Clinical and Mycological Responses to Fluconazole and Fluconazole MIC in Oropharyngeal Candidiasis in HIV-Infected Patients

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Abstract

Introduction : OPC is a common opportunistic infection in HIV-infected patients. Although some patients are asymptomatic, progression of the disease may occur leading to esophageal candidiasis. Fluconazole resistant candidiasis has been reported in several international studies.

Objectives : This study aimed to test the MICs (minimal inhibitory concentrations) to fluconazole of *Candida* species isolated from mouthwash specimens of 54 HIV positive patients with oral candidiasis. Clinical and mycological responses to fluconazole were also assessed in 16 patients.

Material and Method : This was a prospective study. Mouthwash specimens were cultured on sabouraud dextrose agar twice. *Candida* species identification was performed and MICs for fluconazole were obtained using NCCLS guidelines. Clinical and mycological responses were assessed on day 14 and 42 in 16 patients who received a 14-day course of fluconazole.

Results : 48/54 patients (88.89%) were found to carry pure *C. albicans*. The other 6 patients (11.11%) had mixed *Candida* species on cultures. Among these 6 patients, 5 patients had mixed *C. albicans* and *C. glabrata*, and 1 patient had *C. albicans* and *C. krusei*. Fluconazole MICs of *C. albicans*, *C. glabrata*, and *C. krusei* ranged from 0.125-32 (median=0.250), 4-64 (median=2), and 8 g/L respectively. This study showed that the MICs to fluconazole of oropharyngeal *Candida* was a good predictor of the therapeutic responses.

Key word : Oropharyngeal Candidiasis, HIV Infection

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Oropharyngeal candidiasis (OPC), one of the most common conditions seen in HIV-infected patients[1-3], occurring in up to 20 per cent of otherwise asymptomatic HIV infections and up to 70 per cent of patients with advanced HIV disease.

The most common *Candida* species that cause OPC in HIV-infected patients is *C. albicans*[4,5]. Isolation of *C. albicans* with other species has been reported[6]. A small number of patients have had infection caused solely by non-albicans species, such as *C. krusei*, C. *glabrata, C. tropicalis, C. parapsilosis*[7,8].

OPC causes burning sensation or soreness in the mouth especially when patient eats hot and spicy food, and also partial loss of taste sensation or taste alteration[2]. In certain patients, esophageal candidiasis occurs by extension of OPC[5]. It is necessary to provide an appropriate treatment for OPC to maintain good quality of life in these patients.

The recommended treatment for first episode OPC is a trial of topical antifungal such as clotrimazole troche or nystatin suspension. In patients with CD_4+ T cell counts of less than 50 cell/mm^3, or with a high viral load a systemic antifungal is preferred, and fluconazole or itraconazole suspension provides the best efficacy[9,10]. Ketoconazole and itraconazole capsules are less effective than fluconazole because of variable absorption.

There are several reports of emerging azole resistance *Candida*[2,8,11-17]. In HIV-infected patients, this is mostly associated with low CD_4+ T cell count (<50). Increased use of fluconazole especially as maintenance/suppression therapy has the potential to select for drug resistance[9]. Some strains of *C. albicans* resist all existing azoles[2]. There are also reports of fluconazole resistance among *C. krusei*, *C. glabrata*, *C. kefur*[16].

The *in vitro* susceptibility of *Candida* to antifungal drugs has been reported in several international studies. The authors believe this study is the first fluconazole MICs of *Candida* reported in Thailand.

This study was a prospective study on *Candida* species identification and fluconazole MICs of 54 HIV-infected patients suffering from oropharyngeal candidiasis who attended Bamrasnaradura Hospital between September 1998 - September 1999 (Generic fluconazole was just marketed in late 1999). The authors expected that this study would provide *in vitro* susceptibility to fluconazole and also the prevalence of *Candida* species that cause OPC in HIV-infected patients in Thailand. A further study of 16 patients who received fluconazole treatment was conducted to compare the clinical responses and *in vitro* fluconazole sensitivity of *Candida* isolates obtained before and after treatment.

MATERIAL AND METHOD

Study design : prospective study

Study subjects : 54 HIV-infected patients with a diagnosis of oropharyngeal candidiasis (pseudomembranous type) were studied. These patients had positive budding yeasts and pseudo-hyphae on KOH preparation. None were thought to have esophageal candidiasis as they had no symptoms of odynophagia, dysphagia, or retrosternal pain. Symptoms and oropharyngeal examination were performed and recorded including site, characteristics of oral plaques and other associated oral lesion. The extent of the plaques was defined as minimal or diffuse: minimal plaques were defined as 1-5 discrete plaques and/or single confluent plaques 3 centimeter or less in the longest length; diffuse plaques were plaques that were more than minimal extent. Past medical history, Karnofsky score[18] evaluation and blood test for CBC and CD_4+ T cell count were done in every patients at the enrollment. All patients signed informed consent prior to enrollment. None them received antiretroviral agents.

Fluconazole treatment : 16 patients received fluconazole in the dose of 100 mg twice a day on the first day and 100 mg once a day on day 2-14. Clinical response evaluation performed on day 14 and day 42.

Clinical responses were defined as followed.

Cure : absence of pseudomembranous plaques and no, or minimal symptoms

Improvement : partial resolution of pre-treatment signs and symptoms

Clinical failure (for day 14) : no change or worsening in pre-treatment signs and symptoms

Clinical relapse (for day 42) : return of oropharyngeal pseudomembranous plaques now requiring further antifungal therapy

Study sites : Clinical study site was at Bamrasnaradura Hospital, Nonthaburi, Thailand. KOH

preparation for mycological identification was performed at Microbiology laboratory, Bamrasnaradura Hospital. Fungal culture and fluconazole MIC tests were done at the Wellcome unit, Faculty of Tropical Medicine, Mahidol University.

Specimen collection : Each patient was asked to have a saline mouthwash specimen collected in a sterile container on day of enrollment, day 14, and day 42 (only 16 patients) prior to scraping of white plaques for KOH preparation. Only patients with a KOH positive smear had their mouthwash specimens cultured.

Mycological culture : Saline mouth wash specimens were plated on Sabouraud dextrose agar in duplicated.

Fluconazole MICs were determined by broth microdilution technique following guidelines described in National Committee for Clinical Standards (NCCLS)[18]. MICs were performed on every specimen that grew *Candida.*

Mycological responses were defined as colony forming unit (CFU) eradication or persistence.

Mycological eradication : ≤20 CFU/ml *Candida* species

Mycological persistence : >20 CFU/ml *Candida* species

RESULTS

Patient characteristics

Of the 54 patients, 37 (68.52%) were male. The mean (SD) age of patients was 32.65 (±7.95) years.

46 patients had a CD_4+ T cell count below 200.39/46 patients (84.78%) had CD_4+ T cell count below 50. Only 3 patients had CD_4+ T cell count above 200 (223, 286, and 476 respectively). The other 5 patients had no CD_4+ T cell count performed. Mean (SD) CD_4+ T cell count was 46.33 (±86.39) cell/mm^3.

53 patients had a Karnofsky performance score of 80 or above. (Score 80=normal activity with effort, some sign and symptom of disease). Only 1 patient had a Karnofsky performance score of 60 (requires occasional assistance but is able to care for most of his needs).

53 patients were naive to systemic azole therapy. Only 1 patient had previous systemic azole treatment for OPC but discontinued for 3 months prior to enrollment. None of these patients had used topical mucosal antifungal agents at least 48 hours prior to enrollment.

Clinical presentations of OPC

There were 50 patients with diffuse plaques. The other 4 patients had minimal plaques. 8 patients had OPC for the first time, 11 patients had five or fewer episodes of OPC during the previous year, 3 patients had more than five episodes within the past year. 32 patients had no data on previous episode of OPC.

Mycological identification

All fungal cultures were positive for *Candida* species; C. *albicans* (54/54 patients, 100%), *C. glabrata* (5/54 patients, 9.26%), and *C. krusei* (1/54 patients, 1.85%). 48 patients were positive solely for *C. albicans.* The other 6 patients were positive for 2 species of *Candida* (reported as predominant and co-isolated species respectively); *C. albicans* and *C. krusei* 1 patient, *C. albicans* and *C. glabrata* 3 patients, and *C. glabrata* and *C. albicans* 2 patients.

Fluconazole susceptibility *in vitro* (MIC) at baseline : MICs were in the range of 0.125-32 (median=0.250) g/L for *C. albicans*, 4-64 g/L for *C. glabrata* and 8.00 g/L for *C. krusei.* (Table 1)

Fluconazole susceptibility *in vivo* and in vitro of 16 patients

In vitro susceptibility (baseline)

The16 patients had baseline fluconazole MICs of *C. albicans* at a range of 0.125-32 (median=0.50) g/L. MICs of *C. glabrata* were 4 and 64 g/L in 2 patients.

In vivo susceptibility (day 14)

- Clinical assessment

Among 16 patients treated with fluconazole, 14 were cured and 2 had clinical improvement (minimal plaque).

- Mycological assessment

14 patients had mycological eradication (<20 CFU/ml). 2 patients had mycological persistence (>20 CFU/ml). (Case 6, 7, Table 2) These 2 patients had mixed growth of *C. albicans* and *C. glabrata.* Their fluconazole MICs for *C. albicans* were at 4 and 1 gram/L respectively. Fluconazole MICs for *C. glabrata* on these 2 patients were 64 and 4 respectively. (Table 1)

Table 1. Fluconazole MIC at baseline.

CD_4+ T cell count (cell/mm^3)	*Candida* species at baseline	Number of patients	Fluconazole MIC (g/ml) Min-max (median)
0-50	*C. albicans*	39	0.125-32 (0.250)
	C. albicans +	2	1-4
	C. glabrata		4-64
	C. albicans +	1	0.5
	C. krusei		8.00
50-200	*C. albicans*	5	0.125-0.25 (0.125)
	C. albicans +	2	Not done
	C. glabrata		0.125
>200	*C. albicans*	2	0.5-1
	C. albicans +	1	0.5
	C. glabrata		2.0

In vivo and in vitro correlation

14 patients with clinical cure had MICs of *C. albicans*, and *C. glabrata* at the ranges of 0.125-32 and 4-64 g/L, respectively. 2 patients with clinical improvement had MICs of *C. albicans* at 0.250 and 1 g/L.

Follow-up 4-weeks after discontinuation of fluconazole :

Clinical evaluation on day 42 revealed 9 patients who remained cured and 7 patients who presented with clinical relapse. Mycological evaluation revealed 11 patients with mycological relapse, 2 patients who had mycological persistence with higher colony counts, and 3 patients who still had mycological eradication. One mycological relapse patient grew *C. albicans* with MIC>64g/L.

DISCUSSION

These patients with HIV infection had CD_4+ T cell counts between 0 to 476. Only 3 patients had a CD_4+ T cell count above 200, which is consistent with knowledge of increasing risk for OPC in HIV-infected patients as the CD_4+ T cell count falls below 200.

This study revealed all patients had cultures positive for *C. albicans*. Only 5 patients had mixed cultures of *C. albicans* with other species. It is uncertain whether the co-isolated species were pathogenic. Firstly, healthy people and HIV-infected patients appear to have *Candida* colonization(4). Secondly, non-albicans strains of *Candida*, are not clinically relevant in episodes of mixed OPC in HIV 1 infected patients(6). The pathogenicity of *Candida* is mainly dependent on its virulence and the host immune status. The important virulence factor is an ability to adhere to host mucosa and production of a hydrolytic enzyme called secretory aspartyl proteinase (SAP). This enzyme helps *Candida* penetrates host tissue(19). The authors did not test the *Candida* for SAP.

In vitro susceptibility to antifungal agents (MIC) may be helpful when treatment is not successful. Fluconazole MICs of *C. albicans* within the range 0.125-8 g/L are considered susceptible, while an MIC of ≥64 g/L is considered resistant. MICs of 16-32g/L are considered intermediately susceptible in a dose dependent fashion if fluconazole is given ≥100 mg/day(17,20-22) The authors did not find any primary fluconazole resistance *C. albicans* isolated from the baseline specimens. All initial isolates had MICs<64g/L. One specimen collected on day 42 grew *C. albicans* with MIC above 64g/L. This finding raised concern about the selection of fluconazole resistance *C. albicans* in Thailand. The study also confirmed that MIC for *C. glabrata* is usually higher than that of *C. albicans* (Table 1)(8).

MIC of *Candida* is not the only predictive factor for treatment response. Treatment success depends much more on host factors such as CD_4+ T cell count, absolute neutrophil count, serum level of azole, and HAART use. Cell mediated immune responses and neutrophils are crucial in combating fungal infection. Patients with low CD_4+ T cell count tend to have a higher rate of mucosal Candidal colonization(4,14) leading to an increase prevalence of OPC. Refractory OPC is frequently observed in

Table 2. Clinical and mycological characters at baseline and after treatment.

case no.	KS score	Clinical at baseline	symptoms at baseline	Absolute neutrophil count	CD4 count	Fungal culture at baseline			Clinical response at day 14	Mycological response at day 14			Clinical at day 42	Mycological response at day 14		
						species	Colony count (cfu/ml)	Fluconazole MIC (g/L)		species	Colony count (cfu/ml)	Fluconazole MIC (g/L)		species	Colony count (cfu/ml)	Fluconazole MIC (g/L)
1	90	diffuse	none	4608	0	C albicans	7.3×10^2	0.125	cure	no growth	-	-	relapse	C albicans	1.09×10^3	>64
2	90	diffuse	none	2816	4	C albicans	8.0×10^2	32	cure	C glabrata	1.0×10^1	8	relapse	C albicans	5.5×10^2	0.5
3	90	minimal	mild burning	1476	6	C albicans	4.9×10^2	2	cure	no growth	-		relapse	C albicans	$>5.00 \times 10^2$	0.125
4	90	diffuse	none	1196	78	C albicans	3.8×10^2	0.125	cure	no growth	-	-	cure	no growth	-	-
5	60	diffuse	mild soreness	6035	5	C albicans	$>5.0 \times 10^2$	0.125	cure	no growth	-	-	relapse	C albicans	$>5.00 \times 10^2$	0.125
6	80	diffuse	none	4388	5	C albicans	$>5.0 \times 10^3$	4	cure	C albicans	$>5.00 \times 10^2$	0.25	relapse	C albicans	3.52×10^3	0.125
						C glabrata	5.0×10^3	64		C glabrata	$>5.00 \times 10^2$	64		C glabrata	3.52×10^3	64
7	90	minimal	none	5801	15	C albicans	9.9×10^2	1	cure	C albicans	8×10^1	2	relapse	C albicans	9.74×10^3	2
						C glabrata	9.9×10^2	4								
8	90	diffuse	Mild soreness & burning	2860	33	C albicans	3.08×10^3	0.25	improve	no growth	-	-	cure	C albicans	3.2×10^2	2
9	90	diffuse	mild soreness	2854	5	C albicans	1.73×10^3	0.25	cure	no growth	-	-	cure	no growth	-	-
10	80	diffuse	mild soreness	2242	3	C albicans	3.96×10^3	0.5	cure	no growth	-	-	relapse	C albicans	5×10^2	0.5
11	90	diffuse	none	2604	223	C albicans	1.31×10^3	0.5	improve	no growth	-	-	cure	no growth	-	-
12	100	minimal	none	1924	39	C albicans	1.30×10^2	1	cure	no growth	-	-	cure	C albicans	1.4×10^2	1
														C glabrata	1.0×10^1	.0.5
13	100	diffuse	Mild soreness & burning	3469	476	C albicans	2.13×10^3	1	cure	no growth	-	-	cure	C albicans	5.0×10^2	0.5
14	80	diffuse	Mod. Soreness	378	40	C albicans	2.24×10^3	0.125	cure	C albicans	1.0×10^1	0.125	cure	C albicans	5.0×10^3	0.125
15	80	diffuse	none	3443	0	C albicans	2.66×10^3	0.125	cure	no growth	-	-	cure	C albicans	2.84×10^3	0.125
16	90	diffuse	taste alteration	3658	20	C albicans	6.00×10^2	0.5	cure	no growth	-	-	cure	C albicans	5.0×10^1	0.5

patients with low CD_4+ T cell counts[20] or neutropenia. In addition to restoration of host immunity, protease inhibitors also have a direct effect against *Candida* by inhibiting SAP[19], a virulence factor of the organisms. Therefore, HIV-infected patients on HAART have a lower prevalence of OPC than the ones without HAART. In refractory OPC, HAART is considered the treatment of choice. Serum azole level as a surrogate for the level of azole in target tissue, depends on dose, absorption, compliance, and drug interactions.

Although the presented patients were not on HAART and had low CD_4+ T cell counts, fluconazole treatment for OPC was satisfactory. All 16 patients were considered cured on day 14. The two patients with minimal plaque on day 14 had no growth on the cultured specimens. In addition they had clinical cure on day 42. Factors contributing to treatment success were good drug absorption, full compliance to treatment, and no con-committant use of medication that interacted with fluconazole through cytochrome p 450 enzymes, normal white count, no previous systemic azole treatment, and MIC within the susceptible range. *In vitro* susceptibility test and clinical responses to fluconazole in this study showed good correlation. The relationship between *in vitro* susceptibility and clinical response is controversial[5]. In addition to host factors, antifungal susceptibility to the treatment must influence the outcome of treatment. It is well accepted that guidelines for MIC breakpoint determination are methodology specific. When a method is used, its guidelines must be followed.

The authors observed growth of *Candida* after fluconazole therapy in four patients (cases 2, 6, 7, 14). *C. albicans* were the only species isolated at baseline in two patients while the other two patients were positive for both *C. albicans* and *C. glabrata*. Specimens on day 14 and 42 from 3 patients were positive for their initial Candida strains. 1 case (case 2) had minimal growth of *C. glabrata* on day 14 but regrowth of *C. albicans* on day 42. These data support the previous findings that persistence of *Candida* may occur even after systemic azole therapy[6] or during long-term suppressive therapy[21]. In one study 74 per cent of patients had persistent *Candida* after systemic azole therapy[5]. It has been shown that persistent *Candida* occurs especially when non-albicans specie were co-isolated[6]. The presented data is too limited to reach the same conclusion. Case 2 with growth of *C. glabrata* isolated on day 14 may suggest non pathogenicity of *C. glabrata* and then overgrowth of pathogenic *C. albicans* on day 42 after the effect of fluconazole worn out.

In summary, *C. albicans* was the most common pathogenic specie for OPC in Thai HIV-infected patients. The present study showed that fluconazole was effective against OPC, at least during 1998-1999. Most *Candida* isolates were fluconazole sensitive with MICs below 32g/L.

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ผลการรักษาภาวะติดเชื้อรา*แคนดิดา* ในช่องปากผู้ป่วยติดเชื้อเอ็ชไอวี โดยใช้ยาฟลูโคนาโซล และการศึกษาค่าเอ็มไอซี ของยาฟลูโคนาโซลต่อเชื้อแคนดิดา

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บทนำ : ภาวะติดเชื้อรา*แคนดิดา*ในช่องปากเป็นโรคติดเชื้อฉวยโอกาสที่พบบ่อยในผู้ป่วยติดเชื้อไวรัสเอ็ชไอวี แม้ว่าโรคนี้จะไม่ก่อให้เกิดอาการเจ็บปวดใด ๆ ในผู้ป่วยบางราย แต่บางครั้งโรคนี้อาจแพร่เชื้อเข้าสู่หลอดอาหารจนเกิดเป็นโรคติด-เชื้อรา*แคนดิดา*ในหลอดอาหารได้หากไม่ได้รักษาแต่เนิ่น ๆ นอกจากนี้ยังมีรายงานจากต่างประเทศพบเชื้อรา*แคนดิดา*ดื้อยาฟลูโค-นาโซล

วัตถุประสงค์ : การศึกษาครั้งนี้เพื่อทดสอบค่าเอ็มไอซี ของยาฟลูโคนาโซลต่อเชื้อรา*แคนดิดา*ซึ่งแยกเชื้อเหล่านี้ได้จากช่องปากของผู้ป่วยติดเชื้อไวรัสเอ็ชไอวี จำนวน 54 ราย และได้ศึกษาผลการรักษาโรคติดเชื้อรา*แคนดิดา*ในช่องปากของผู้ป่วยจำนวน 16 ราย

วิธีวิจัย : เป็นการศึกษาโดยเพาะเชื้อราบนจานเลี้ยงเชื้อ (sabouraud dextrose agar) ซ้ำ 2 ครั้งต่อ 1 ตัวอย่างส่งตรวจ จากนั้นจะทดสอบแยกชนิดของเชื้อรา*แคนดิดา*และตรวจค่าเอ็มไอซีของ ยาฟลูโคนาโซลต่อเชื้อรา*แคนดิดา*โดยวิธีที่กำหนดโดย NCCLS สำหรับผู้ป่วย 16 ราย ที่ได้รับการรักษาด้วยยาฟลูโคนาโซลนาน 14 วันจะได้รับการตรวจเยื่อบุช่องปากและเพาะเชื้อราในวันแรกรับ วันที่ 14 และวันที่ 42 ด้วย

ผลการวิจัย : พบผู้ป่วย 48 ราย (88.89%) มีผลเพาะเชื้อราเป็นเชื้อ*แคนดิดา*ชนิดอัลบิแคน (*C. albicans*) ส่วนผู้ป่วยที่เหลืออีก 6 ราย (11.11%) มีผลเพาะเชื้อราเป็นชนิดอัลบิแคน (*C. albicans*) ร่วมกับชนิดอื่น ๆ (other species) โดย 5 ราย เป็นเชื้อ *C. albicans* ร่วมกับ *C. glabrata* และ 1 รายเป็นเชื้อ *C. albicans* ร่วมกับ *C. krusei* ค่าเอ็มไอซี ของยาฟลูโคนาโซลต่อเชื้อรา*แคนดิดา*ชนิดอัลบิแคน (*C. albicans*) ชนิดกลาบราตา (*C. glabrata*) ชนิดครูไซ (*C. krusei*) เท่ากับ 0.125–32, 4–64, และ 8 กรัมต่อลิตร ตามลำดับ ผลการศึกษานี้พบว่าค่าเอ็มไอซี สามารถช่วยทำนายผลการรักษาได้

คำสำคัญ : โรคติดเชื้อรา*แคนดิดา*ในช่องปาก, โรคติดเชื้อไวรัสเอ็ช ไอ วี

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