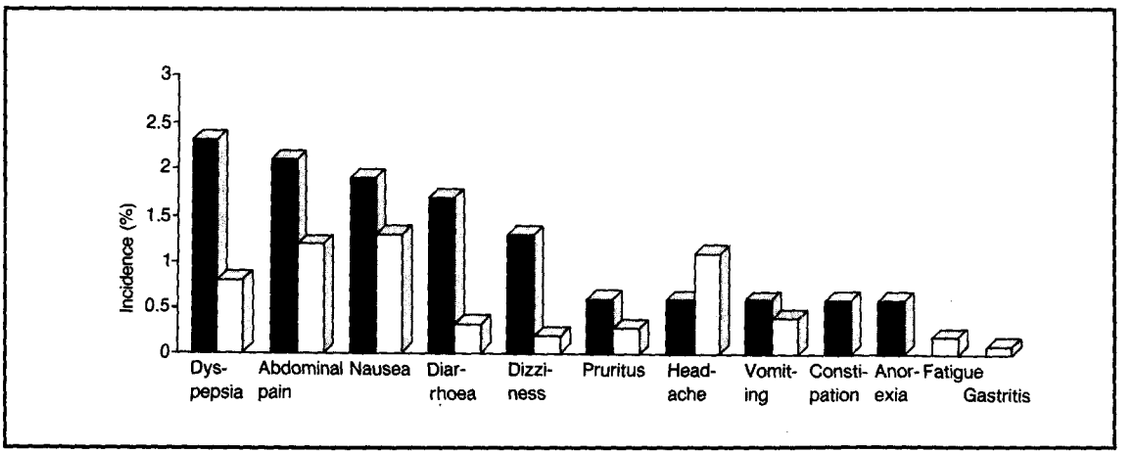

Fig. 7. The 10 most common side effects reported during treatment with itraconazole for ≤ 1 month (□; n = 2976) and > 1 month (■; n = 470) [after Cauwenbergh et al. 1988b].

ther has itraconazole demonstrated drug metabolism inhibition (Gumbleton et al. 1987; Heykants et al. 1987). Rifampicin (rifampin) appears to decrease itraconazole plasma concentrations and 1 patient experienced complete disappearance of itraconazole from plasma following concurrent administration of rifampicin. Itraconazole plasma concentrations returned to 'normal' 1 week after rifampicin was discontinued (Heykants et al. 1987). Decreased itraconazole plasma concentrations (< 0.05 mg/L) were reported in 2 patients receiving itraconazole 100 to 200mg daily for onychomycosis while maintained on phenobarbitone and phenytoin for control of epilepsy (Hay et al. 1988b). These low itraconazole plasma concentrations were associated with treatment failure in these patients.

Elevated whole blood cyclosporin concentrations have been reported in a renal transplant patient (Kwan et al. 1987) and a cardiac transplant patient (Trenk et al. 1987) during 6 weeks' concurrent treatment with itraconazole 200mg daily. Trenk et al. (1987) suggest that the interaction may be due to a metabolite of itraconazole interfering with the clearance of cyclosporin because the onset and recovery of elevated cyclosporin concentrations were slower than expected for a direct effect by the drug itself. Nováková et al. (1987) found no difference in whole blood cyclosporin concentrations relative to cyclosporin dosage between 14 bone marrow transplant patients treated with the combination and a cohort of non-itraconazole treated transplant patients. Itraconazole administration was prophylactic in 13 of these patients and was continued for a mean of 3.3 weeks; thus, the interaction suggested by Trenk and associates (1987) may not have manifested within this period. Caution is advisable when cyclosporin and itraconazole are administered together, with frequent monitoring of cyclosporin concentrations to guide adjustments of cyclosporin dosage.

6. Dosage and Administration

The recommended adult dosage for superficial fungal infections (except vaginal candidiasis) is 100mg once daily at mealtime. The duration of treatment depends on the type of infection: 15 days for oral candidiasis, tinea corporis and tinea cruris; 30 days for tinea pedis and tinea manuum; 4 to 8 weeks for tinea capitis, and 3 to 6 months for onychomycoses. Pityriasis versicolor generally responds to itraconazole 200mg once daily for 5 to 7 days; assessment of efficacy in this mycosis is best performed 3 weeks post-treatment since significant clearing of lesions occurs after completion of therapy. The recommended dosage for acute and chronic vaginal candidiasis is itraconazole 200mg once daily for 3 days, although there is preliminary evidence that 200mg twice daily for 1 day may be equally effective in women with acute infections. The recommended itraconazole dosage for fungal keratitis is 200mg once daily for 3 weeks.

Generally speaking, higher itraconazole dosages have been employed in patients with deep mycoses; the initial recommended dosage is 200mg once daily, although this may be increased to 200mg twice daily or 400mg once daily if a satisfactory response has not been achieved. Treatment duration should be individualised to obtain optimum clinical and mycological responses and should be continued after eradication of the infecting fungus, perhaps for as long as twice the initial treatment period, to ensure clinical cure. Some groups of patients treated with itraconazole, such as neutropenic patients receiving concomitant antineoplastic therapy, seem to achieve lower than expected plasma concentrations and it would seem prudent in such patients to measure plasma concentrations of itraconazole.

Certain groups of patients are very susceptible to fungal infections and recurrence tends to be a problem (AIDS patients, other immunocompromised patients, vaginal candidiasis, etc.), and itraconazole has been evaluated for longer term prophylaxis. Although no dosage recommendations are currently available, the following regimens have been evaluated: 100mg twice daily and 200mg once daily for cryptococcal prophylaxis in AIDS patients; 200mg twice daily in immunosuppressed patients, and 200mg on the first day of menses in women with recurrent vaginal candidiasis who had previ-

ously been successfully treated with a short course of itraconazole.

Preliminary results suggest that dosage modifications are not necessary in patients with impaired renal or hepatic function. In children the recommended itraconazole dosage is 3 to 5 mg/kg/day. Itraconazole is contraindicated in pregnancy and appropriate means of contraception should be employed in women of childbearing potential.

7. *The Place of Itraconazole in Therapy*

Only a limited range of drugs is currently available for the oral treatment of fungal diseases, particularly deep mycoses, and all have shortcomings in terms of efficacy or safety. Thus, a new oral agent, especially one such as itraconazole which is well tolerated with a broad spectrum of activity and a favourable pharmacokinetic profile, is of considerable interest.

Clinical experience with itraconazole in superficial fungal infections shows it is very effective in dermatophytosis, pityriasis versicolor, onychomycosis, and oral or chronic mucocutaneous candidiasis. In particular, the broad spectrum of activity and tissue kinetics of itraconazole recommend it for shortened treatment regimens in tinea infections and pityriasis versicolor. Itraconazole is an effective 1-day oral treatment of vaginal candidiasis but, at this stage, its use in pregnant women with this condition cannot be justified.

Only small numbers of patients with deep mycoses have been treated with itraconazole as yet and conclusions about its efficacy in these mycoses would be premature. However, early results in systemic candidiasis, paracoccidioidomycosis, histoplasmosis, blastomycosis and sporotrichosis have been extremely encouraging. It seems somewhat less effective in coccidioidomycosis and chromomycoses although, considering the refractory nature of these diseases to currently available drugs, itraconazole may prove a valuable addition to the treatment of these conditions. Of considerable interest is the efficacy of itraconazole monotherapy in aspergillosis, aspergilloma, disseminated cryptococcosis and cryptococcal meningitis. What role orally administered antifungals have in treating systemic disease, particularly meningeal infection, has not been clarified; however, itraconazole would seem to be a promising agent for these indications.

As would be expected at this stage of the drug's development, there are areas which require further study. For example, fungal infections characteristically relapse or recur and few patients have been followed for long enough to determine the rate of relapse after itraconazole therapy. Long term maintenance treatment has received some initial investigation, and preliminary data support further study in this area and in the area of prophylaxis for at-risk patients.

Determining the relative place of itraconazole in therapy is difficult because controlled, comparative trials are lacking. A small number of well-designed studies, particularly using amphotericin B or ketoconazole as comparative agents, would be helpful in this regard. Clinical experience with ketoconazole has shown there are many situations in which oral azole therapy is effective, convenient and well tolerated. It is tempting to speculate that itraconazole use will mimic the ketoconazole experience and, because of its broader spectrum of activity, will 'fill some gaps' in the list of indications. Only further clinical experience will establish this more clearly and determine whether itraconazole is free from the liver toxicity that ketoconazole produces in a small proportion of patients. Despite these remaining uncertainties, itraconazole is clearly a useful addition to the small number of systemic antifungal drugs available.

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