The Comparison of the Effects of 1 % Terbinafine and Izoconasole Creams in Treatment of Ptyriasis Versicolor

PİTİRİAZİS VERSİKOLORUN TEDAVİSİNDE %1 TERBİNAFİN VE İZOKONAZOL KREM ETKİLERİNİN KARŞİLAŞTİRİLMASİ

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SUMMARY

To investigate the efficacy of terbinafine and izoconasole creams in patients with pityriasis versicolor, 92 patients who between June 1993 and January 1994 had applied to the out patient clinic of CU Faculty of Medicine Dermatology Department, were included in the study.

The ages of the cases had been randomized into 3 treatment groups, varied between 9-60 and the mean age was 28.47'±4.7. All the cases were called for weekly follow-up for a period of 4 weeks following the initial examination and they were all evaluated by wood lamp, clinical and microscopical examinations. At their initial application and at the end of the treatment, cultures were performed in a microbiology laboratory.

Comparing the weekly results of each treatment group, terbinafine cream was found to be more effective than both placebo and izoconasole cream.

As a result, it has been concluded that terbinafine cream reaches high efficacy in a shorter period than izoconasole cream and thus it is a defter alternative in pityriasis versicolor treatment.

Key Words: Terbinafin, Izoconasole, Pityriasis versicolor

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ÖZET

Pifyriasis versicoior'lu hastalarda terbinafin ve izokonazol kremlerin etkinliğini araştırmak için Haziran 1993-Ocak 1994 tarihleri arasında CÜ Tıp Fakültesi Dermatoloji Anadilim Dalı polikliniğine başvuran pityrlasıs versicolorlu 92 hasta çalışmaya alındı. Rastgeie seçilerek 3 tedavi grubunda toplanan olguların yaşları 9-60 arasında değişmekte olup yaş ortalaması 28.47±4.7 idi. Olguların tamamı ilk muayene sonrası 4 hafta süresince haftalık kontrollere çağrılıp wood lambası, klinik ve mikroskopik muayene yönünden değerlendirildi, ilk başvurduklarında ve tedavi sonunda mikrobiyoloji laboratuarında kültür vasatlarına ekim yapıldı. Her 3 tedavi grubunun haftalık kontrol sonuçları gruplar arasında karşılaştırıldığında terbinafin kremin hem piasebodan hem de izokonazol kremden daha etkin olduğu gözlenmiştir. Sonuç olarak terbinafin kremin izokonazol kremden daha kısa sürede daha yüksek etkinliğine ulaştığı ve bu nedenle pifyriasis versicoior tedavisinde iyi bir alternatif olabileceği kanaatine varılmıştın

Anahtar Kelimeler: Terbinafin, İzokonazol, Pityriasis versicolor

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Pityriasis versicolor (P. versicolor) is a fungal infection characterised by **multiple** hypo-or hyperpigmented patches of lesions on the seborrheic areas of the body (1-6). The disease is caused by pityrosporum orbiculare, a dimorphic yeast. Being a saprophyte on the human skin, this yeast can become pathogenic by **va-***horn* factors and cause lesions (7-8). The disease occurs worldwide, but it is more common m tropical regions due to high temperature and humidity, its incidence is hiqher **in** summer and lower in winter **(1-3,8-10).**

Keratolyses and local antifungals usually give successful results In the treatment of P. versicolor (7,9-12). Topical treatment can **be** associated **with** relapses and reinfections, necessitating alternative systemic treatments (8,12-14). However, systemic treatment has a limited use due to high cost, equivalent success rates to topical treatment and systemic side effects (8,10,15).

Terbinafine, a **recently** introduced antifungal, belongs to **allylamine** group and **has** fungicidal activity. It

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prevents biosynthesis of ergosterole by selectively inhibitgn fungal squalene epoxyacles. In vitro terbinafine sensitivity testing covers dermatophytes, aspergillus species, yeasts such as etyptococcus neofornians and pityrosporum capsulatum as well as protozoa such as trypanosoma cruzi and leishmaina mexicana (16).

In order to Investigate the efficacy this new agent, we planned a controlled study in which terbinafine was compared with a well known antifungal agent, isoconazoie nitrate, and placebo,

Kir - -: IALS AND METHODS

Patients with the clinical and laboratory diagnosis of p. versicolor who admitted to Cumhuriyet University, Dermatology Clinic between June 1993-Jamtary 1994 were included In this study.

Patients who had no previous treatment for p. versicolor and those who are not receiving systemic drugs for any other medical condition were selected. Pregnant women were excluded. None of the patients had predisposing illness such as diabetes mellitus. tuberculosis, immunosupression or malnutrition.

Each patient's age, duration of the disease, localization of lesions, features of macules, results of wood's light examination and mycologlcal test were recorded. On the initial admission and at the end of therapy, a swab sampling was placed in special culture media containing olive oil.

Scoring was carried out In order to stage lesions. According to this scoring, lesions were classified as 4-very severe, 3=severe, 2-mild and 1-none. Results of microscopic examination were evaluated as 4-abundant fungal elements, 3-moderate, 2-few and 1»no fungal element

On the weekly follow-ups, changes In clinical findings, wood's light examination and microscopic examination were recorded. A native preparation was made form each patient at each visit. Cultures were obtained on first admission and at the end of fourth week. Microbiological evaluation was carried out at Cumhuriyet University, Microbiology Laboratory.

Since P. orbicular©, the etloiogic agent of P. versicolor, can not be cultured in Sabouraud's agar media, it was cultured in a more specific media containing Tween 80, cycloheximide, chloramphenicol and covered by sterile olive oil. Specially prepared Ozapek Dox culture media was also used. When these latter two media gave positive results, Sabouraud's media was used to determine our findings since it was expected to give negative result. Therefore negative result in Sabouraud's media was considered In favour of P. orbicuiare (24).

Patients weie all randomised into 3 treatment groups. Group I consisted of 32 patients using isoconasoie nitrate; group II consisted of 30 patients using terbinafine aearn and group ill had 30 patients receiving placebo.

Terbinafine cream was supplied from Switzerland, by manufacturer, SANDOZ, since it was not available in Turkey. Isoconasole nitrate cream was obtained by patients. A base cream containing no active ingredient but Steady alcohol 8, liquid paraffin 10, white vaseline 10, and water was used as placebo (18).

For statistical evaluation of data, variance analysis and Tukey test were used (19).

RESULTS

There were 92 patients with P. versicolor in whom diagnosis was confirmed by native preparation and culture. Of these, 50 were male and 42 were female. The ages of the patients varied between 9 to 80, with the mean of 28.47±4.7.

Duration of complaints was less than 1 year in 39(42.3%) cases whereas 22(23.9%) had complaints for 1 to 5 years. Thirty-one (33.6%) patients suffered over 5 years. Lesions were limited to trunk in 67(72.82%) cases. Lesions were localized on neck in 10 patient (10%), on limbs in 9 patients (9%), and on abdomen in 6 patients (6.5%).

Lesions were hyperpigmented In 65(70%) of all cases. 17 patients (18%) had hypopigmented, and 10(12%) had erythematous lesions. Both hyphae and spores were seen equally in native preparations of 47 patients (51%). Hyphae were dominant in 31 cases (33%) while spores were more common in 14(16%) patients.

During wood's light examination, 25 of 92 cases (27%) gave golden (yellow) fluorescence. Thirty of 67 patients (63%) with no fluorescence had microscopically dominant hyphae. Culture results were positive in 51 cases whereas they were negative in 41 patients. Ratio of culture-positive patients was 55%.

Weekly comparison of clinical examination scores in group I is shown in Table 1. When all the weeks were taken into account, difference among the scores were statistically significant ($p<0.01$). As weeks were compared to each other, difference between the 1st week and the 2nd, the 3rd and the 4th weeks was statistically significant. Difference between the 2nd week and the 3rd and the 4th weeks also statistically significant. Furthermore, difference between the 3rd and the 4th week was found to be statistically significant too ($p<0.05$).

As shown in Table 2, in terms of microscopical examination scores, difference among treatment weeks was statistically significant ($p<0.01$). As weeks were compared to each other, difference between the 1st week and 2nd, the 3rd and the 4th weeks was statistically significant. Difference between the 2nd week and the 3rd and the 4th weeks was also statistically significant. Furthermore, difference between the 3rd and the 4th week was found to be statistically significant as well ($p<0.05$).

Table 1. Weekly comparison of clinical examination scores in group I

Weeks	x±Sx	Decision
1st week	4.0±0.00	F=7.05, p<0.01, T=0.504
2nd week	3.03±0.13	$\|x_1-x_2\|$=0.97* $\|x_2-x_3\|$=0.94*
3rd week	2.09±0.07	$\|x_1-x_2\|$=1.91* $\|x_2-x_4\|$=1.94*
4th week	1.09±0.05	$\|x_1-x_4\|$=2.91* $\|x_3-x_4\|$=1.00* *p<0.05

Table 2. Weekly comparison of microscopic examination scores in group I

Weeks	x±Sx	Decision
1st week	4.0±0.00	F=830, p<0.01, T=0.147
2nd week	3.81±0.07	$\|x_1-x_2\|$=0.19* $\|x_2-x_3\|$=0.87*
3rd week	2.94±0.04	$\|x_1-x_3\|$=1.06* $\|x_2-x_4\|$=2.72*
4th week	1.09±0.05	$\|x_1-x_4\|$=1.85 $\|x_3-x_4\|$=1.85* *p<0.05

Table 3. Weekly comparison of clinical examination scores in group II

Weeks	x±Sx	Decision
1st week	4.0±0.00	F=12.53, p<0.01, T=0.168
2nd week	2.03±0.09	$\|x_1-x_2\|$=1.97* $\|x_2-x_3\|$=0.83* *p<0.05
3rd week	1.2±0.07	$\|x_1-x_3\|$=2.8* $\|x_2-x_4\|$=0.96*
4th week	1.07±0.06	$\|x_1-x_4\|$=2.93* $\|x_3-x_4\|$=0.13, p>0.05

Table 4. Comparison of microscopic examination scores in group II

Weeks	x±Sx	Decision
1st week	4.0±0.00	F=57.84, p<0.01, T=0.336
2nd week	3.1±0.09	$\|x_1-x_2\|$=0.9* $\|x2-x3\|$=1.84* *p<0.05
3rd week	1.26±0.11	$\|x_1-x_3\|$=2.74* $\|x_2-x_4\|$=2.04*
4th week	1.06±0.05	$\|x_1-x_4\|$=2.93* $\|x_3-x_4\|$=0.206, p>0.05

As shown in Table 3, in terms of clinical examination cores, difference among treatment weeks was statistically significant (p<0.01). As weeks were compared to each other, difference between the 1st week and the 2nd, the 3rd and the 4th weeks was statistically significant. Difference between the 2nd week and the 3rd and the 4th weeks was also statistically significant (p<0.05). Only difference between the 3rd and the 4th week was found to be statistically insignificant (p>0.05).

Comparison of microscopic examination scores for each treatment week in group II is shown In Table 4. Difference among treatment weeks was statistically significant (p<0.01). As weeks were compared to each other, difference between the 1st week and the 2nd, the 3rd and the 4th weeks was statistically significant. Difference between the 2nd week and the 3rd and the 4th week was also statistically significant (p<0,05). However, difference between 3rd and 4th week was found to be statistically insignificant (p>0.05).

In terms of clinical and microscopic examination scores of group Hi in 2nd, 3rd, and 4th weeks, difference was found to be statistically significant (p<0.05).

Results of second treatment week In all groups were compared and found to be statistically significant in Table 5 (p<0.01). As means of groups were compared to each other two at a time, statistically significant difference was noted between group I and II, group I and III, and group II and II! (p<0.05).

As seen in Table 6, results of second treatment week in all groups were compared and found to be statistically significant (p<0.01). As means of groups were compared to each other two at a time, statistically significant difference was noted between group I and II, group I and III, and group II and III (p<0.05).

Comparison of fourth week results in three treatment groups is shown in Table 7. When results belonging to 4th week were compared in all groups, difference among the groups was statistically significant (p<0.01). As means of groups were compared to each other two at a time, stastistically significant difference was noted between group I and III, group II and III (p<0.05). while difference between group I and II was not statistically significant (p>0.05).

Clinical cure rates of the groups for treatment weeks are shown in Table 8, here was no cure in group I and III in 2nd "week, while clinical cure rate was 10% in group II. No clinical cure was noted in

Table 5. Comparison of second week results **in** three treatment groups

Groups	n	x+Sx	Decision
1st group	32	**3.03+0.13**	F-56.16, p<0.01, T-0**.379**
2nd group	30	**2**.03+0.09	$\|xi-x_2\|$=1.00*
3rd group	30	**3.6±0.11**	**$\|xi-x_1\|$-0.57***
			$\|xi$-**X2I»1.57****p<0**.05**

Table 6. Comparison of third week results In three treatment **groups**

Groups	n	x±Sx	Decision
1st group	32	2.09±0.07	**F-73,73, p<0.01, T-0.302**
2nd group	30	**1.2±0.07**	$\|xi-x_2\|$=0**.89***
3rd group	30	**2.7**+0**.12**	**$\|xi-x_3\|$=0.61***
			$\|xi-x_3\|$=1.5* "p<0.05

Table 7. Comparison of fourth week results in three treatment groups

Groups	n	xiSx	Decision
Istgroup	32	**1.09+0**.05	F»10t ,92, p<0.01**,T=0.252**
2nd group	30	1,07+0.05	**lxi-xjl-0.02 p<0.05**
3rd group	30	**2.4+0.11**	**lxi-x?l«1.31 p<0.05**
			lxi-X2l-1.33 p<0.05

Table 8. Comparison of all treatment groups according to clinical cure

Drugs	1 st week	2nd **week**	3rd week
1st group	0%	3%	90.6%
2nd group	10%	76.6%	93,3%
3rd group	0%	0%	6%

group III in third treatment week. At this time, clinical cure rate was 3% in group I, and 76% in group 11. By the end of 4th treatment week clinical cure rates were as follows: 6% in group iII, 90% in group I and 93% group II.

DISCUSSION

Pityriasis versicolor is a superficial fungal infection localized mainly on seborrheaic areas of the body. It occurs more commonly in hot and humid regions (1-5,8,9). in order to diagnose P. versicolor, causative agent must he demonstrated in native preparation. It has a characteristic appearance with hyphae and grape-like spores, in some cases spores are found more dominantly, there is higher change to obtain fluorescence through Wood's light examination. In some cases when hyphae are seen more frequently, while in others both elements may be equal in amount (1-5,20).

In a study on the agent of P. versicolor, Erbakan et al reported that 30% of all cases gave fluorescence and 54% of these had dominant hyphae in microscopic examination. Spores and hyphae were equal In 38% and hyphae were dominant in 8% of those patients with positive Wood's night examination.

In our study, 27% of 92 cases gave fluorescence. Spore-dominating cases constituted 56% of these patients. Pour percent of he patients who gave no fluorescence had abundant hyphae and 40% of them had equal amount of spores and hyphae. Our results agreed with those obtained by Erbakan et al (20).

Culture is not routinely employed in diagnosis of P. versicolor. fV'oroscopic examination is sufficient for diagnosis. Fungal culture for P. versicolor is difficult and special media is required (1-5,20,21).

In a clinical and microbiological study, Roberts has shown, that 2 of 25 oases with P. versicolor had negative culturde result. In this study, positive culture rate was 92% (21), in Erbakan et al's study (20), sixty-two of 121 cases had positive culture results and 59 had negative results. Culture positivity rate was 51%,

In our study, 51 of 92 cases had positive culture while in 41 patients, culture was negative. Culture positivity rate in our series was 55%. This ratio is somewhat lower than that of Robert's study (21) and close to the Erbakan et al's study (20). The higher culture positivity rate in Robert's study may be due to special culture media he had used. It is also possible that because we and Erbakan et al (20) used the same culture media, our results seem to be similar.

Results of clinical and microscopic examinations in group I during 4 'weeks are compared in Table t and 2. Differences among the treatment weeks were statistically significant (p<0.01). As a consequence, it can be stated that each week has shown better results than the previous one. We could not make a comparison since we were unable to find a similar study in 'which isoconasole cream was used.

In a study using isoconasole c-nn 44 patients with P. versicolor, Varol et al (22) reported that clinical cure rate was 86'% by the end of 4th week.

In our study we found that clinical cure rate was 90.6% in group 1 by* the end of 4 week. Although this figure is higher than Varol et ai's result (22), it is quite close.

Clinical cure rate in second week and by the end of the third week was 10% and 80% for patients who used terbinafine cream. Aste et al (23) found that in patients with P. versicolor, terbinafine produced a clinical cure rate of 10% by the end of 2nd week and 80% by the end of the 3rd week. Clinical cure rate in our study was in accord 'with the results of study performed by Aste et ai (23),

In a study performed by .Jones in 1990 (24) mycologicai cure rate was reported to be 85% in patients who were treated with terbinafine. Similarly, Viilard et ai (25) reported that their clinical cure rate was 90%, In Aste et ai's study (23), clinical cure rate was reported as 100% in patients who received terbinafine cream. In our study, we obtained a higher result than Jones (24) and Viilard et al (25) did. Our result was lower than that of Aste et al (23),. Nevertheless, in our study, we had a result similar to results of studies performed by Villaed et al and Aste et al.

In Tables 3 and 4, clinical and microscopic examination result were compared according to treatment weeks in patients who used terbinafine cream. Except for the 3rd and the 4th week, there was a significant difference among the treatment weeks. It is likely that terbinafine can reach full efficacy by the 3rd week

since there was no statistically significant difference between the 3rd and the 4th week. This feature enables a. short treatment period.

When clinical and microscopic results of the 2nd, 3rd, and the 4th week were compared in group **ill,** a statistically significant difference was found ($p<0.05$). This difference is mainly due to severe cases with copious microscopic findings. In regara of this result, if can be stated that placebo cream isas no antimyeotic effect.

Although 6% **of** the cases who used placebo showed clinical **improvement** by fne end **of** the 4th week, microscopic examination of these patients revealed persistence of fungal elements. All of these cases came back with reiapse within 15 days to 2 months.

In a study performed by Abdel-Aal et a) (26), lesions improved in 30% of 16 patients **who** used placebo; but there was no complete resolution and clínica! cure was reported to be 0%.

Although our study showed a higher clinical cure rate than that of Abdel-Aal ef al (26), presence of fungal elements in microscopic examination can be attributed to the absence of absolute cure.

As seen in Table 5, 6, and 7. when the results of the 2nd, 3rd, and 4th weeks were taken into account in three treatment groups, isoconasole and terbinafine cream were more effective than placebo; besides, comparison of two drugs revealed a statistically significant difference. This difference was originated from higher efficacy of terbinafine cream compared to isoconasole cream. We could not make a comparison on this subject, since we were unable to find a similar study.

As shown in Table 8, by the end of the 3rd week, clinical cure rate of isoconasole cream was 3% while it was 80% in terbinafine group. Terbinafine become effective in the 2nd week and if. keeps this high efficacy during the 3rd week.

When all results are taken into account, terbinafine cream showed its efficacy by an apparent Improvement in 2nd treatment week, it reached **to** sufficient success rates in 3rd week. Its efficacy was shown to be signifcanty higher than isoconasole.

As a conclusion, because of its rapid action and higher efficacy, terbinafine cream **was** found to be a veny good alternative in the treatment of P. versicolor.

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