Safety and efficacy of fluconazole treatment for *Candida* oesophagitis in AIDS

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Summary: The efficacy and safety of fluconazole in the treatment of oesophageal candidiasis in patients with the acquired immunodeficiency syndrome (AIDS) was assessed in 36 patients. Fluconazole, 200 mg orally, was given on the first day, followed by 100 mg daily for 4 weeks. Clinical and mycological evaluation was performed in 31 patients at the end of treatment and 24 were also assessed after 8 weeks of starting treatment. In 1 patient fluconazole was discontinued, 5 patients were lost to follow-up and 6 patients died during the study.

Clinical and mycological cure was achieved in all patients; in 31 of 36 patients the clinical picture resolved within a week. The cure was confirmed in 27 patients by oesophagoscopy. Two patients relapsed 1 month after stopping fluconazole but the reinstitution of therapy achieved cure. Asymptomatic fungal oropharynx colonization was evident in about 40% of patients during treatment and follow-up period. Fluconazole was well tolerated by all patients but mild to moderate increase of liver enzymes values occurred in 16. Treatment had to be discontinued in 1 patient with hepatic tuberculosis because of severe liver function abnormalities, but their relation with the drug was uncertain.

Fluconazole is an effective and safe treatment of oesophageal candidiasis in AIDS patients.

Introduction

Oesophageal candidiasis occurs in about 90% of acquired immunodeficiency syndrome (AIDS) patients.¹ The conventional but unsatisfactory treatment for *Candida* oesophagitis in AIDS was parenteral amphotericin in short-course therapy of 8–10 days² despite the need for intravenous administration and marked drug toxicity. Ketoconazole has also been useful to treat oesophageal candidiasis and it has been proposed³ as the treatment of choice for this condition. Problems associated with ketoconazole include ketoconazole-resistant *Candida* strains,⁴ impaired gastrointestinal absorption secondary to the hyposecretory gastropathy that occurs in AIDS patients,^{5–7} the risk of hepatitis,⁸ the interaction with other drugs, particularly rifampicin,⁹ and the unavailability of an intravenous preparation.

The new triazole agents (fluconazole, itraconazole) may overcome some of these difficulties.^{10–12} Fluconazole is effective in treatment of deep and superficial *Candida* infections in

both healthy and immunosuppressed rats.^{13,14} Oropharyngeal candidiasis in AIDS patients responds satisfactorily to fluconazole¹⁵ as may oesophageal candidiasis.¹⁶

We describe the results of treatment with fluconazole of oesophageal candidiasis in a series of AIDS patients.

Materials and methods

Thirty six AIDS patients of mean age 28 years (25 male and 11 female), diagnosed according to criteria established by the Centers for Disease Control,¹⁷ were studied. The most important risk factor for AIDS was illicit drug use (31 patients). In 15 the diagnosis of AIDS had been established in the preceding year (11 cases) or before (4 cases). Thirty one patients had a total of 38 human immunodeficiency virus (HIV)-associated opportunistic infections or neoplasias. Previous liver disease was documented in 6 patients and 15 patients had elevated liver enzymes values at entry. Twenty six patients were also receiving potentially hepatotoxic therapy including isoniazid and rifampicin (7 patients), sulphonamides (9), zidovudine (11) and benzodiazepines (15).

Supported in part by a grant from Caja de Madrid
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Accepted: 30 January 1991

Mean total lymphocyte count was 892/ μ l (range 150 to 2,360/ μ l) at entry with a mean CD4 + cells count of 170/ μ l (range 0 to 795/ μ l) and a CD4/CD8 ratio of 0.23 (range 0–1).

Treatment protocol

All patients gave written informed consent and the study was approved by the Hospital Ethics Committee.

Endoscopic diagnosis of oesophageal candidiasis was required for inclusion of a patient in the study. Patients were excluded from study if: (i) aged less than 18 years; (ii) pregnant or breast feeding; (iii) had active liver disease with aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) and alkaline phosphatase (AP) values above three times the upper normal limits, and bilirubin higher than 51.3 μ mol/l; (iv) previous hypersensitivity to azole derivatives; (v) concomitant use of other antifungal or liver enzyme inducing drugs (barbiturates, coumarin anticoagulants, oral hypoglycaemics or cyclosporin) or (vi) administration of any other investigational agent.

Patients were treated for 4 weeks, and followed-up for 8 weeks after starting treatment (Figure 1). Fluconazole, 200 mg orally, was given on day one followed by 100 mg daily for 4 weeks. Follow on prophylactic fluconazole, 200 mg once weekly, was given in 22 patients. Clinical assessment was performed daily in patients admitted to the hospital and weekly for outpatients.

Methods

HIV antibody was determined by ELISA¹⁸ and Western Blot¹⁹ methods. Lymphocyte subset determinations were performed by indirect immunofluorescence method.²⁰ Candida serology was performed by haemagglutination (Lab. Roche) and immunoprecipitation (Lab. Pasteur). A Fuji FP3 endoscope with a Fuji Mod K24 16R biopsy punch was used for oesophagoscopy. Three tissue samples were obtained; two of them were processed for pathological examination and the third was cultured for fungi in Sabouraud's dextrose agar medium with and without chloramphenicol. The culture was incubated at 30°C and 37°C, and fungus identification was performed using the Vitek system.²¹ Patients were monitored closely for adverse reactions. Student *t* test applying Yate's correction was used for statistical analysis.

Results

Clinical course and mycological results

Thirty six patients entered the study; 31 completed the treatment period and 24 the follow-up. Six patients died of a non-Candida opportunistic infection during the study, two in the treatment period. Postmortem examination in 4 revealed no evidence of candidiasis. Five patients were lost to follow-up and fluconazole was discontinued in 1 patient after

Figure 1 Study protocol.

the first week because of deteriorating liver function tests. The results are summarized in Table I. All 36 patients had a positive pharyngeal swab for *Candida albicans* and oral thrush was present in 35 patients at entry. Nineteen patients complained of dysphagia. Oesophagoscopy showed typical appearance of candidiasis in 34 patients. *Candida albicans* was grown from biopsies in 30/32 patients and identified histologically in 23/33 oesophageal biopsies.

Clinical remission occurred in all 31 patients who completed the treatment. Signs or symptoms of oropharyngeal or oesophageal candidiasis were absent in all patients within 10 days of starting treatment, in 31 patients (87%) within the first week. Oesophagoscopy was repeated in 27 patients 4 weeks after entry. Cure was confirmed by biopsy in 26 and by culture in 25 patients.

The results of fungal investigation from oropharyngeal swab are shown in Table II. After 2 weeks of therapy, cultures were negative in 19 patients (60%). In the remaining patients, *Candida albicans* was the predominant isolated microorganism. After 4 weeks of treatment, there was still a predominance of *Candida albicans*, although other

species and mixed fungal infections were also present. *Candida albicans* was present in oropharyngeal swab from 10 out of 24 patients who completed the follow-up; there were less than 5 colonies in all cases.

Relapse of oesophageal candidiasis was observed in 2 patients 1 month after completion of fluconazole.

Adverse reactions

Fluconazole therapy was well tolerated by all patients and there was no haematological, renal, neurological, gastrointestinal or cutaneous toxicity. Increases in liver enzyme levels occurred in 17 patients, 13 during the first week and 4 during the second. These abnormalities were considered as mild (if liver enzymes were less than 3 times basal levels) in 15 patients, moderate (between 3 and 5 times) in 1 patient and severe (greater than 5 times basal levels) in another. In this latter patient, whose liver enzyme values were initially normal, fluconazole therapy was discontinued on the 7th day of treatment because of grossly abnormal liver function tests (AP 1640 U/l, GGT 870 U/l). A liver

Table I Clinical, endoscopic and mycological results

		Week		
		0 (n: 36)	4 (n: 31)	8 (n: 24)
Clinical picture:	Thrush	35	0	2
	Dysphagia	19	0	2
Pharyngeal swab:	Positive	36	12	11
	Negative	0	16	13
Oesophagoscopy:	Diagnostic	34	0	2
	Non-specific	2	27	0
Oesophageal biopsy:	Mycosis	23	0	2
	oesophagitis	8	8	0
	Normal	2	18	0
Oesophageal culture:	<i>C. albicans</i>	30	0	2
	Negative	2	25	0

Table II Fungal colonization of oropharynx during and after fluconazole

	Week			
	0 (n: 36)	2 (n: 32)	4 (n: 28)	8 (n: 24)
<i>C. albicans</i>	36	10	7	10
<i>C. glabrata</i>			1	
<i>C. krusei</i>		1	1	
<i>T. pullulans</i>			1	
Mixed		2	2	1
Positive cultures (%)	100	41	43	46

biopsy revealed *Mycobacterium tuberculosis* infection. Thus fluconazole toxicity was unlikely, but cannot be excluded. In the patients whose liver function tests became abnormal no changes in their fluconazole therapeutic regime were required. At follow-up liver function tests tended to return to normal. No correlation was found between liver enzyme abnormalities and the patients' age, sex, weight, previous liver disease, or abnormal liver enzyme values, ethanol intake, concomitant infections or drug treatment. A marked decrease in CD4 + cell count and the simultaneous administration of more than 3 drugs seemed to confer a higher risk of possible fluconazole-induced hepatotoxicity, although this was not statistically significant ($P < 0.1$).

Discussion

The present report is the most extensive one published as yet on fluconazole treatment for oesophageal candidiasis in AIDS patients. In all cases, the endoscopic findings, the histological picture and the mycological culture confirmed the efficacy of fluconazole. Clinical cure was rapid with symptoms of oesophageal involvement resolving within the first week of treatment in 87% of patients and in all patients after 10 days of therapy.

After successful fluconazole therapy asymptomatic fungal colonization of the oropharynx is commonly observed in AIDS patients²² and may cause recurrence of clinical illness. In our series (Table II) oropharyngeal colonization was present in 43% at the end of the treatment period and some of the most azole-resistant *Candida* species were recovered. The early appearance of relapses after completing fluconazole treatment in our initial 2 patients prompted us to devise a prophylactic regime. Oral fluconazole, 200 mg once a week, was given to a further 22 patients and none presented relapses during the follow-up period. If this simple prophylactic regime proves to be effective in more extended series, this will represent an obvious advantage over existing preventive regimens for *Candida* oesophagitis. This regimen would increase patients' compliance and decrease the risk of interaction with drugs used for prophylaxis and

treatment of other opportunistic infections in AIDS patients.

Fluconazole has shown little toxicity in experimental fungal infection models and clinical studies.²³ Increases of liver enzymes²⁴⁻²⁶ have been reported during fluconazole therapy but in only 16 (0.4%) of the first 4057 patients treated with fluconazole was it necessary to discontinue treatment due to significant hepatotoxicity (Pfizer Central Research – Data on file). In our series, an unexpectedly high incidence (47%) of mild (15 patients) to moderate (1 patient) increase in liver enzymes values was observed. Several factors must be taken into account in considering the high incidence of hepatic abnormalities observed in our patients. A higher incidence of adverse drug effects has been reported to occur in AIDS patients.²⁷ Moreover, most of our patients were in advanced stages of the disease as demonstrated by the severe decrease in CD4 lymphocyte count and the high mortality rate (6 out of 36) observed during the time of the study. Other opportunistic infections which might have involved the liver coexisted in 31 patients. Potentially hepatotoxic drugs were administered to 26 patients. Thus, patients in this series constitute a subgroup with a greater tendency to develop hepatic abnormalities than non-AIDS (or even HIV-positive with good general health status) patients with superficial mycoses who are not receiving other potentially hepatotoxic drugs and who usually receive smaller doses of fluconazole.

The rapidity of the clinical response in our treated patients as well as the results from other studies on AIDS patients with oropharyngeal candidiasis treated with lower doses (50 mg/day) of fluconazole for shorter periods,^{28,29} suggests that with treatment for less than 4 weeks it might be possible to achieve cure in most patients.

We conclude that 4 weeks of fluconazole is a very effective treatment for oesophageal candidiasis in AIDS patients. Shorter treatment periods (i.e. 7–10 days) may be eventually efficacious. Further studies are necessary to establish the most effective follow-up prophylactic regimen for oesophageal candidiasis in AIDS. Such studies should also examine the potential for hepatotoxicity and predictive risk factors.

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