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THERAPEUTIC EFFICACY OF DIFFERENT AZOLE ANTIFUNGAL REGIMENS IN TREATMENT OF TINEA VERSICOLOR

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ABSTRACT
Systemic antifungal are used in severe tinea versicolor or in cases not responding to topical therapy, different regimen modalities with different efficacy result and cure rates have been tried in this experiment. To compare different modalities regimens of the azoles group in the treatment of tinea versicolor. This study was carried out in Department of dermatology and venereology in AL –KINDY teaching Hospital in Baghdad during the Period between May 2006- May 2009. One hundred seventeen Patients complaining of tinea versicolor were assessed and randomized into six groups:1st group was given Itraconazole 400 mg single dose (n=20); 2nd group was given Itraconazole 200 mg /day for one week (n=19); 3rd group was given Fluconazole 300 mg single dose (n = 20); 4th group was given Fluconazole extended regimen 150 mg weekly for four weeks(n=19); 5th group was given Ketoconazole 400 mg single dose (n=19); 6th group was given Ketoconazole 200 mg daily for 10 days (n=20). The response was assessed after 2 weeks and 6 weeks of follow up. The patients who did not respond to treatment regimen during the first 2 weeks were followed for another 4 weeks and were evaluated again for their response. After 2 weeks of treatment the highest rate (52.6%) was observed in the Itraconazole extended regimen group, while (35%) was observed in the Fluconazole single dose regimen, Response rate for non-respondents at 2 weeks after another 4 weeks of follow up show highest 55.6 % for Itraconazole extended regimen and lowest 23.1% for Fluconazole single dose, Response rate after 6 weeks of follow up was highest 78.9% for Itraconazole extended regimen, and lowest 35% for Fluconazole single dose regimen. Relapse of a previously cured skin lesion after 6 weeks was 42.9% for Fluconazole single dose and zero% for the Itraconazole and fluconazole extended regime. Different regimens of systemic azole are used for treatment of pityriasis versicolor both for a single and extended dose regimens. All were found to be effective in different success rates. Single and extended regimen of itraconazole showed the highest response figure in this experiment.

KEY WORDS: Pityriasis versicolor, Itraconazole, fluconazole.

INTRODUCTION

pityriasis versicolor, or "Tinea versicolor"[1] is a common fungal infection of the skin, affects mainly teens and young adults, caused in majority by *Malassezia globosa* although *M. furfur* is responsible for a small number of cases.[2][3]. The fungus interferes with the normal pigmentation of the skin, resulting in small, discolored patches. [4] Sun exposure may make tinea versicolor more apparent [5].

Systemic azole antifungals have revolutionized the treatment in pityriasis versicolor in both single and divided dose regimens, due to better acceptance by the patients.

Azole antifungal drugs inhibit the enzyme lanosterol 14 α-demethylase,the enzyme necessary to convert lanosterol to ergosterol. Depletion of ergosterol in fungal membrane disrupts the structure and many functions of fungal membrane leading to inhibition of fungal growth. It has a broad spectrum of activity that includes both dermatophytes and yeasts [6].

Ketoconazole is an oral or topical synthetic dioxolane imidazole compound that interferes with the biosynthesis of ergosterol, leading to alterations in certain membrane-associated cell functions [7].

Fluconazole is an oral synthetic bis-triazole compound that inhibits the cytochrome P450-dependent 14 alpha-demethylation step in the formation of ergosterol. This leads to alterations in a number of membrane-associated cell functions [7]. Itraconazole, is an oral synthetic dioxolane triazole compound that functions in much the same way as fluconazole.[7]

PATIENTS AND METHODS

A total of (117) Patients recruited in this study from both sexes attending department of dermatology and venereology in AL –Kindy teaching Hospital in Baghdad during the Period between May, 2006- May, 2009 complaining of tinea versicolor on different sites of trunk and extremities. Patients who fulfilled the inclusion and exclusion criteria at the first visit (baseline) was being assessed both clinically with woods light and by direct KOH examination.

Exclusion criteria for subjects included those with:

1. Known hypersensitivity to any of the drugs used in treatment
2. Any topical antifungal agents, shampoos with active ingredients against *Malassezia*, were not allowed during the course of therapy

Clinical assessment was thoroughly done for the patients. Woods lamp exam and KOH test were done. The patients randomized into six groups:

1st group given Itraconazole 400mg single dose.

2nd group given Itraconazole 200mg /day for one week.

3rd. group Fluconazole 300mg single dose.
4th. group given Fluconazole extended regimens 150 mg weekly for four weeks
5th group given Ketoconazole 4oomg single dose.
6th group given Ketoconazole 2oomg daily for 10 days.

The patients were followed up at 2 and 6 weeks after completion of each treatment regimen. At each time clinical examination, wood's light and KOH test were done. Patients were regarded cured clinically when the skin lesions or hyperpigmentation have disappeared, and mycologically cured when no hyphi is seen by KOH test. Cases regarded as relapsed if worsening of skin lesion happened, reappearance of new lesion seen or the KOH test is turning positive after it was negative.

RESULTS

A total of 117 patients complaining of tinea versicolor of the skin attending the dermatology department clinic in Al-Kindy Teaching Hospital where randomized into 6 treatment groups with sex difference and mean age according to each group as shown In table (1)and table (2).

TABLE 1: The difference in gender distribution between the 6 treatment groups

Study group	Gender					
	Female		Male		Total	
	N	%	N	%	N	%
Itraconazole single dose 400mg	9	45	11	55	20	100
Itraconazole extended regimen 200mg / day for 1wk	10	52.6	9	47.4	19	100
Fluconazole single dose regimen 300mg	6	30	14	70	20	100
Fluconazole extended regimen 150mg weekly for 4 wks	7	36.8	12	63.2	19	100
ketoconazole single dose 400mg	8	42.1	11	57.9	19	100
ketoconazole extended regimen 200mg dialy for 10 days	10	50	10	50	20	100

P (Chi-square) = 0.74[NS]

TABLE 2: The difference in mean age between the 6 treatment groups

Age (years)	Itraconazole single dose 400mg	Itraconazole extended regimen 200mg/day for 1wk	Fluconazole single dose regimen 300mg	Fluconazole extended regimen 150mg/ wk for 4 wks	Ketoconazole single dose 400mg	ketoconazole extended regimen 200mg/day for 10 days
Range	(16 - 38)	(17 - 41)	(16 - 39)	(17 - 41)	(16 - 42)	(17 - 42)
Mean	24.5	26.4	24.9	25.7	23.9	26.5
SD	6.9	7.1	6.9	7.6	7.1	6.7
N	20	19	20	19	19	20

P (ANOVA) = 0.83[NS]

As shown in table (1) and (2) there were no important or statistically significant difference in mean age or gender distribution between the 6 treatment groups, which point out to the fact that the randomization procedure was effective in canceling the possible effect of known and unknown confounders for the treatment effect. The response to treatment was evaluated by the absence of clinical skin lesion and/or negative KOH test. The response was assessed after (2) and (6) weeks of follow up. Table (3)

TABLE 3: Response rate (incidence rate of clinical/laboratory cure) after 2 weeks of follow up in the 6 treatment groups.

Study Groups	Total n	Response after 2 weeks of treatment	
		No. of patients	%
Itraconazole single dose 400mg	20	9	45
Itraconazole extended regimen 200mg / day for 1week	19	10	52.6
Fluconazole single dose regimen 300mg	20	7	35
Fluconazole extended regimen 150mg/week for 4 weeks	19	8	42.1
ketoconazole single dose 400mg	19	8	42.1
ketoconazole extended regimen 200mg daily for 10 days	20	10	50

P (Chi-square) for difference in response rate between the 6 treatment groups = 0.90[NS]
P (Chi-square) for difference in response rate between the 3 drugs at a single treatment schedule=0.8[NS]
P (Chi-square) for difference in response rate between the 3 drugs at the extended treatment schedule=0.79[NS]
P (Fisher's exact) for difference in response rate between the single dose and extended treatment schedules for Itraconazole = 0.75[NS]
P (Fisher's exact) for difference in response rate between the single dose and extended treatment schedules for Fluconazole=0.75[NS]
P (Fisher's exact) for difference in response rate between the single dose and extended treatment schedules for ketoconazole=0.8[NS]

As shown in table (3), the lowest response rate after 2 weeks of treatment (35%) was observed in the fluconazole single dose REGIMEN, while the highest rate (52.6%) was observed in the itraconazole extended REGIMEN group. The differences in response rate were small and not significant statistically. Among the single dose regimen groups, itraconazole had a slightly higher response rate(45%).The P-value for difference in response rate between the 3 drugs at a single treatment schedule was 0.8 which is not significant.The same finding was applicable to the extended schedule regimen groups. These findings were, however , non-significant statistically. The P-value for difference in response rate between the 3 drugs at the extended treatment schedule was 0.79. The extended regimen was associated with a slightly higher, although not significant statistically, response rate than the single dose group of the same drug. Each patient who did not respond to treatment during the first 2 weeks were followed for another 4 weeks and evaluated again for their response at week 6 from the starting of treatment regimen table (4).

TABLE 4: Response rate for non-respondents at 2 weeks after another 4 weeks of follow up in the 6 treatment groups

	Response to treatment after 6 weeks			
Response to treatment after 2 weeks	Respondent (-ve skin lesion)	Non-response (+ve skin lesion)	Total	Response rate for non-respondents at 2 weeks after another 4 weeks of follow up (%)
Itraconazole single dose 400mg				
Respondent (-ve skin lesion)	8	1	9	
Non-response (+ve skin lesion)	0	11	11	0
Total	8	12	20	
Itraconazole extended regimen 200mg / day for 1week				
Respondent (-ve skin lesion)	10	0	10	
Non-response (+ve skin lesion)	5	4	9	55.6
Total	15	4	19	
Fluconazole single dose regimen 300mg				
Respondent (-ve skin lesion)	4	3	7	
Non-response (+ve skin lesion)	3	10	13	23.1
Total	7	13	20	
Fluconazole extended reg 150mg weekly for 4 weeks				
Respondent (-ve skin lesion)	8	0	8	
Non-response (+ve skin lesion)	5	6	11	45.5
Total	13	6	19	
Ketoconazole single dose 400mg				
Respondent (-ve skin lesion)	6	2	8	
Non-response (+ve skin lesion)	0	11	11	0
Total	6	13	19	
Ketoconazole extended regimen 200mg daily for 10 days				
Respondent (-ve skin lesion)	9	1	10	
Non-response (+ve skin lesion)	4	6	10	40
Total	13	7	20	

P (Chi-square) for difference in response rate between the 6 treatment groups=0.01
P (Chi-square) for difference in response rate between the 3 drugs at a single treatment schedule=0.06[NS]
P (Chi-square) for difference in response rate between the 3 drugs at the extended treatment schedule=0.8[NS]
P (Fisher's exact) for difference in response rate between the single dose and extended treatment schedules for Itraconazole=0.008
P (Fisher's exact) for difference in response rate between the single dose and extended treatment schedules for Fluconazole=0.39[NS]
P (Fisher's exact) for difference in response rate between the single dose and extended treatment schedules for Ketoconazole=0.035.

As shown in table (4), the itraconazole and fluconazole single dose groups showed no further response (0% response rate), while the extended schedule groups showed a noticeably high response rate that being highest in the itraconazole group (55.6%). The difference in response rate between the 6 treatment groups was statistically significant. The P-value for difference in response rate between the 6 treatment groups was 0.01. The fluconazole single dose regimen showed a noticeably higher response rate (23.1%) compared to the zero response rate for other 2 drugs with a similar single dose regimen; the difference however failed short of statistical significance. P-value for difference in response rate between the 3 drugs at a single treatment schedule was 0.06. The difference in response rate between the extended dose schedules of the 3 drugs was small and not significant statistically. P-value for difference in response rate between the 3 drugs at the extended treatment

schedule 0.8. The extended regimen was associated with a significantly higher response rate compared to single dose regimen for itraconazole and ketoconazole, but the difference observed with fluconazole was not significant statistically. As shown in table(5) , the response rate for all of the patients included in this study at the end of 6 weeks of follow up, revealed that the lowest response rate (35%) was observed in the fluconazole single dose regimen, while the highest rate (78.9%) was observed in the itraconazole extended regimen group. The differences in response rate between the 6 treatment groups were significant statistically. P_ value for difference in response rate between the 6 treatment groups=0.008. Among the single dose groups, itraconazole had a slightly higher response rate. The same finding was applicable to the extended schedule regimen groups. These findings were however non-significant statistically. The extended regimen was associated with a significant higher response rate than the single dose group of the same drug. The risk of being a respondent with the extended regimen was almost 2 times that of the counterpart single dose regimen. As appointed in table(6), subjects who responded to 2 weeks of treatment and showed no evidence (clinical or laboratory) of skin lesions at that point of time, were followed for also for another 4 weeks with recurrence of skin lesion as the anticipated outcome. The relapse rate was lowest (zero %) with the itraconazole and fluconazole extended dose regimen and highest with the fluconazole single dose regimen. The differences in relapse rate between the 6 treatment groups failed short of statistical significance, possibly because of small sample size for subjects who had a response at the 2 weeks of follow up. P-value for difference in relapse rate between the 6 treatment groups was 0.11. Among the single dose groups, fluconazole had a slightly the highest relapse rate (42.9%), while itraconazole had the lowest relapse rate (11.1%). In the extended schedule regimen groups, ketoconazole had a slightly higher relapse rate of (10%) compared to(zero) rate for the other 2 tested drugs, the differences were small and not significant statistically. The relapse rate was always higher for the single dose compared to extended dose regimen for the same drug, but the differences were not significant statistically. table (6).

TABLE 5: Response rate (incidence rate of clinical/laboratory cure) after 6 weeks of follow up in the 6 treatment groups.

Study group	Total	Respondent (-ve skin lesion) after 6 weeks of treatment	
	N	N	%
Itraconazole single dose 400mg	20	8	40
Itraconazole extended regimen 200mg / day for 1week	19	15	78.9
Fluconazole single dose regimen 300mg	20	7	35
Fluconazole extended regimen 150mg weekly for 4 weeks	19	13	68.4
ketoconazole single dose 400mg	19	6	31.6
ketoconazole extended regimen 200mg daily for 10 days	20	13	65

P (Chi-square) for difference in response rate between the 6 treatment groups=0.008

P (Chi-square) for difference in response rate between the 3 drugs at a single treatment schedule=0.85[NS]

P (Chi-square) for difference in response rate between the 3 drugs at the extended treatment schedule=0.61[NS]

	RR	95% confidence interval for RR
P (Fisher's exact) for difference in response rate between the single dose and extended treatment schedules for Itraconazole = 0.02	1.97	(1.1-3.54)
P (Fisher's exact) for difference in response rate between the single dose and extended treatment schedules for Fluconazoleconazole = 0.056[NS]	1.95	(1-3.82)
P (Fisher's exact) for difference in response rate between the single dose and extended treatment schedules for Ketoconazole=0.056[NS]	2.06	(0.99-3.4)

Note: RR is the relative risk of being a respondent when treated with the extended dose compared to single dose.

TABLE 6: Relapse rate after 6 weeks of treatment

Study group	Total	Relapse of a previously cured skin lesion after 6 weeks	
	N	N	%
Itraconazole single dose 400mg	9	1	11.1
Itraconazole extended regimen 200mg / day for 1week	10	0	0
Fluconazole single dose regimen 300mg	7	3	42.9
Fluconazole extended regimen 150mg weekly for 4 weeks	8	0	0
Ketoconazole single dose 400mg	8	2	25
Ketoconazole extended regimen 200mg daily for 10 days	10	1	10

P (Chi-square) for difference in relapse rate between the 6 treatment groups=0.11[NS]

P (Fisher's exact) for difference in relapse rate between the single dose and extended treatment schedules for Fluconazole =0.35[NS]

P (Fisher's exact) for difference in relapse rate between the single dose and extended treatment schedules for Itraconazole=0.39[NS]
P (Fisher's exact) for difference in relapse rate between the single dose and extended treatment schedules for Ketoconazole=0.47[NS]
P (Chi-square) for difference in relapse rate between the 3 drugs at the extended treatment schedule=0.077[NS]
P (Chi-square) for difference in relapse rate between the 3 drugs at a single treatment schedule=0.56[NS]

DISCUSSION

pityriasis versicolor, also called tinea versicolor, is a common skin condition which is caused by a superficial cutaneous infection with the fungal agent Malassezia furfur (previously : Pityrosporum versicolor or Pityrosporum orbiculare). The infection occurs worldwide, with prevalence from 0.5% in temperate climates up to 18% in humid tropical climates reported in the literature.[8][9],tinea versicolor predominately affects adolescents and adults, but infection as early as in infancy has been described. Although the infection does not pose a significant health risk to the affected individual, the psychological and social implications can be profound. Spontaneous remission is generally rare. Topical treatment as a first line intervention can be curative, for which purpose clotrimazole, econazole, ketoconazole, miconazole or terbinafine can be used. However, some patients do not respond satisfactorily or experience multiple relapses and may require systemic treatment, particularly when large areas are affected. In these circumstances "azole" antifungal drugs, which include fluconazole, itraconazole and ketoconazole, are considered to be the treatment of choice. There is little consensus regarding the optimal dosing regimen and duration of treatment with systemic antifungal agents. The BNFC suggests a 7- day course with itraconazole or a 2–4- week course with fluconazole for the treatment of tinea versicolor. Interestingly, a randomized controlled trial in adults has demonstrated that single high dose (400 mg) fluconazole treatment can be as effective as a prolonged 4- week course with lower doses with regard to clinical cure. [10] Another study by O Köse, *et al*., 2002. concluded that a single dose of itraconazole 400mg/day was as effective as the 7-day 200mg daily dose in the treatment of pityriasis versicolor[11]. Our study shows that extended itraconazole regimen group show highest response rate (78.9%) vs (40%) single dose regimen. The extended regimen was associated with a slightly higher, although it is not significant statistically, response rate than the single dose group of the same drug .In addition, the relapse rate was lowest (zero %) with the itraconazole and fluconazole extended dose regimen and highest with the fluconazole single dose regimen. Itraconazole is a member of a group of antifungal compounds that is an ideal drug for oral treatment of pityriasis versicolor Itraconazole has been generally used in pityriasis versicolor at 200mg/day for 1–2 weeks. [12], [13]Hickmann investigated the efficacy and safety of a 7-day course of itraconazole (200mg/day) in pityriasis versicolor, and reported that itraconazole was signicantly more effective than placebo. [13]. This study revealed that a single dose 400mg itraconazole is superior to a single dose regimen of fluconazole 300mg with acure rate of 40% vs. 35%. This result was concomitant with Partap R in 2004[14] and against Kokturk A in 2002 who concluded that the regimen of 400 mg/day itraconazole for 1 day was found to be ineffective[15]. The response rate of the extended regimen of fluconazole 150 mg weekly for four weeks (68.4%) was higher than single dose regimen of 300 mg(35%).Previous study done by Bhogal et al 2001[10] found that a single dose regimen of 400 mg of fluconazole had shown a best response rate (80%) than extended regimen of the same drug. This variation in response may be attributed to the difference in the dose of the drug between both studies.

The response rate of extended regimen of ketoconazole in this study(65%) is slightly lower than the fluconazole extended regimen(68.4) and more than the response rate of single dose ketoconazole. This result in our study again goes with Bhogal *et al.,* 2001[10]. Among the single dose groups, it was found that fluconazole had a slightly the highest relapse rate (42.9%), while itraconazole had the lowest relapse rate (11.1%). In the extended schedule regimen groups, ketoconazole had a slightly higher relapse rate of (10%) compared to zero% rate for the other 2 tested drugs; the difference was small and not significant statistically. The relapse rate was always higher for the single dose compared to extended dose regimen for the same drug, in spite of the fact that the differences were not statistically significant.

CONCLUSION

Different regimens of systemic azole are used for treatment of pityriasis versicolor both for a single and extended dose regimens. All were found to be effective in different success rates. Single and extended regimen of itraconazole showed the highest response figure.

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