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Review

The use of fluconazole and itraconazole in the treatment of *Candida albicans* infections: a review

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Candida albicans **is responsible for most fungal infections in humans. Fluconazole is well established as a first-line management option for the treatment and prophylaxis of localized and systemic *C. albicans* infections. Fluconazole exhibits predictable pharmacokinetics and is effective, well tolerated and suitable for use in most patients with *C. albicans* infections, including children, the elderly and those with impaired immunity. Prophylactic administration of fluconazole can help to prevent fungal infections in patients receiving cytotoxic cancer therapy. The increasing use of fluconazole for the long-term prophylaxis and treatment of recurrent oral candidosis in AIDS patients has led to the emergence of *C. albicans* infections that are not responsive to conventional doses. Second-line therapy with a wider spectrum antifungal, such as itraconazole, should be sought if treatment with fluconazole fails. A solution formulation of itraconazole has recently been introduced to overcome the poor and variable absorption of its original capsule formulation. Efficacy and tolerability studies in HIV-positive or immunocompromised patients with *C. albicans* infections have shown that, although itraconazole solution is as effective as fluconazole, it is less well tolerated as first-line therapy. Itraconazole solution can be effective in AIDS patients with *C. albicans* infections that are non-responsive to fluconazole. No efficacy or tolerability data are available on the use of itraconazole solution in children or the elderly.**

Introduction

Candida albicans is the most common fungal pathogen, and is the organism responsible for the majority of localized fungal infections in humans.[1–3] Patients with impaired immunity, such as those who have AIDS or are neutropenic as a result of cancer therapy, are at particular risk of developing *C. albicans* infections, which may become systemic.[3–6]

Fluconazole (an orally active triazole agent) is well established as a first-line management option for both localized and systemic *C. albicans* infections.[7,8] Until recently, itraconazole (the other triazole licensed in the UK) was available only as a highly lipophilic capsule formulation with poor and variable absorption, and its use was therefore limited.[9,10] A solution formulation with improved absorption, resulting from the combination of itraconazole with the carrier hydroxypropyl-β-cyclodextrin (HPCD), has recently been developed and is currently undergoing clinical evaluation.[11–13]

The aim of this paper is to compare the pharmacokinetics of fluconazole, itraconazole capsules and itraconazole solution, and to evaluate their efficacy, safety and place in the treatment of *C. albicans* infections. Their use in children, the elderly and patients with impaired immunity will be considered.

Pharmacokinetics

Fluconazole

Adults. Fluconazole is water soluble and available in oral capsule, oral solution and saline-based iv solution formulations. All formulations exhibit predictable pharmacokinetics.[14–16] When given orally, fluconazole is rapidly absorbed, with peak plasma levels occurring 1–3 h after dosing.

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Absorption is unaffected by food or gastric acidity,[17,18] and peak plasma concentrations are proportional to dose over a wide range (25–400 mg).[15] The parent compound is active and has a plasma elimination half-life of around 30 h. Bioavailability is consistently high (approximately 90%) and distribution to body sites and tissues is widespread and rapid. This pharmacokinetic profile of fluconazole allows the convenience of once daily dosing, and the treatment of both localized and systemic *C. albicans* infections.

Special patient populations. The volume of distribution and clearance of fluconazole are greater in children than in adults;[19] a relatively high mg/kg dose of fluconazole is therefore necessary in young patients. For those aged greater than 4 weeks, once daily dosing is appropriate. Neonates (aged ≤4 weeks) excrete fluconazole slowly, and less frequent dosing is therefore desirable.[19,20] The pharmacokinetics of fluconazole in the elderly are similar to those in non-elderly adults.[15] Immune status has no effect on the pharmacokinetics of fluconazole in either adultsor children.[7,21,22]

Itraconazole

Adults. Itraconazole is a lipophilic agent and its absorption is therefore poor and variable.[9,10] Itraconazole capsules should be taken with food, as their water-solubility (and hence absorption) improves when gastric pH falls.[17,18] Absorption is lower when itraconazole capsules are administered together with H_2-blockers.[23] Owing to its lipophilicity, itraconazole is not found in body fluids, such as cerebrospinal fluid, ocular fluids and saliva, but in many organs and tissues (skin, lung, kidney, liver, fat, spleen, brain, muscle, bone), the drug concentration exceeds the corresponding plasma concentration by a factor of 1.5–20.[10] Clinical trials have demonstrated that itraconazole concentrations remain high in the skin and nails after treatment for dermatomycosis or onychomycosis for up to 2 weeks and 3 months, respectively, after the end of therapy.[24,25]

A solution formulation of itraconazole has been developed recently to improve its water solubility, and thereby to improve, and minimize variations in, absorption.[11] The solution contains itraconazole 10 mg/mL solubilized in 40% (v/v) HPCD, which has a 'cage-like' structure with a hydrophobic interior but hydrophilic exterior. Only a few small studies have evaluated the pharmacokinetics of itraconazole solution, but available data suggest an overall improvement in absorption and bioavailability over the capsule formulation.[12,26] In healthy volunteers, the bioavailability of itraconazole from solution was 30% greater than from capsules.[11]

Special patient populations. No published study has examined the pharmacokinetics of either itraconazole formulation in children or the elderly. Variations in the absorption of itraconazole from capsules are particularly marked in patients with impaired immunity, who frequently experience reduced gastric function, hypoacidity and mucositis.[9,27] Greater absorption of itraconazole from solution than from capsules was observed in small studies of patients with neutropenia owing to chemotherapy before autologous bone marrow transplantation[11] and AIDS;[12] wide inter-patient variation, nevertheless, remained.

Efficacy

Fluconazole

Fluconazole has excellent in-vitro activity against *C. albicans*.[28] Fluconazole can also be effective against some non-*albicans Candida* species, including *Candida parapsilosis*, *Candida tropicalis* and *Candida glabrata*, although higher doses may be required.[28,29]

Fluconazole is effective against *C. albicans* infections at a wide range of body sites and tissues, irrespective of the patient's immune status.[7,30,31] Indications in adults include vaginal,[32,33] mucosal,[31] dermal and systemic[30,34–36] candidosis (Table I). Prophylactic administration of fluconazole can be useful in patients considered at risk of fungal infections as a consequence of neutropenia following chemotherapy or radiotherapy.[37–41] Experimental evidence[42] and clinical case reports[43] suggest that prophylaxis with fluconazole may be useful in preventing *C. albicans*-associated endocarditis.

Fluconazole is suitable and effective for use in children,[44–52] but appropriate mg/kg dosage adjustments should be made (Table I). In the elderly, normal adult dose regimens should be used if there is no evidence of renal impairment. In those with renal impairment, no adjustments in single-dose therapy are required; for multiple-dose therapy, either the dosage interval should be increased or the daily dosage should be reduced.[7]

Itraconazole

Itraconazole has in-vitro activity against a greater range of *Candida* species than fluconazole.[9]

Capsule formulation. Itraconazole capsules are effective and indicated for the treatment of a number of localized and systemic fungal infections in adults, irrespective of their immune status (Table II).[9] These include vulvovaginal[53] and oropharyngeal candidosis. Because of its lipophilicity, itraconazole distributes to the nails, and the capsule formulation is effective in the treatment of onychomycosis.[54] Itraconazole capsules can be used as maintenance therapy in patients with AIDS and as prophylaxis before expected neutropenia, but as absorption is often impaired, blood monitoring should be performed and, if necessary, the dose should be increased.

There are inadequate data on itraconazole capsules in children (<12 years) and the elderly for their use to be

Table I. Indications and recommended dose for fluconazole based on UK data sheet

Indication	Recommended dose regimen
Adults	
Vaginal candidosis, acute or recurrent	150 mg single oral dose
Mucosal candidosis	
oropharyngeal candidosis	50 mg od for 7–14 days
atrophic oral candidosis	50 mg od for 14 days
other	50 mg od for 14–30 days
Dermal candida infections	50 mg od for 2–6 weeks
Systemic candidosis	400 mg on day 1, then 200–400 mg od until clinical response achieved
Prophylaxis in neutropenia	50–400 mg daily from several days before anticipated neutropenia to 7 days after neutrophil count rises above 1000 cells/mm^3
Children[a]	
Mucosal candidosis	3 mg/kg daily; loading dose of 6 mg daily may be used on day 1
Systemic candidosis	6–12 mg/kg daily
Prophylaxis in neutropenia	3–12 mg/kg daily

[a]In the first 2 weeks of life, the same mg/kg dosing as in older children should be used but administered every 72 h; during weeks 2–4 of life, the same dose should be given every 48 h.

Table II. Indications for itraconazole capsules

Indication	Recommended dose regimen[a]
Vulvo-vaginal candidosis	200 mg bd for 1 day
Oropharyngeal candidosis	100 mg od for 15 days (200 mg od for 15 days in AIDS or neutropenic patients)
Onychomycosis	200 mg od for 3 months
Candidosis	100–200 mg od (200 mg od in the case of invasive or disseminated disease)
Maintenance in AIDS	200 mg od[b]
Prophylaxis in neutropenia	200 mg od[b]

[a]Capsules must be swallowed whole immediately after food.
[b]In AIDS and neutropenic patients, blood level monitoring and, if necessary, an increase in itraconazole dose to 200 mg bd is recommended.

recommended in these special patient populations (unless the potential benefits outweigh the risks).

Solution formulation. Most studies examining the efficacy of itraconazole solution have been in patients with impaired immunity.[13,55–61] Two large comparative studies with fluconazole (Table III) were in HIV-positive patients with oral (n = 244),[57] or oropharyngeal (n = 190)[58] candidosis: 14 days of itraconazole solution was at least as effective as fluconazole in effecting a clinical response (≥87%). In a further study of 126 immunocompromised patients with oesophageal candidosis, itraconazole solution and fluconazole led to a clinical response in 94% and 91% of cases, respectively.[60] A comparative study examining the prophylactic use of itraconazole solution and fluconazole in 445 patients who were expected to be neutropenic following chemotherapy demonstrated that both agents prevent fungal infections in most cases (>97%).[59]

At present, itraconazole solution, in a dosage of 200 mg od or 100 mg bd for 1 week, repeated as necessary, is indicated solely for the treatment of oral and oesophageal candidosis in HIV-positive or immunocompromised adults. No data are available on the suitability of itraconazole solution for use in children and the elderly and, as with the capsule formulation, itraconazole solution should not be used routinely in these patients.

Table III. Studies comparing the efficacy and safety of itraconazole solution (ITRA) and fluconazole (FLUC)

Study patients	*n*	Regimen	Efficacy				Withdrawals owing to adverse events
HIV-positive, oral candidosis[57]	244		*Cure/improved*	*Relapse*			not reported
		ITRA 200 mg/day × 7 days	84%	24%			
		ITRA 100 mg/day × 14 days	91%	20%			
		FLUC 100 mg/day × 14 days	91%	22%			
HIV-positive, oropharyngeal candidosis[58]	190		*Success*	*Mycological cure*	*Relapse*		
		ITRA 200 mg/day × 7 days	83%	52%	59%	4	
		ITRA 200 mg/day × 14 days	97%	88%	44%	3	
		FLUC 100 mg/day × 14 days	87%	77%	50%	1	
Neutropenic, prophylactic study[59]	445		*Proven systemic fungal infections:*				
			Number	*Fatal*			
		ITRA 5 mg/kg/day	6	4		18%	
		FLUC 100 mg/day	1	0		4%	
Immunocompromised, oesophageal candidosis[60]	126		*Cure/improved*	*Mycological cure*			
		ITRA 100–200 mg/day × 3–8 weeks	94%	92%		5%	
		FLUC 100–200 mg/day × 3–8 weeks	91%	78%		6%	

Management of patients not responding to fluconazole

Emergence of resistance to antifungal drugs does not appear to be a problem during their short-term use. Long-term use of fluconazole as prophylaxis and treatment of recurrent oral candidosis in AIDS patients has, however, led to an increase in the number of reported fluconazole-resistant cases.[62–64] In most cases, the term 'resistance' has been used to describe non-responsiveness to conventional doses of fluconazole (rather than classical mycological resistance, for which in-vitro determination of the MIC is required). Immunocompetent hosts and those with transient immune suppression, owing, for example, to chemotherapy, are only rarely non-responsive to fluconazole.[65,66]

A number of options are available for managing patients who are non-responsive to conventional doses of fluconazole.[67] Higher doses of fluconazole have been tried and found to be successful.[68,69] In addition, most patients who are non-responsive to fluconazole remain susceptible to wider-spectrum antifungals.

In-vitro testing of isolates can help to identify the fungal species involved and its antifungal sensitivity. An antifungal susceptibility test method (M27) has been proposed by the NCCLS as a result of several collaborative studies.[70] During the development process of the susceptibility testing differences were observed in inter-laboratory reproducibility. Recent papers have discussed the technical advances and potential clinical applications of the susceptibility method and the development of interpretive breakpoints aimed to reduce this variability.[71,72] Although such sensitivity testing can be a useful guide to clinical outcome, caution should be exercised, as there is no absolute correlation between sensitivity testing to triazoles and clinical outcome.[67] Some studies have reported a general correlation between clinical failure and high fluconazole MIC levels,[73–75] whereas others have noted an overlap or poor correlation.[76,77] The apparently contradictory literature probably reflects complex clinical differences between patients, for example, in their immune status.

Approximately 70% of fluconazole-resistant isolates (MIC $\geqslant$ 25 mg/L) remain susceptible to itraconazole *in vitro*, although data are limited,[78] and itraconazole solution can be effective in treating patients who are non-responsive to fluconazole treatment.[56] In a study of 25 AIDS patients with candidosis (oral or oesophageal) who were non-responsive to other azoles (fluconazole and/or ketoconazole), itraconazole solution led to clinical cure in over 70% of cases; the success rate was 50% in those who were non-responsive to itraconazole capsules.[56] Among 36 HIV-positive patients who were non-responsive to fluconazole for oropharyngeal candidosis, 65% responded to itraconazole solution.[79] Itraconazole solution is recommended for the treatment of oral and oesophageal candidosis in AIDS patients who are non-responsive to fluconazole, but a

higher dose (up to 400 mg daily) and a longer treatment period (2 weeks, repeated if necessary) than for first-line therapy are recommended.[80]

To date there have been only a few reports of non-responsiveness to itraconazole among patients with *C. albicans* infections. The relatively low number could reflect the fact that itraconazole has been prescribed to a much lesser extent than fluconazole.[62] A recent in-vitro study revealed that some isolates obtained from HIV patients with oral thrush show resistance to itraconazole *in vitro*, but that none of these resistant strains are susceptible to fluconazole.[56] To avoid the emergence of strains that are cross-resistant to a range of antifungals, it may be prudent to reserve itraconazole for use as second-line therapy in patients who fail to respond to fluconazole.

There is evidence to suggest that voriconazole, a newly developed triazole agent, may be useful in the management of *C. albicans* infections in patients who are non-responsive to fluconazole.[81] In an in-vitro study of 105 isolates from the oral cavities of patients with HIV infection, voriconazole showed good activity against both fluconazole-susceptible and -resistant isolates (MIC $\geq$ 25 mg/L), although the voriconazole MIC was higher with the latter (0.39 versus 0.19 mg/L).[81] Of six patients with *C. albicans* showing in-vitro resistance to fluconazole but not to voriconazole (MIC $\leq$ 0.39 mg/L), all had a clinical response to voriconazole. Although these data are promising, further studies are necessary to determine the clinical usefulness of voriconazole relative to fluconazole and itraconazole.

Safety

Fluconazole

Fluconazole is generally well tolerated over a wide dose range.[7,82–84] Clinical experience is extensive, with over 16 million patient-days of treatment with fluconazole since its introduction in the UK, and 300 million patient-days world-wide. The incidence of side effects is low, and symptoms are generally mild and do not require discontinuation from therapy.[7] The most common side effects are associated with the gastrointestinal tract (nausea, abdominal discomfort, vomiting, diarrhoea). Others include headache and rashes, but these are rarely encountered (incidence of $<$2%). Tolerability is high even in special patient groups including children and severely ill patients with AIDS or cancer.[7,85]

Although not licensed, high doses of fluconazole (up to 800 mg/day) are well tolerated in the treatment of immunocompromised patients with severe systemic mycoses.[86,87] Doses of up to 1600 mg fluconazole have been shown to be well tolerated in studies of AIDS patients with histoplasmosis[88] and cryptococcal meningitis.[83,87]

In rare cases, particularly in patients with serious underlying diseases such as AIDS and cancer, abnormalities of hepatic, renal, haematological and other biochemical function tests have been observed, but the clinical significance and relationship of these to treatment is uncertain.[7] Very rarely, post-mortem examinations of patients who died with severe underlying disease and had received multiple-dose fluconazole therapy have revealed hepatic necrosis: an assessment of the risk–benefit ratio of continued fluconazole administration for patients in whom a significant rise in liver enzymes occurs is, therefore, recommended.[89,90]

Itraconazole

Like fluconazole, the most frequently reported side effects associated with itraconazole are gastrointestinal (abdominal pain, nausea and vomiting, dyspepsia).[9] Other side effects include dizziness, pruritus and headache. Owing to a risk of transient increases in hepatic enzymes, itraconazole capsules are not suitable for the routine treatment of infections in patients with raised liver enzymes, a history of liver disease, or who have experienced liver toxicity with other drugs. In instances when prolonged ($>$1 month) treatment is given, liver enzyme monitoring should be undertaken.

Only limited safety data are available for itraconazole solution. Comparative studies of itraconazole solution and fluconazole indicated similar types and incidences of side effects, but higher withdrawal frequencies with itraconazole solution (Table III).[57–60] In HIV-positive patients with oral or oropharyngeal candidosis, treatment discontinuations as a result of adverse events occurred in only one of 60 patients treated with fluconazole, but in seven of 119 patients who received itraconazole oral solution.[58] Similar types (nausea, vomiting, diarrhoea and rash) and frequencies of adverse events were also seen following itraconazole solution or fluconazole prophylaxis in 445 neutropenic patients, but 18% of patients who received itraconazole solution therapy were withdrawn prematurely, compared with only 4% on fluconazole.[59]

With the improved absorption of the oral solution formulation of itraconazole, it is possible that the maximum-tolerated dose may be lower than that of the capsule formulation, and it should be borne in mind that at high doses, β-cyclodextrins can cause depletion of membrane components, thereby affecting the gastric mucosa with long-term exposure.[91] In murine toxicity studies, HPCD has been found to induce liver enlargement.[92]

Experience with itraconazole solution at more than 400 mg/day is limited: no published study has established the maximum limit for the new formulation. A small clinical study demonstrated that 600 mg/day may be near the upper limit of itraconazole capsules: patients started to experience side effects such as adrenal insufficiency, hypertension and gynaecomastia at this level.[93]

Other considerations

Formulation

Fluconazole is available in oral capsule, pleasant-tasting solution and saline-based iv formulations; all are well tolerated. There is anecdotal evidence of patients refusing itraconazole solution, especially once any symptoms of oral thrush diminish and taste sensation is restored:[66] this suggests an unpleasant taste.

Cost

An important advantage of fluconazole over itraconazole is its cost. A weekly supply of the UK-recommended daily dose of 200 mg itraconazole solution for the treatment of oral candidosis in AIDS patients costs £52.28. This compares with the UK-recommended od 50 mg fluconazole regimen, which costs £16.61 per week.

Conclusions

Fluconazole remains a first-line antifungal agent of choice for the treatment of *C. albicans* infections, because of its well-known efficacy and safety profile; its suitability for use in children, the elderly and patients with impaired immunity; its range of formulations; and its cost. As a result of its lipophilicity, itraconazole is the appropriate choice for the treatment of nail and skin infections. Although non-responsiveness to conventional doses of fluconazole is occasionally encountered (most commonly in the prophylaxis and treatment of recurrent oral candidosis in AIDS patients), there is evidence that higher doses can be successful. If fluconazole fails, then the wider spectrum antifungal itraconazole appears reasonable as a second-line alternative: although some candida infections exhibiting resistance to fluconazole are also resistant to itraconazole, a proportion remain susceptible. Early data suggest that itraconazole solution has a favourable pharmacokinetic profile compared with its capsule formulation, which is associated with unpredictable absorption and hence bioavailability. Further studies are, however, required to establish the pharmacokinetics of itraconazole solution in children and the elderly, and to fully determine its clinical usefulness relative to fluconazole.

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References

1. Beck-Sagúe, C. & Jarvis, W. R. (1993). Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980–1990. National Nocosomial Infections Surveillance System. *Journal of Infectious Diseases* **167**, 1247–51.

2. Dupont, P. F. (1995). *Candida albicans*, the opportunist. A cellular and molecular perspective. *Journal of the American Pediatric Medical Association* **85**, 104–15.

3. McCullough, M. J., Ross, B. C. & Reade, P. C. (1996). *Candida albicans*: a review of its history, taxonomy, epidemiology, virulence attributes, and methods of strain differentiation. *International Journal of Oral and Maxillofacial Surgery* **25**, 136–44.

4. Barchiesi, F., Morbiducci, V., Ancarani, F. & Scalise, G. (1993). Emergence of oropharyngeal candidiasis caused by non-*albicans* species of *Candida* in HIV-infected patients. *European Journal of Epidemiology* **9**, 455–6.

5. Powderly, W. G., Robinson, K. & Keath, E. J. (1993). Molecular epidemiology of recurrent oral candidiasis in human immunodeficiency virus-positive patients: evidence for two patterns of recurrence. *Journal of Infectious Diseases* **168**, 463–6.

6. Vazquez, J. A. (1999). Options for the management of mucosal candidiasis in patients with AIDS and HIV infection. *Pharmacotherapy* **19**, 76–87.

7. Goa, K. L. & Barradell, L. B. (1995). Fluconazole. An update of its pharmacodynamic and pharmacokinetic properties and therapeutic use in major superficial and systemic mycoses in immunocompromised patients. *Drugs* **50**, 658–90.

8. Edwards, J. E., Jr, Bodey, G. P., Bowden, R. A., Buchner, T., de Pauw, B. E., Filler, S. G. *et al*. (1997). International Conference for the Development of a Consensus on the Management and Prevention of Severe Candidal Infections. *Clinical Infectious Diseases* **25**, 43–59.

9. Haria, M., Bryson, H. M. & Goa, K. L. (1996). Itraconazole. A reappraisal of its pharmacological properties and therapeutic use in the management of superficial fungal infections. *Drugs* **51**, 585–620.

10. De Beule, K. (1996). Itraconazole: pharmacology, clinical experience and future development. *International Journal of Antimicrobial Agents* **6**, 175–81.

11. Prentice, A. G., Warnock, D. W., Johnson, S. A. N., Phillips, M. J. & Oliver, D. A. (1994). Multiple dose pharmacokinetics of an oral solution of itraconazole in autologous bone marrow transplant recipients. *Journal of Antimicrobial Chemotherapy* **34**, 247–52.

12. Cartledge, J. D., Midgley, J. & Gazzard, B. G. (1997). Itraconazole solution: higher serum drug concentrations and better clinical response rates than the capsule formulation in acquired immunodeficiency syndrome patients with candidosis. *Journal of Clinical Pathology* **50**, 477–80.

13. Graybill, J. R., Vazquez, J., Darouiche, R. O., Morhart, R., Greenspan, D., Tuazon, C. *et al*. (1998). Randomized trial of itraconazole oral solution for oropharyngeal candidiasis in HIV/AIDS patients. *American Journal of Medicine* **104**, 33–9.

14. Humphrey, M. J., Jevons, S. & Tarbit, M. H. (1985). Pharmacokinetic evaluation of UK-49,858, a metabolically stable triazole antifungal drug in animals and humans. *Antimicrobial Agents and Chemotherapy* **28**, 648–53.

15. Debruyne, D. & Ryckelynck, J. P. (1993). Clinical pharmacokinetics of fluconazole. *Clinical Pharmacokinetics* **24**, 10–27.

16. Koks, C. H., Meenhorst, P. L., Hillebrand, M. J., Bult, A. & Beijnen, J. H. (1996). Pharmacokinetics of fluconazole in saliva and plasma after administration of an oral suspension and capsules. *Antimicrobial Agents and Chemotherapy* **40**, 1935–7.

17. Lim, S. G., Sawyerr, A. W., Hudson, M., Sercombe, J. & Pounder, R. E. (1993). Short report: the absorption of fluconazole and itraconazole under conditions of low intragastric acidity. *Alimentary Pharmacology and Therapeutics* **7**, 317–21.

18. Zimmermann, T., Yeates, R. A., Laufen, H., Pfaff, G. & Wildfeuer, A. (1994). Influence of concomitant food intake on the oral absorption of two triazole antifungal agents, itraconazole and fluconazole. *European Journal of Clinical Pharmacology* **46**, 147–50.

19. Brammer, K. W. & Coates, P. E. (1994). Pharmacokinetics of fluconazole in pediatric patients. *European Journal of Clinical Microbiology and Infectious Diseases* **13**, 325–9.

20. Saxén, H., Hoppu, K. & Pohjavuori, M. (1993). Pharmacokinetics of fluconazole in very low birth weight infants during the first two weeks of life. *Clinical Pharmacology and Therapeutics* **54**, 269–77.

21. Nahata, M. C. & Brady, M. T. (1995). Pharmacokinetics of fluconazole after oral administration in children with human immunodeficiency virus infection. *European Journal of Clinical Pharmacology* **48**, 291–3.

22. Seay, R. E., Larson, T. A., Toscano, J. P., Bostrom, B. C., O'Leary, M. C. & Uden, D. L. (1995). Pharmacokinetics of fluconazole in immune-compromised children with leukaemia or other hematological diseases. *Pharmacotherapy* **15**, 52–8.

23. Stein, A. G., Daneshmend, T. K., Warnock, D. W., Bhaskar, N., Burke, J. & Hawkey, C. J. (1989). The effects of the H_2 receptor antagonists on the pharmacokinetics of itraconazole, a new oral antifungal. *British Journal of Clinical Pharmacology* **27**, 105P–106P.

24. De Doncker, P. & Cauwenbergh, G. (1990). Management of fungal skin infections with 15 days itraconazole treatment: a worldwide review. *British Journal of Clinical Practice. Supplement 71*, 118–22.

25. Willemsen, M., De Doncker, P., Willems, J., Woestenborghs, R., Van de Velde, V., Heykants, J. *et al*. (1992) Posttreatment itraconazole levels in the nail. New implications for treatment in onychomycosis. *Journal of the American Academy of Dermatology* **26**, 731–5.

26. Van de Velde, V. J., Van Peer, A. P., Heykants, J. J., Woestenborghs, R. J., Van Rooy, P., De Beule, K. L. *et al*. (1996). Effect of food on the pharmacokinetics of a new hydroxypropyl-beta cyclodextrin formulation of itraconazole. *Pharmacotherapy* **16**, 424–8.

27. Smith, D., Van de Velde, V., Woestenborghs, R. & Gazzard, B. G. (1992). The pharmacokinetics of oral itraconazole in AIDS patients. *Journal of Pharmacy and Pharmacology* **44**, 618–19.

28. Arévalo, M. P., Arias, A., Andreu, A., Rodríguez, C. & Sierra, A. (1994). Fluconazole, itraconazole and ketoconazole *in vitro* activity against *Candida* sp. *Journal of Chemotherapy* **6**, 226–9.

29. Van't Wout, J. W. (1996). Fluconazole treatment of candidal infections caused by non-*albicans Candida* species. *European Journal of Clinical Microbiology and Infectious Diseases* **15**, 238–42.

30. Anaissie, E., Bodey, G. P., Kantarjian, H., David, C., Barnett, K. & Bow, E. *et al.* (1991). Fluconazole therapy for chronic disseminated candidiasis in patients with leukemia and prior amphotericin B therapy. *American Journal of Medicine* **91**, 142–50.

31. Finlay, P. M., Richardson, M. D. & Robertson, A. G. (1996). A comparative study of the efficacy of fluconazole and amphotericin B in the treatment of oropharyngeal candidosis in patients undergoing radiotherapy for head and neck tumours. *British Journal of Oraland Maxillofacial Surgery* **34**, 23–5.

32. Perry, C. M., Whittington, R. & McTavish, D. (1995). Fluconazole. An update of its antimicrobial activity, pharmacokinetic properties, and therapeutic use in vaginal candidiasis. *Drugs* **49**, 984–1006.

33. Kaplan, B., Rabinerson, D. & Gibor, Y. (1997). Single-dose systemic oral fluconazole for the treatment of vaginal candidiasis. *International Journal of Gynaecology and Obstetrics* **57**, 281–6.

34. Ikemoto, H. (1989). A clinical study of fluconazole for the treatment of deep mycoses. *Diagnostic Microbiology and Infectious Disease* **12**, 239S–47S.

35. Rex, J. H., Bennett, J. E., Sugar, A. M., Pappas, P. G., van der Horst, C. M., Edwards, J. E. *et al*. (1994). A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. *New England Journal of Medicine* **331**, 1325–30.

36. Debruyne, D. (1997). Clinical pharmacokinetics of fluconazole in superficial and systemic mycoses. *Clinical Pharmacokinetics* **33**, 52–77.

37. Samonis, G., Rolston, K., Karl, C., Miller, P. & Bodey, G. P. (1990). Prophylaxis of oropharyngeal candidiasis with fluconazole. *Reviews of Infectious Diseases* **12**, *Suppl. 3*, S369–73.

38. Goodman, J. L., Winston, D. J., Greenfield, R. A., Chandrasekar, P. H., Fox, B., Kaizer, H. *et al*. (1992). A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *New England Journal of Medicine* **326**, 845–51.

39. Philpott-Howard, J. N., Wade, J. J., Mufti, G. J., Brammer, K. W. & Ehninger, G. (1993). Randomized comparison of oral fluconazole versus oral polyenes for the prevention of fungal infection in patients at risk of neutropenia. Multicentre Study Group. *Journal of Antimicrobial Chemotherapy* **31**, 973–84.

40. Mucke, R., Kaben, U., Libera, T., Knauerhase, H., Ziegler, P. G., Hamann, D. *et al*. (1998). Fluconazole prophylaxis in patients with head and neck tumours undergoing radiation and radiochemotherapy. *Mycoses* **41**, 421–3.

41. Van Burik, J. H., Leisenring, W., Myerson, D., Hackman, R. C., Shulman, H. M., Sale, G. E. *et al*. (1998). The effect of prophylactic fluconazole on the clinical spectrum of fungal diseases in bone marrow transplant recipients with special attention to hepatic candidiasis. An autopsy study of 355 patients. *Medicine* **77**, 246–54.

42. Longman, L. P., Hibbert, S. A. & Martin, M. V. (1990). Efficacy of fluconazole in prophylaxis and treatment of experimental *Candida* endocarditis. *Reviews of Infectious Diseases* **12**, *Suppl. 3*, S294–8.

43. Nguyen, M. H., Nguyen, M. L., Lu, V. L., McMahon, D., Keys, T. F. & Amidi, M. (1996). Candida prosthetic valve endocarditis: prospective study of six cases and review of the literature. *Clinical Infectious Diseases* **22**, 262–7.

44. Viscoli, C., Castagnola, E., Fioredda, F., Ciravegna, B., Barigione, G. & Terragna, A. (1991). Fluconazole in the treatment of candidiasis in immunocompromised children. *Antimicrobial Agents and Chemotherapy* **35**, 365–7.

45. Fasano, C., O'Keefe, J. & Gibbs, D. (1994). Fluconazole treatment of children with severe fungal infections not treatable with conventional agents. *European Journal of Clinical Microbiology and Infectious Disease* **13**, 344–7.

46. Flynn, P. M., Cunningham, C. K., Kerkering, T., San Jorge, A. R., Peters, V. B., Pitel, P. A. *et al.* (1995). Oropharyngeal candidiasis in immunocompromised children: a randomized, multicenter study of

orally administered fluconazole suspension versus nystatin. *Journal of Paediatrics* **127**, 322–8.

47. Presterl, E. & Graninger, W. (1994). Efficacy and safety of fluconazole in the treatment of systemic fungal infections in pediatric patients. Multicentre Study Group. *European Journal of Clinical Microbiology and Infectious Diseases* **13**, 347–51.

48. Cáp, J., Mojzesova, A., Kayserova, E., Bubánska, E., Hatiar, K., Trupl, J. *et al*. (1993). Fluconazole in children: first experience with prophylaxis in chemotherapy-induced neutropenia in paediatric patients with cancer. *Chemotherapy* **39**, 438–42.

49. Ninane, J. (1994). A multicentre study of fluconazole versus oral polyenes in the prevention of fungal infection in children with hematological or oncological malignancies. Multicentre Study Group. *European Journal of Clinical Microbiology and Infectious Diseases* **13**, 330–7.

50. Driessen, M., Ellis, J. B., Muwazi, F. & De Villiers, F. P. (1997). The treatment of systemic candidiasis in neonates with oral fluconazole. *Annals of Tropical Paediatrics* **17**, 263–71.

51. Groll, A. H., Just-Nuebling, G., Kurz, M., Mueller, C., Nowak-Goettl, U., Schwabe, D. *et al*. (1997). Fluconazole versus nystatin in the prevention of candida infections in children and adolescents undergoing remission induction or consolidation chemotherapy for cancer. *Journal of Antimicrobial Chemotherapy* **40**, 855–62.

52. Wenzl, T. G., Schefels, J., Hornchen, H. & Skopnik, H. (1998). Pharmacokinetics of oral fluconazole in premature infants. *European Journal of Pediatrics* **157**, 661–2.

53. Rees, T. & Phillips, R. (1992). Multicenter comparison of one-day oral therapy with fluconazole or itraconazole in vaginal candidiasis. *International Journal of Gynecology and Obstetrics* **37**, *Suppl. 1*, 33S–38S.

54. Rongioletti, F., Robert, E., Tripodi, S. & Persi, A. (1992). Treatment of onychomycosis with itraconazole. *Journal of Dermatological Treatment* **2**, 145–6.

55. Blatchford, N. R. (1990). Treatment of oral candidosis with itraconazole: a review. *Journal of the American Academy of Dermatology* **23**, 565–7.

56. Cartledge, J. D., Midgley, J., Youle, M. & Gazzard, B. G. (1994). Itraconazole cyclodextrin solution—effective treatment for HIV-related candidiasis unresponsive to other azole therapy. *Journal of Antimicrobial Chemotherapy* **33**, 1071–3.

57. Frechette, G., De Beule, K., Weinke, W., Tchamouroff, S. E. & Stoffels, P. (1995). Effects of itraconazole in the treatment of oral candidosis in HIV patients. A double-blind, double-dummy, randomized comparison with fluconazole. In *Program and Abstracts of the Thirty-Fifth Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 1995*. Abstract 1219, p. 244. American Society for Microbiology, Washington, DC.

58. Graybill, J. R., Vazquez, J., Darouiche, R. O., Mohart, R., Moskovitz, B. L. & Mallegol, I. (1995). Itraconazole oral solution (IS) versus fluconazole (F) treatment of oropharyngeal candidiasis (OC). In *Program and Abstracts of the Thirty-Fifth Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 1995*. Abstract 1009, p. 244. American Society for Microbiology, Washington, DC.

59. Morgenstern, G. R., Prentice, A. G., Prentice, H. G., Ropner, J. E., Schey, S. A. & Warnock, D. W. (1996). Itraconazole oral solution versus fluconazole suspension for antifungal prophylaxis in neutropenic patients. In *Program and Abstracts of the Thirty-Sixth Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, 1996*. Abstract LM34. American Society for Microbiology, Washington, DC.

60. Wilcox, C. M., Darouiche, R. O., Laine, L., Moskovitz, B. L., Mallegol, I. & Wu, J. (1997). A randomized, double-blind comparison of itraconazole oral solution and fluconazole tablets in the treatment of esophageal candidiasis. *Journal of Infectious Diseases* **176**, 227–32.

61. Phillips, P., De Beule, K., Frechette, G., Tchamouroff, S., Vandercam, B., Weitner, L. *et al*. (1998). A double-blind comparison of itraconazole oral solution and fluconazole capsules for the treatment of oropharyngeal candidiasis in patients with AIDS. *Clinical Infectious Diseases* **26**, 1368–73.

62. Johnson, E. M. & Warnock, D. W. (1995). Azole drug resistance in yeasts. *Journal of Antimicrobial Chemotherapy* **36**, 751–5.

63. Rex, J. H., Rinaldi, M. G. & Pfaller, M. A. (1995). Resistance of *Candida* species to fluconazole. *Antimicrobial Agents and Chemotherapy* **39**, 1–8.

64. Hunter, K. D., Gibson, J., Lockhart, P., Pithie, A. & Bagg, J. (1998). Fluconazole-resistant *Candida* species in the oral flora of fluconazole-exposed HIV-positive patients. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics* **85**, 558–64.

65. Field, E. A., Millns, B., Pearce, P. K., Martin, M. V., Parkinson, T. & Hitchcock, C. A. (1996). Fluconazole therapy of oropharyngeal candidiasis in a patient with multiple endocrine failure does not correlate with *Candida albicans* susceptibility to fluconazole *in vitro*. *Journal of Medical and Veterinary Mycology* **34**, 205–8.

66. Marr, K. A., White, T. C., van Burik, J.-A. H. & Bowden, R. A. (1997). Development of fluconazole resistance in *Candida albicans* causing disseminated infection in a patient undergoing marrow transplantation. *Clinical Infectious Diseases* **25**, 908–10.

67. Milne, L. J. R. (1997). The antifungal triazoles in oropharyngeal candidosis in AIDS. *Opinion in Microbiology*, 9–12.

68. Ansari, A. M., Gould, I. M. & Douglas, J. G. (1990). High dose oral fluconazole for oropharyngeal candidosis in AIDS. *Journal of Antimicrobial Chemotherapy* **25**, 720–1.

69. Redding, S. W., Pfaller, M. A., Messer, S. A., Smith, J. A., Prows, J., Bradley, L. L. *et al*. (1997). Variations in fluconazole susceptibility and DNA subtyping of multiple *Candida albicans* colonies from patients with AIDS and oral candidiasis suffering one or more episodes of infection. *Journal of Clinical Microbiology* **35**, 1761–5.

70. National Committee for Clinical Laboratory Standards. (1992). *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts. Proposed Standard M27-P*. NCCLS, Villanova, PA.

71. Pfaller, M. A., Rex, J. H. & Rinaldi, M. G. (1997). Antifungal susceptibility testing: technical advances and potential clinical applications. *Clinical Infectious Diseases* **24**, 776–84.

72. Rex, J. H., Pfaller, M. A., Galgiani, J. N., Bartlett, M. S., Espinel Ingroff, A., Ghannoum, M. A. *et al*. (1997). Development of interpretive breakpoints for antifungal susceptibility testing: conceptual framework and analysis of *in vitro–in vivo* correlation data for fluconazole, itraconazole, and candida infections. Subcommittee on Antifungal Susceptibility Testing of the National Committee for Clinical Laboratory Standards. *Clinical Infectious Diseases* **24**, 235–47.

73. Troillet, N., Durussel, C., Bille, J., Glauser, M. P. & Chave, J. P. (1993). Correlation between *in vitro* susceptibility of *Candida*

albicans and fluconazole-resistant oropharyngeal candidiasis in HIV-infected patients. *European Journal of Clinical Microbiology and Infectious Diseases* **12**, 911–5.

74. Redding, S., Smith, J., Farinacci, G., Rinaldi, M., Fothergill, A., Rhine-Chalberg, J. *et al.* (1994). Resistance of *Candida albicans* to fluconazole during treatment of oropharyngeal candidiasis in a patient with AIDS: documentation by *in vitro* susceptibility and DNA subtype analysis. *Clinical Infectious Diseases* **18**, 240–2.

75. Ruhnke, M., Eigler, A., Engelmann, E., Geiseler, B. & Trautmann, M. (1994). Correlation between antifungal susceptibility testing of *Candida* isolates from patients with HIV infection and clinical results after treatment with fluconazole. *Infection* **22**, 132–6.

76. Cameron, M. L., Schell, W. A., Bruch, S., Bartlett, J. A., Waskin, H. A. & Perfect, J. R. (1993). Correlation of *in vitro* fungal resistance of *Candida* isolates in relation to therapy and symptoms of individuals seropositive for human immunodeficiency virus type I. *Antimicrobial Agents and Chemotherapy* **37**, 2449–53.

77. Rex, J. H., Pfaller, M. A., Barry, A. L., Nelson, P. W. & Webb, C. D. (1995). Antifungal susceptibility testing of isolates from a randomized, multicenter trial of fluconazole versus amphotericin B as treatment of nonneutropenic patients with candidemia. NIALD Mycoses Study Group and the Candidemia Study Group. *Antimicrobial Agents and Chemotherapy* **39**, 40–4.

78. Ruhnke, M., Eigler, A., Tennagen, I., Geiseler, B., Engelmann, E. & Trautmann, M. (1994). Emergence of fluconazole-resistant strains of *Candida albicans* in patients with recurrent oropharyngeal candidosis in human immunodeficiency virus infection. *Journal of Clinical Microbiology* **32**, 2092–8.

79. Phillips, P., Zemcov, J., Mahmood, W., Montaner, J. S., Craib, K. & Clarke, A. M. (1996). Itraconazole cyclodextrin solution for fluconazole-refractory oropharyngeal candidiasis in AIDS: correlation of clinical response with *in vitro* susceptibility. *AIDS* **10**, 1369–76.

80. Johnson, E. M., Davey, K. G., Szekely, A. & Warnock, D. W. (1995). Itraconazole susceptibilities of fluconazole susceptible and resistant isolates of five *Candida* species. *Journal of Antimicrobial Chemotherapy* **36**, 787–93.

81. Ruhnke, M., Schmidt-Westhausen, A. & Trautmann, M. (1997). *In vitro* activities of voriconazole (UK-109,496) against fluconazole-susceptible and -resistant *Candida albicans* isolates from oral cavities of patients with human immunodeficiency virus infection. *Antimicrobial Agents and Chemotherapy* **41**, 575–7.

82. Inman, W., Kubota, K., Pearce, G. & Wilton, L. (1993). PEM Report Number 3—Fluconazole. *Pharmacoepidemiology and Drug Safety* **2**, 321–40.

83. Duswald, K. H., Penk, A. & Pittrow, L. (1997). High-dose therapy with fluconazole $\geqslant$800 mg day^{-1}. *Mycoses* **40**, 267–77.

84. Stevens, D. A., Diaz, M., Negroni, R., Montero Gei, F., Castro, L. G., Sampaio, S. A. *et al*. (1997). Safety evaluation of chronic fluconazole therapy. Fluconazole Pan-American Study Group. *Chemotherapy* **43**, 371–7.

85. Osterloh, I. H. (1992). Fluconazole. In *The Antifungal Agents, Vol. 1,* (Johnson, S. & Johnson, F. N., Eds), pp. 40–60. Marius Press.

86. Berry, A. J., Rinaldi, M. G. & Graybill, J. R. (1992). Use of high-dose fluconazole as salvage therapy for cryptococcal meningitis in patients with AIDS. *Antimicrobial Agents and Chemotherapy* **36**, 690–2.

87. Haubrich, R. H., Haghighat, D., Bozzette, S. A., Tilles, J. & McCutchan, J. A. (1994). High-dose fluconazole for treatment of cryptococcal disease in patients with human immunodeficiency virus infection. The California Collaborative Treatment Group. *Journal of Infectious Diseases* **170**, 238–42.

88. Wheat, L., Mawhinney, S., Hafner, R. & McKinsey, D. (1994). Fluconazole treatment for histoplasmosis in AIDS: prospective multi-center non-comparative trial. In *Program and Abstracts of the Thirty-Fourth Interscience Conference on Antimicrobial Agents and Chemotherapy, Orlando, FL, 1994*. Abstract 1233. American Society for Microbiology, Washington, DC.

89. Jacobson, M. A., Hanks, D. K. & Ferrell, L. D. (1994). Fatal acute hepatic necrosis due to fluconazole. *American Journal of Medicine* **96**, 188–90.

90. Bronstein, J. A., Gros, P., Hernandez, E., Larroque, P. & Molinie, C. (1997). Fatal acute hepatic necrosis due to dose-dependent fluconazole hepatotoxicity. *Clinical Infectious Diseases* **25**, 1266–7.

91. Uekama, K. & Otagiri, M. (1987). Cyclodextrins in drug carrier systems. *Critical Reviews in Therapeutic Drug Carrier Systems* **3**, 1–40.

92. Gerloczy, A., Hoshino, T. & Pitha, J. (1994). Safety of oral cyclodextrins: effects of hydroxypropyl cyclodextrins, cyclodextrin sulfates and cationic cyclodextrins on steroid balance in rats. *Journal of Pharmaceutical Sciences* **83**, 193–6.

93. Sharkey, P. K., Rinaldi, M. G., Dunn, J. F., Hardin, T. C., Fetchick, R. J. & Graybill, J. R. (1991). High-dose itraconazole in the treatment of severe mycoses. *Antimicrobial Agents and Chemotherapy* **35**, 707–13.

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