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The Treatment of Oropharyngeal Candidiasis in HIV-Infected Patients with Oral Amphotericin B Suspension

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ABSTRACT

Oropharyngeal candidiasis (OPC) is the most frequent opportunistic infection associated with HIV infection. Therapies such as topical clotrimazole and nystatin, as well as oral azoles, which had previously been effective prior to the advent of HIV, are increasingly only partially effective in OPC in HIV infection. The effectiveness of oral amphotericin B suspension for OPC is described in 17 HIV-infected patients whose response to other therapies had been unsatisfactory. Three patients yielded isolates of *Candida albicans* with a minimum inhibitory concentration (MIC) to fluconazole of ≥16 μg/mL. Eleven patients received amphotericin B suspension monotherapy. Of the 17 patients, the symptoms of six resolved entirely, seven patients partially responded, and four failed therapy. These data suggest that amphotericin B suspension may be a useful additional therapy for OPC in HIV-infected patients.

INTRODUCTION

AMPHOTERICIN B, a macrocyclic polyene produced by *Streptomyces nodosus*, is a potent anticandidal agent. Amphotericin B has been used as prophylaxis in neutropenic patients.[1] Intravenous use, in the form of a colloidal suspension in deoxycholate (Fungizone, Squibb), is limited by its toxicity, particularly its effect on renal function, which can be irreversible. Few data have been presented regarding the use of oral preparations of amphotericin B in the treatment of OPC in HIV. Prior to the introduction of fluconazole, topical agents were widely used, often as single agents. Since the introduction and application of topical agents such as oral amphotericin B in HIV disease, nystatin and clotrimazole have been perceived as being effective in the treatment of OPC only during the early stages of HIV infection.[2]

METHODS

Along with interview data the case notes were reviewed of 17 patients prescribed oral formulations of amphotericin B between April 1996 and April 1997. Demographic data, previous episodes of OPC, signs and symptoms of oropharyngeal candidiasis, and CD4 cell counts, at the time, were recorded for patients prescribed amphotericin B suspension. Details

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of previous and concomitant antifungal therapy were confirmed from pharmacy records. The tolerability and efficacy of therapy (graded as resolved, improved, unchanged, or worse) was recorded. Mycologic data, including results of susceptibility tests on fungal isolates from oral swabs, were collected. Samples were incubated on Sabouraud's medium. One representative isolate of each type (based on color and colony morphology) was selected. Isolates were identified by germ-tube examination and standard biochemical tests (bioMerieux). Amphotericin B, in the form of a yellow, sugar-free suspension with a concentration of 100 mg/mL (Squibb), was prescribed in doses of 200 mg four times daily. Patients were instructed to retain 2 mL of the suspension in the mouth, near oral lesions if disease was localized, or to swill the suspension around the mouth and gargle for at least 10 seconds if the disease was generalized.

Susceptibility testing to fluconazole and amphotericin B was performed using methods previously described.[3,4]

RESULTS

Seventeen patients (15 male, two female) who had received oral amphotericin B suspension for the treatment of OPC between April 1996 and June 1997 were identified. The mean age was 39.2 years (range 21 to 64 years). The mean $CD4^+$ cell count was 64.9×10^6 cells/mm^3 (range 2 to 340). Sixteen patients had signs of pseudomembranous candidiasis. The remaining patient had signs consistent with atrophic candidiasis. All patients received daily amphotericin B suspension for a mean duration of 10 days (range 2 to 60). The medication was well tolerated, and no patient failed to complete therapy due to adverse events. In six patients, amphotericin suspension was given concomitantly with other antifungal medication (itraconazole 200 mg capsules, three patients; itraconazole-cyclodextrin solution 200 mg twice daily, two patients; intravenous amphotericin B, one patient). In the remaining 11 patients, amphotericin suspension was the sole therapy. Four patients failed therapy (no improvement was noted or there was a deterioration in symptoms), seven patients achieved partial resolution of symptoms, and for the remaining six patients, symptoms resolved entirely (five of these were patients taking amphotericin suspension alone).

The results of susceptibility testing of isolates to fluconazole and amphotericin are shown (Table 1). Although seven patients reported having had prior episodes of OPC refractory to treatment with fluconazole, only three yielded

TABLE 1. RESULTS OF SUSCEPTIBILITY TESTING

Patient	*Age (yr)*	*Sex*	*CD4 count*	*Previous azole*	*Fluconazole MIC mg/L*	*Amp B MIC mg/L*	*Concomitant therapy*	*Response to amp B suspension*
1	29	M	9	NA	1	0.06	No	Resolved
2	32	M	8	NA	3.12	0.03	No	Partial
3	21	M	219	Fail flu	6.25	0.03	No	Partial
4	43	M	38	NA	0.78	0.03	No	Partial
5	42	M	30	Fail flu	8	0.06	itra sol 200	Partial
6	26	M	80	Fail flu	100	0.12	itra 200 od	Failed
7	31	F	14	NA	25	0.06	itra 200 od	Resolved
8	30	M	19	Fail flu	0.78	<0.03	itra 200 od	Partial
9	31	F	131	Fail itra	1.56	0.03	No	Partial
10	59	M	340	NA	50	0.06	No	Partial
11	30	M	160	Fail flu	32	0.03	Amp B iv	Fai
12	34	M	13	Fail flu	0.25	0.03	itra sol 200	Fail
13	30	M	67	Partial	8	0.03	No	Fail
14	51	M	60	Partial	—	—	No	Resolved
15	51	M	78	Resolved	8	0.12	No	Resolved
16	42	M	2	Resolved	6.25	0.03	No	Resolved
17	30	M	5	Failed flu	16	0.06	No	Partial

Amp, amphotericin; NA, not applicable; itra sol, itraconazole-cyclodextrin solution; od, ; iv, intravenously.

isolates of *Candida albicans* with reduced susceptibility to fluconazole (MIC $\geq$ 16 μg/mL).

DISCUSSION

These data suggest that amphotericin suspension is useful both as a combination and a single therapy for OPC in HIV-infected patients. The wide range of durations of treatment was explained by poor compliance in one patient and the use of the suspension as prophylaxis in another.

Conventionally, prior to the advent of HIV infection, a number of topical agents such as nystatin or amphotericin B oral suspension have been used to treat OPC with reasonable efficacy. Clotrimazole troches have been used successfully for OPC in HIV-infected patients in the United States.[5,6] Brookmeyer et al.[7] found that amphotericin B oral suspension 2.4 g/day (following intravenous amphotericin B 0.4 mg/kg/day and flucytosine 150 mg/kg for 8 days) was equal to fluconazole 50 mg/day (following fluconazole 400 mg/day for 8 days) as secondary prophylaxis for *Candida* esophagitis. More recently, oral suspensions of azoles with the advantages of combined topical and systemic effect have been used.[8,9]

The occasional reports of the use of oral preparations of amphotericin B such as lozenges[10] and solution[11] to treat OPC in non–HIV-infected patients have usually demonstrated good efficacy. Ten-milligram amphotericin B lozenges, which can be slowly dissolved in the mouth, are also available (Squibb). Lozenges had been prescribed in two of our patients, with tolerability and efficacy comparable with amphotericin B suspension. The advantage of the lozenge is that it may be retained in the mouth for longer periods of time than the suspension.

The only previous report of the use of amphotericin B suspension to treat fluconazole refractory OPC in HIV described the treatment of two patients; improvement was seen in both cases.[12]

Our data are consistent with these findings and suggest that oral amphotericin B suspension is a useful supplementary preparation in the treatment of OPC in HIV-infected individuals.

REFERENCES

1. Perfect JR, Klotman ME, Gilbert CC, et al. Prophylactic intravenous amphotericin B in neutropenic autologous bone marrow transplant patients. J Infect Dis 1992;165:891–897.
2. BSAC Working Party. Review articles. Antifungal chemotherapy in patients with acquired immunodeficiency syndrome. Lancet 1992;340:648–651.
3. Law D, Moore CB, Wardle HM, Ganguli LA, Keaney MGL, Denning DW. High prevalence of antifungal resistance in *Candida* spp. from patients with AIDS. J Antimicrob Chemother 1994;34:659–668.
4. Law D, Moore CB, Denning DW. Amphotericin B resistance testing of *Candida* spp.: A comparison of methods. J Antimicrob Chemother 1997;40:109–112.
5. Pons V, Greenspan D, Debruin M, and the Multicenter Group. Therapy for oropharyngeal candidiasis in HIV-infected patients: A randomized, prospective multicenter study of oral fluconazole versus clotrimazole troches. J AIDS 1993;6:1311–1316.
6. Powderley WG, Finkelstein DM, Feinberg J, et al., for the NIAID AIDS Clinical Trials group. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced HIV infection. N Engl J Med 1995;332: 700–705.
7. Brookmeyer NH, Hantschke D, Olbricht T, Hengge UA, Goos M. Comparative study of the therapy of *Candida* oesphagitis in HIV-1 infected patients with fluconazole or amphotericin B and flucytosine. Mycoses 1991;34:83–86.
8. Cartledge JD, Midgley J, Youle M, Gazzard BG. Itraconazole cyclodextrin solution—effective treatment for HIV-related candidosis unresponsive to other azole therapy. J Antimicrob Chemother 1994;33: 1071–1073.
9. Laine L, Rabeneck L. Prospective study of fluconazole suspension for the treatment of oesophageal candidiasis in patients with AIDS. Aliment Pharmacol Ther 1995;9:553–556.
10. Ewing AE. Amphotericin B lozenges in the treatment of oral thrush. Practitioner 1967:199:62–67.
11. Brandell R, Chase SL, Cohn JR. Treatment of oral candidiasis with amphotericin B solution. Clin Pharmacol 1988;7:70–72.
12. Dewsnup DH, Stevens DA. Efficacy of oral amphotericin B in AIDS patients with thrush clinically resistant to fluconazole. J Med Vet Mycol 1994;32: 389–393.

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