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Activities of fluconazole in combination with terbinafine against non-*albicans* *Candida* species isolated from the patients with recurrent vulvovaginal candidiasis in comparison with ciclopirox olamine

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Original Article

Abstract

Introduction: Recent epidemiological studies show that episodes due to non-*albicans* species of *Candida* (*C*) such as *Candida tropicalis*, *C. glabrata, C, krusei, C. parapsilosis* appear to be increasing in recurrent vulvovaginal candidiasis (RVVC). Increased use of the current antifungal drugs cause drug resistance among *Candida* species. In order to gain suitable antifungal therapy for this disease, we investigated the activity of synergism of fluconazole and terbinafine comparing with cyclopirox olamine, against non-*albicans* *Candida* species isolated from recurrent candidal vaginitis.

Methods: This study was carried out on 44 strains of non-*albicans* *Candida* species that were isolated from patients with recurrent vulvovaginal candidiasis. Antifungal susceptibility testing of fluconazole and terbinafine alone and combination of these drugs on non- *albicans* species were determined by Clinical and Laboratory Standard Institute (CLSI) microdilution method (document M27-A2).

Results: The mean of MICs of fluconazole, terbinafine and cyclopirox olamine was 93.8, 104.7 and 18 μg/ml, respectively, after 48 hours of incubation. FICs of fluconazole in combination with terbinafine were shown ineffective and additive in 42 isolates (95.5%), synergism and relative-synergism were obtained in two isolates (4.5%). Additionally, the mean of cyclopirox olamine MFCs (32 μg/ml) had the most effective and the mean of terbinafine MFCs (177 μg/ml) showed the lowest effectiveness on non-*albicans* isolates (P>0.05).

Conclusion: Most of isolates were resistant against fluconazole and terbinafine, and combination of these drugs did not affect clinical isolates. But cyclopirox olamine with the lowest mean of MICs and MFCs showed the highest activity in non-*albicans* isolates.

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Introduction:

Vulvovaginal Candidiasis (VVC) is a disease caused by abnormal growth of yeasts in the female genital tract (1,2). It is one of the most common problems of women during their sexually active years (3). The prevalence of VVC has increased during recent years (1). Almost 75% of women experience at least an episode of this disease during lifetime (4). However, about 5-10% of the patients complain about complicated candidiasis which is featured severe and recurrent. This kind of VVC is called Recurrent Vulvovaginal Candidiasis (RRVC) where patients are infected at least 4 episodes in a year (5,6). This disease is characterized by yellowish discharge with milky color and grey pseudo membrane on mucosa of vagina. Moreover, it may be associated with eczematous reaction with mild to severe erythema, pustule and ulcer (7, 8). Although Candida albicans accounts for 80-90% of vaginal candidiasis, most of researches have reported increase of non-albicans species Candida particularly glabrata which is probably due to widely use of antibiotics for a long time and also short time use of azoles and antifungal drugs (28, 29). C. glabrata shortly acquire resistance against azoles (30). Nowadays, prophylactic fluconazole for high risk patients has resulted in the reduction of albicans-induced infections and increased incidence of non-albicans induced infections such as C. glabrata and C. krusei (30). Ten to thirty-three percent of RRVC are caused by non-albicans species like C. glabrata, C. tropicalis, C. krusei and C. parapsilosis (31). This type of the disease infects about 6 million women per annum (32).

Different treatments have been introduced for candida-induced vaginitis during 2 last decades. The most common options are azoles which are prescribed either topically in various concentrations and formula or systematically (33). Since susceptibility of various species of candida against antifungal drugs including azoles vary, non-albicans candidiasis requires more investigations (34,35).

Hence, given the importance of the subject, the present study was designed to study the susceptibility of various species of non-albicans candida isolated from the patients with RRVC to fluconazole and terbinafine individually and in combination with each other and also to evaluate the results in comparison with the effects of ciclopirox olamine – as a new synthetic drug with exclusive properties including broad spectrum antibacterial and antifungal properties as well as anti-inflammatory properties for treatment of cutaneous infections (17).

Methods:

The entire procedure of this experimental study was evaluated based on the agenda of the Clinical and Laboratory Standard Institute for yeasts (CLSI M27-A2) (11). This study included 44 strains of non-*albicans Candida* species that were isolated from patients with recurrent vulvovaginal candidiasis. For standardization and processing of the stages of the procedure, a standard strain of C krusei (ATCC 6258) was used at the initial stages.

Medicines used in the study included fluconazole (070209/90) donated by Tehran Daru Company, terbinafine supplied by Behvazan Company, and ciclopirox olamine by USP ROCKVILLE (American).

Appropriate basic concentrations of fluconazole, terbinafine and ciclopirox olamine were prepared using Dimethyl sulfoxide (DMSO) supplied by Merck (Germany) as a solvent

Culture Media Preparation

A) Liquid Culture Media Preparation: to prepare liquid culture media (Subaru broth), the instructions of the manufacturing was followed (12, 13)

B) Solid Culture Media Preparation: to prepare solid culture media, the instruction of the manufacturing company was followed (10-12).

Drug sensitivity Testing

Fungal specimen culture: the identified species of candida were cultured on Subaru Dextrose Agar at 30°C for 24 hours to produce fungal colonies. Then the fungal colonies were used for yeast suspension preparation.

Yeast suspension preparation: to prepare a candida yeast suspension with concentration of 1 X 10^3 cells in 1 ml, a colony grown on the Subaru Dextrose Agar was added to 1 ml of sterile physiologic serum. An appropriate cell suspension was obtained through a spectrophotometer at 530 nm wavelength adjusted by 90% translucency

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which is equal to 1 X 10^6 cells in 1 milliliter. Then the solution was diluted 1000 times (13,14).

Preparation of pharmaceutical solution: initially, 0.0128 gram of the medicines was weighted (fluconazole, terbinafine and ciclopirox olamine) using a sensitive balance scale. Then each item was dissolved in 10 ml of DMSO. It was kept at the laboratory temperature for 30 minutes to get it completely dissolved following which a 1280 μg/ml solution was obtained. Then to prepare a solution for measuring MIC, 1 ml of the stock solution of the drug under the study was diluted by 9 ml of sterile Subaru culture media (final concentration: 128 μg/ml). To prepare consecutive concentrations from 128 to 1 μg/ml, they were diluted by Subaru (13,15).

The procedure of the test: at the beginning, 50 μl of the consecutive concentrations of fluconazole was added to the wells at 8 horizontal rows of a sterilized gated 96-well micro plate with U-bottom-shape. Then an additional 50 μl of terbinafine was added to the wells at 8 vertical rows. Hence, the concentration of the drug in the first horizontal and vertical row was 128 and in the 8th row 1 μg/ml. Then 100μl of the above medicines and ciclopirox olamine – which had been prepared in consecutive concentrations – were individually added to 9 other wells to assess the MIC of the medicines. Finally, 100 μl of the fungal suspension was added to all the wells (except one well to which only Subaru broth was added as negative control).And for positive control, 100 μl of fungal suspension was added to another well in which there was Subaru broth. The lid of the micro plate was closed. The plate was shaken for 3-5 minutes. It was then incubated for 48 hours and checked after 48 hours. This process was repeated 3 times for each case. The average was considered as MIC. The FIC obtained from the combination of the medicines was calculated as per the formula and the results were interpreted in the following way: synergistic if FIC≤0.5, relative synergistic if 0.5<FIC<1, additive effect if FIC=1, ineffective if 1<FIC<4 and antagonism if FIC>4 (11,13,14)

$$FIC = \frac{\text{MIC of the 2nd combined medicine}}{\text{MIC of the 2nd medication alone}} + \frac{\text{MIC of the 1st combined medicine}}{\text{MIC of the 1st medication alone}}$$

The analysis of the findings of the study was performed by SPSS software (Version 16). The statistical tests used to determine the relationships between variables including Chi-square, Fisher's exact, logistic regression by GEE parametric method and paired tukey's test. P-value less than 0.05 was considered as significant.

Results:

The mean of MICs of fluconazole, terbinafine and ciclopirox olamine was 93.8, 104.7 and 18 μg/ml, respectively, after 48 hours of incubation. FIC of the medicines was additive and ineffective in 42 cases (95.5%) while it was synergistic and relatively synergistic in 2 cases (4.5%). Moreover, studying the fungicidal effects of the medicines revealed that the mean of MFC of ciclopirox olamine, terbinafine and fluconazole was 32, 177 and 154 μg/ml respectively.

The results showed that the range of MIC for fluconazole on 29 isolates of C. glabrata – which were under study–was MIC=32-128 μg/ml (Table 1), MIC 50= 128 μg/ml and MIC90=128 μg/ml.

Table 1. Range of the MIC of the medicines based on μg/ml

Species	Number of Species	MIC Fluconazole	MIC Terbinafine	MIC Ciclopirox Olamine
glabrata	29	32-128	64-128	8-128
kefyr	10	32-128	64-128	8-64
krusei	3	128	128	8
parapsilosis	2	64-128	64	8-32

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Table 2. Frequency of FIC based on the various species after 48 hours

Species	Synergistic and relative synergistic effect	Additive effect and ineffectiveness	Total
glabrata	2 (6.9%)	27 (93.1%)	29 (100%)
Others	0%	15 (100%)	15 (100%)
Total	2 (4.5%)	42 (95.5%)	44 (100%)

According to NCCLS, MIC≤8 μg/ml considered sensitive, MIC=16-32 μg/ml dose-dependent and MIC≥64 μg/ml was resistant. Hence, out of 29 strains of C. grabrata, 25 cases (86.2%) were resistant to fluconazole and 4 cases (13.8%) were dose-dependent.

Studying dual combined medicines after 48 hours through paired tukey's test showed that there was a significant difference between "ciclopirox olamine" and "terbinafine and fluconazole" while there was no significant difference between terbinafine and fluconazole. In other words, the mean of MIC for both terbinafine and fluconazole is equal and the mean of MIC for ciclopirox has the minimum value.

Studying the FIC of the combined medicines after 24 hours on the candida strains isolated from RRVC revealed that 1 case (2.3%) had synergistic effect, 5 cases (11.4%) relative synergistic effect, 2 cases (4.5%) additive effect and 36 cases (81.8%) were ineffective. After 48 hours the rates changed to 2 cases (4.5%) with relative synergism, 3 cases (6.8%) with additive effect and 39 cases (88.6%) without effect (Figure 1).

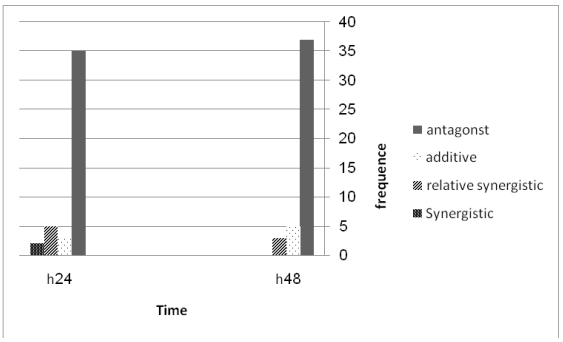

Figure 1. Frequency of synergistic, relative synergistic and additive effects

Conclusion:

Epidemiologic studies show that RRVC infections are mainly caused by the species resistant to antifungal medicines (9). Therefore, tendency towards finding new antifungal combinations increased.

Mahmodirad et al studied 191 species of candida isolated from 175 patients with VVC referred to Mahdieh hospital from 2006 to 2008. They found that out of 135 strains of C. glabrata, 11 strains (31.4%) were resistant, 6 cases (17.1%) were sensitive and 18 cases (51.4%) were dose-dependent sensitive to fluconazole. They reported the range of MIC=0.5-64 μg/ml. The obtained results are somewhat consistent with our study (17).

The results of the present study is consistent with the results of another study by Pfaller et al (2011) who studied 120 strains of C. glabrata reported range of MIC=0.5-128 μg/ml, MIC50=8 μg/ml and MIC90=31 μg/ml (18).

Ozcelik et al (2006) introduced all of 8 strains of C. kefyr isolated from a variety of clinical specimen with a range of MIC:≤3-4% μg/ml sensitive to fluconazole (20).

Badiei et al reported 7 strains of C. kefyr isolated from mouth and vagina of patients suffering from AIDS with a range of MIC=0.25-1 μg/ml, MIC50=0.25 μg/ml and MIC90= 0.5 μg/ml (19).

Researchers reported the range of specimen isolated from vagina differently: Padua et al (2003) MIC90=0.5-64 μg/ml, Sojakova et al (2004) MIC=4 μg/ml and Mahmodirad MIC=0.5-16 μg/ml (16,17,22).

All of 3 strains of C. krusei had MIC=128 μg/ml. Therefore, both their MIC50 and MIC90 are also 128 μg/ml. According to NCCLS, all of isolates are resistant to fluconazole.

Sataha et al (2010) studying 2 strains of C. kruzei isolated from mouth of patients with AIDS obtained range of MIC=4-64 μg/ml and MIC50=8 μg/ml (27).

In the same study, it was suggested that the range of MIC for terbinafine obtained from 29 strains of C. glabrata ranged from 64 to 128 μg/ml (Table 1).

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MIC50 and MIC90 is equal to 128 μg/ml. Out of 10 cases of C. kefyr under study, 7 cases (70%) showed MIC=128 μg/ml and 3 cases (30%) had MIC=64 μg/ml for terbinafine. MIC50 and MIC90 were also equal to 128 μg/ml. Both cases of C. parapsilosis isolates showed MIC= 64 μg/ml to terbinafine. Therefore, MIC50 and MIC90 are also equal to 64 μg/ml. All of three isolates of C. kruzei showed MIC=128 μg/ml to terbinafine. In this case, MIC50 was also equal to MIC90 (128μg/ml).

In the present study, comparison of the MFC mean of the medicine showed that ciclopirox olamine with mean MFC of 32 μg/ml had the minimum value and the maximum fungicidal effect. However, terbinafine with mean MFC of 177μg/ml had the maximum value and the minimum fungicidal effect. Studying the effect of MIC and MFC of the medicines showed that fluconazole with mean MIC of 93 μg/ml inhibited growth of fungus and with mean MFC of 154μg/ml had fungicidal effect. In other words, mechanism of action is dose-dependent: fungistatic at lower dosage and fungicide at higher dosage. Sharifinia et al also showed that fluconazole was dose-dependent which is consistent with the present study (27).

Evaluating the effect of MIC and MFC regarding terbinafine revealed that this drug with mean MIC of 104 μg/ml and mean MFC of 177 was fungistatic and its fungicidal effects were dose-dependent.

Ciclopirox olamine with mean MIC of 18 μg/ml and mean MFC of 32μg/ml was fungistatic. Because it is fungistatic at low dosage, it turns fungicide at higher dosage.

Ciclopirox olamine in comparison with other medicines was more effective on isolates of non-albicans candidiasis. It was fungistatic with lower MIC. Fluconazole and terbinafine were less effective and most of the isolates were resistant to them.

The present study revealed that combination of fluconazole and terbinafine was not so effective on the isolates and their combination was not synergistic on isolates.

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بررسی اثر همبست فلوکونازول وتربینافین در مقایسه با اثر سیکلوپیروکس اولامین بر روی گونه های کاندیدای غیر آلبیکنس در بیماران ووللوواژنیت عود کننده کاندیدیایی

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مجله پزشکی هرمزگان سال هجدهم شماره ششم ۹۳ صفحات ۴۷۳-۴۶۶

چکیده

مقدمه: *اخیراً مطالعات اپیدمیولوژیک نشان داده است که عوامل کاندیداهای غیرآلبیکنس مانند: کاندیدا تروپیکالیس، کاندیدا گلابراتا، کاندیدا کروزه ای و کاندیدا پاراپسیلوزیس در ایجاد بیماری ولوواژینیت عودکننده کاندیدایی (RVVC) رو به افزایش است. تجویز طولانی مدت داروهای متداول سبب ایجاد مقاومت دارویی می‌شوند. در این مطالعه، اثر توأم فلوکونازول با تربینافین و مقایسه اثر آنها با سیکلوپیروکس اولامین بر روی گونه‌های غیرآلبیکنس جدا شده از ولوواژینیت عود کننده کاندیدایی بررسی گردید.*

روش کار: *این مطالعه یک روش تجربی آزمایشگاهی است که بر روی ۴۴ ایزوله کاندیدای غیرآلبیکنس جدا شده از بیماران واژینیت کاندیدایی عود کننده انجام شد و اثر داروهای فلوکونازول و تربینافین به تنهایی ودر همبست با یکدیگر و مقایسه آنها با اثر سیکلوپیروکس اولامین به روش استاندارد میکرودایلوشن (CLSI M27-A2) مورد ارزیابی قرار گرفتند.*

نتایج: *میانگین MIC فلوکونازول، تربینافین و سیکلوپیروکس اولامین بعد از ۴۸ ساعت گرماگذاری به ترتیب ۹۳/۸، ۱۰۴/۷ و ۱۸ میکروگرم بر میلی‌لیتر بدست آمد و FIC داروها به صورت (۹۵/۵٪) ۴۲ مورد اثر افزایشی و بی‌اثر و (۴/۵٪) ۲ مورد اثر هم‌افزایی و هم‌افزایی نسبی بدست آمد. همچنین در بررسی اثر قارچ‌کشی داروهای سیکلو پیروکس اولامین با میانگین ۳۲ =MFC میکروگرم بر میلی‌لیتر بیشترین اثر وتربینافین با میانگین ۱۷۷ =MFC میکروگرم بر میلی‌لیتر کمترین اثر دیده شد (P< ۰/۰۵).*

نتیجه‌گیری: *اکثر ایزوله‌ها نسبت به داروهای فلوکونازول و تربینافین مقاوم بودند و همبست کردن آنها نیز تأثیر چندانی نداشت ولی سیکلوپیروکس اولامین دارای بیشترین اثر بوده و میزان MIC و MFC کمتری را دارا می‌باشد.*

کلیدواژه‌ها: *کاندیدیاز – تربینافین – سیکلوپیروکس*

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