Comparison of the efficacy of terconazole 0.8% vaginal cream / 80 mg. ovules and clotrimazole 100 mg.vaginal ovules in the management of vulvo-vaginal candidiasis.

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Summary : **The present study was an open trial undertaken to compare the efficacy of three antifungal medicaments in the treatment of vulvovaginal candidiasis. These included Terconazole vaginal cream 0.8%, Terconazole Vaginal Ovules 80 mg., and Clotrimazole Vaginal Ovules 100 mg. respectively. Fifty patients were included in each group of the study only after a firm mycologial diagnosis had been established. They were allocated randomly to the three trial groups, and followed up at one week, one month, and three months intervals and examined clinically and mycologically for evaluating the comparative efficacy of these drugs. The study revealed that Cultures were more accurate in detecting candida positive cases than KOH treated smears of vaginal discharges. The recurrance of symptoms and resurgence of candida progressively increased with the passage of time. In the overall analysis of the cases, it appeared that Terconazole cream gave the best mycological outcome. However, when the clinical profile of these patients was compared for relief of their most distressing symptoms, it emerged that terconazole vaginal cream and terconazole ovules were comparable in their efficacy. The rate of recurrence of severe pruritus at the end of three months after treatment with terconazole cream and terconazole ovules was found to be 11.1% and 11.4% respectively, and this was higher than the reccurrance rate of 33.3% with Clotrimazole. Similar results were found in patients complaining of leucorrhoea, and dysuria. However clinical examination of the lower genital tract revealed equally good improvement in all three groups of cases. The details have been explained in the text of the paper.**

Introduction :

Terconazole is yet another new antifungal drug which exerts a powerful antifungal activity on candida and other fungi. The MIC values for terconazole against most species of lactic acid bacteria typically found in the human vagina were > 128 mcg/ml. Its pharmacological activity is attributed to its capacity to disrupt normal fungal cell membrane permeability. No resistance to terconazole has been shown to develop during successive exposure of Cl albicans to the drug. The drug was evaluated dispersed in a cream base as well as in the form of vaginal ovules, and the drug efficacy compared to the more standard and currently popular antifungal medicament in common usage, namely clotrimazole vaginal ovules.

Materials and Method :

Three groups each of 50 patients having mycologically confirmed vulvovaginal candidiasis were included in this study. Group 1 was treated with 0.8% terconazole intravaginal cream for 3 nights. Group 2 was treated with terconazole vaginal tablets (ovules), one ovule inserted deep in the vagina at bed time for 3 nights. Group 3 was treated with clotrimazole vaginal tablets (ovules) of 100 mg. each, inserted deep in the vagina at bed time for 6 nights.

In all the patients included in the study the following investigations were routinely undertaken, I.CBC 2. Urinalysis, 3. Random blood sugar, 4. Wet smear to rule out trichomoniasis and presence of clue cells, 5.A KOH treated smear to demonstrate candida, and 6. Culture on Nickersons / Sabouraud's media to confirm the diagnosis. KOH smears and culture of vaginal discharge were repeated at every follow-up visit.

Exclusion criteria included 1. Presence of concomittant infection as evidenced by the presence of trichomonas or clue cells, 2. Negative cultures for candida, 3. H/O drug sensitivity, 4. H/O using antimycotic drugs or any vaginal medicaments in the preceding one week, and 5. Proven diabetics.

Observations and results :

Observations made during the course of the study were documented in standard data sheets, the results computerised, and tabulated as shown in the following tables.

1. Age . The age distribution of the cases in the various age groups included in the study are shown in a comparative form in the following table.

Table 1 Comparison of age distribution :

AGE GROUPS	Terconazole 0.8% cream		Terconazole Vag. Ovules		Clotrimazole Vag. Ovules	
	No.	%	No.	%	No.	%
>20 yrs.	1	2	-	-	2	4
21 - 25 yrs.	11	22	8	16	9	18
26 - 30 yrs.	19	38	25	50	16	32
31 - 35 yrs.	16	32	13	26	13	26
> 35 yrs.	3	6	4	8	10	20

The above table shows that the majority of cases in all the treatment groups were within the age groups of 21 to 35 years respectively.

2. Parity. The parity distribution in the 3 groups studied is shown in comparative form in table 2.

Table 2. Comparison on parity distribution :

Parity	Terconazole 0.8% cream		Terconazole Vag. Ovules		Clotrimazole Vag. Ovules	
	No.	%	No.	%	No.	%
0	11	22	8	16	6	12
1	16	32	9	18	10	20
2	18	36	21	42	20	40
3	3	6	11	22	10	20
4	2	4	1	2	1	1
5	-	-	-	-	3	6

The majority of cases were in the parity group 0-2 respectively in all the 3 groups.

3. Haemoglobin distribution : This distribution is shown in table 3.

Table 3.

Haemoglobin distribution in the study groups.

Haemoglobin Levels	Terconazole Cream		Terconazole Ovules		Clotrimazole Ovules	
	No.	%	No	%	No.	%
8.0 - 10.0 gm	14	28	11	22	26	52
10.1 - 11.0 gm	23	46	22	44	13	26
11.1 - 12.0 gm	8	16	15	30	6	12
> 12.0 gm	5	10	2	4	5	10

Many women in the study (Hb. between 8 - 10 gm%) in all the three groups were modertely anaemic.

4. Blood Sugar levels :

These have been compared in table No. 4

Table 4. Comparative distribution of the blood sugar values in the study groups :

Blood Sugar Levels	Terconazole Cream		Terconazole Ovules		Clotrimazole Ovules	
	No.	%	No.	%	No.	%
Upto 80.0 mg%	12	24	26	52	18	36
81.0 - 100.0 mg%	35	70	22	44	32	64
100.0 - 120.0 mg%	2	4	2	4	-	-

No diabetic patient was included in the present study.

5. Mycological Studies :

Only patients who revealed a positive smear on the KOH treated wet mount at the initial examination were included in the study. In all cases registered for the study, a KOH smear and Culture of the vaginal discharges was performed at the first visit and at every subsequent follow-up visits. The results of the present study have been tabulated below.

Table 5. Comparitive results of mycological examination in the study groups :

Visit	Positive KOH Smears						Positive Mycological Cultures					
	Terc. Cream		Terc.Ovules		Clot Ovules		Terc. Cream		Terc. Ovules		Clot. Ovules	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Initial	50	100	50	100	50	100	50	100	50	100	50	100
1st. Week	3/50	6	4/50	8	10/50	20	5/50	10	7/50	14	13/50	26
1-Month	4/47	8.5	16/45	35.5	14/40	35	7/47	14.8	19/45	42.2	18/40	45
2-3 month	2/27	7.4	10/35	28.5	5/21	23.8	4/27	14.8	13/35	37.1	6/21	28.5

The above table reveals that the myological recurrance rates tend to increase with passage of time. Cultures pick up more cases of recurrance as compared to KOH smears. Terconazole cream gave better mycological improvement than the terconazole ovules because the patients often did not introduce the ovules deep enough. The mycological recurrance rates for terconazole ovules and clotrimazole ovules in the present study were similar. The progressively increasing recurrance rates in all the three groups can be partly attributed to the lack of concommitant treatment of the male partners, and the failure to eradicate the fungi from other potential sites for reinfection like the bowels, nailbeds, etc. in the patient herself.

The Results of candida cultures revealed positivity at the end of one week in 10% (terconazole cream), 14% (terconazole ovules), and 26% (candid ovules) respectively. At the end of one month, these figures were 14.8%, 14%, and 20% (candid ovules) respectively. At the end of one month, these figures were 14.8%, 37% and 35% respectively. These figures indicate that terconazole cream gives the best long term results and the terconazole / clotrimazole ovules are largely comparable in their efficacy. The above data also confirms that clinical cure rates and the mycological cure rates differ in the patients to a considerable extent.

Clinical response of the distressing symptoms to therapy and the progressive changes in Symptomatology :

It is important to realise that clinical improvement and mycological cures do not always go hand in hand. Often the treatment helps in reducing the mycological load, the fungi lie dormant, the patient becomes asymptomatic and appears to be clinically cured, however in due course of time recurrance takes place either due to reactivation of the dormant organisms under more favourable circumstances, or as a result of reinfection from the male partner or another source which the patient may be harbouring which has been left unattended to. The gut is often the source from which reinfection occurs. Many clinicians have recognized the importance of treating the male partners simultaneously, and also treating both the partners with oral antifungal drugs concommitantly to eliminate other potential sources of fungi which could favour occurance of reinfections.

Progress analysis of the severely affected patients. This is detailed in table 6 shown below.

Table 6 : Change in the incidence of severe distressing symptoms under treatment.

Distribution of incidences of severe distressing symptoms with the passage of time

Drug Regime & Complaint.	Initial	After 1 - week	After 1-month	After 3-months
Pruritus Vulvae.				
Moderate - Severe				
1. Terconazole Cream	33/50 - 66%	3/50-6%	4/47 - 8.5% (P<0.05)	3/27 - 11.1%(N.S)
2. Terconazole ovules	40/50-80%	1/50-2%	2/45 - 4.4% (P<0.01)	4/35-11.4% (N.S)
3. Clotrimazole ovule	46/50-92%	12/50-24%	3/40-32.5%	5/21 -28.8%
Profuse Leucorrhoea				
1. Terconazole cream	21/50 - 42%	2/50 - 4%	2/47 - 4.2% (N.S)	nil
2. Terconazole ovules	42/50-84%	nil	nil	5/35 - 14.2% (N.S)
3. Clotrimazole ovule	17/50 - 34%	5/50 - 10%	5/40 - 15%	2/21 - 9.5%
Dysuria				
1. Terconazole cream	10/50 -20%	1/50 - 2%	2/47 - 4.2% (N.S)	nil
2. Terconazole ovules	4/50-8%	nil	nil	1/35 - 2.8% (N.S)
3. Clotrimazole ovule	12/50-24%	5/50-10%	4/40-10%	2/21-9.5%
Vulvovaginitis				
1. Terconazole cream	12/50-24%	2/50-4%	3/47-6.3%(N.S)	2/27-7.4% (N.S)
2. Terconazole ovules	30/50 - 60%	2/50 - 4%	2/45-4.4% (N.S)	4/35 - 11.4% (N.S)
3. Clotrimazole ovule	13/50 - 26%	3/50 - 4%	6/40 - 15%	3/21 - 14.2%

The above table shows that all the antifungal medicaments have been effective in controlling the distressing symptoms attributed to vulvovaginal candidiasis. The immediate response to the treatment was satisfactory at the time of the first follow-up visit after one week. However the recurrance of symptoms was evident in all three groups of patients, The improvement in the cardinal symptom of vulval pruritus was more sustained in women treated with terconazole cream/ovules, and was significantly better than with clotrimazole ovules. The recurrance rates continued to rise with the passage of time. However the overall results were better with terconazole cream / ovules as compared to the clotrimazole ovules.

Of the three groups of 50 patients of proven vulvovaginal candidiasis included in the study, Pruritus vulva was the cardinal symptom. It was moderate to severe in intensity accounting for 66% (terconazole cream), 80% (terconazole ovules) and 92% (clotrimazole ovules) in the three groups studied. After commemcement of therapy, the incidence of vulval pruritus dropped to 6%, 4% and 24% respectively in the three groups studied at the end of the first week after commencement of the treatment. At the end of one month, some of the earlier cases had a recurrance, so that the numbers complaining of vulval pruritus at the end of one month was 8.5%, 4.4%, and 32.5% in the three groups studied. At the end of 3 months the follow-up cases revealed that pruritus was present in 11.1%, 11.4%, and 23.8% of cases in the three groups respectively. However since many of the symptomatic cases had insisted on taking some other medicaments, and hence were required to be excluded from the study, or had been lost to follow-up. The number of cases available for the final evaluation of the long-term drug response became limited. These figures however still continue to be statistically significant (Chi-square values), and en-

couraging enough to recommend for widespread clinical application. The figures for all the other complaints though statistically not significant, do however reflect that recurrance of the disease is common. Unless the male partner is also concommitantly treated and the intestinal pool of the candidal organisms which is often responsible for re-infection is effectively eradicated, the incidence of recurrance is bound to be high.

Discussion :

Vulvo-vaginal candidiasis is a very common affliction in women, The condition can be suspected quite easily during clinical examination. A KOH treated preparation helps to establish the mycological condition satisfactorily in many cases and the test is recommended for office practice, however, the demonstration of candida at culture examination is far more accurate in establishing the diagnosis in the less evident cases.

Terconazole is a triazole derivative and metabolically more stable than clotrimazole which is an imidazole compound. Both compounds bind with the intracellular cytochrome P-450 involved in the ergosterol synthesis within the fungal cell and also it exerts a lipophilic property, a combination of these actions renders terconazole a superior antifungal molecule with a higher affinity and efficacy at low concentrations. (Cowenbergh 1986). Terconazole is effective against a large number of candidal species, particularly when they are growing in their mycelial form. In comparative studies with other antimycotic agents including miconazole nitrate and clotrimazole, the superior potency of terconazole has been well established. Also subpassage of fungal strains through increasing levels of terconazole had little effect on the minimal inhibitory concentration (MIC). Thus there appears to be little risk of development of resistance to terconazole with repeated exposure to the drug. In vitro studies have also established that terconazole has no activity against bacterial isolates from normal vginal flora including the lactobacilli. (Cutsem van J. et al 1983). In a Comparative study of antifungal agents, Willemsens G. et al (1981) established the superiority of the anticandidal activity of terconazole over many other antifungal agents. Singh V.P. et al (1994) compared the efficacy of 0.8% terconazole cream and 100 mg clotrimazole vaginal ovules in two groups of 50 women each and concluded that terconazole cream appeared to be a more potent and better tolerated antifungal agent in the treatment of vaginal candidiasis.

Our studies have also revealed the superiority of terconazole over clotrimazole as an antifungal drug in the management of vulvo-vaginal candidiasis, and indicates that terconazole cream possibly has a therapeutic edge in its efficiency over the terconazole ovule, however, both forms of medicaments must be made available to suit the individual preferances of the patients.

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