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KEYWORDS: Terbinafine, Griseofulvin, Tinea corporis

A COMPARATIVE STUDY ON SAFETY OF TERBINAFINE AND GRISEOFULVIN IN PATIENTS WITH TINEA CORPORIS

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ABSTRACT

BACKGROUND:

The treatment of dermatophytosis usually involves the use of topical or oral antifungal agents. Due to poor compliance of our patients, they may not adhere to prolonged oral medication. They should receive oral antifungal agents which are more safer with a short course of therapy

AIM AND OBJECTIVES:

To compare the safety of Terbinafine and Griseofulvin in patients with Tinea Corporis in a Tertiary care Hospital, Madurai

MATERIALS AND METHODS:

About 60 patients are selected from the OPD of Dermatology according to inclusion & exclusion criterias. They were divided into 2 groups of 30 patients each. Group 1 received Tab. Terbinafine 250mg OD and group 2 received 250mg BD for 4 weeks. All patients were investigated at baseline, end of 2nd week and at end of 4 weeks. Safety profile was assessed by occurrence of adverse drug effects. The results were recorded, tabulated and analysed using student's t test.

RESULTS:

In our study, Griseofulvin treated patients have experienced more adverse effects such as headache 66.6%, vomiting 20%, peripheral neuritis13.3%, photosensitivity 16.6% heartburns 23.3%, and rashes 6.6%,vomiting 10%, heartburns13.3%. Terbinafine is found to be superior to griseofulvin in our study.

CONCLUSION:

Oral Terbinafine is the safest antifungal agent in the treatment of extensive tinea corporis infection when compared to griseofulvin.

Introduction

Fungi are a large and diverse group of organisms.[1] These organisms may coexist with humans as commensals without causing any overt risks to health. About 200,000 known species of fungi available of which only 400 fungi cause disease in animals and even fewer cause significant human disease.[2] One of the causative factors has been the widespread use of broadspectrum antibiotics in critically ill patients and inadvertent use of antibiotics.[3].The non-pathogenic bacterial populations that normally compete with fungi are eliminated or decreased by these antibiotics. Other causes are the most frequent use of immunosuppresants after organ transplantations or the widespread use of cancerchemotherapy agents. As a result, there is an increased prevalence of opportunistic infections.

Superficial mycoses are the infections of the skin and mucosal surface and these can be split into superficial and cutaneous mycoses. It includes dermatophytosis and candidiasis. Dermatophytosis involves the infections of the skin, hair and nails.Various types of 'tinea' infections are caused by Trichophyton, Microsporum orEpidermophyton.[4]Those affecting the scalp is called as tinea capitis and those involving - the body is known as corporis and tinea cruris which affects the groin.Tinea corporis is defined as dermatophytosis of the glabrous skin with the exclusion of the palms, soles and groins[5]The predisposing factors are poor personal hygiene, poor nutrition, and debilitating systemic diseases like diabetes, leukemia, andother endocrine disorders. Tinea corporis has a worldwide distribution, but a higher prevalence is reported from tropical and subtropical areas. The prevalence of tinea corporis is high (41%) among all fungal infections in Southern region of Tamil Nadu.[6]

The treatment of dermatophytosis usually involves the use of one of several well tried topical preparations. . Mild and isolated lesions may respond to topical antifungal agents. When the lesion is widespread or extensive, along with topical anti fungal preparations, systemic therapy can be used.[7]Since 1956, Amphotericin B was the only efficacious antifungal drug available for systemic use for many years. Though it was highly effective in many serious infections, it is toxic. Then, griseofulvin which was first isolated from Penicillium griseofulvum, in 1939 by Oxford and colleague came to the market, but its efficacy as an oral antifungal agent was first shown in 1958. It is largely restricted to dermatophyte infections[7]. The formation of intracellular microtubules is inhibited by griseofulvin and is fungistatic.[8]When compared with other newer antifungal agents,the relapse frequency is higher with griseofulvin. Thus the relatively non-toxic azole drugs and the echinocandins were introducted and they have revolutionized pharmacotherapy of fungal infection in the last several decades. They provide more targeted, less toxic therapy than older agents.

Newer antifungal agent such as Terbinafine is an allylamine derivative and was developed by chemical modification of naftifine.It is highly lipophilic and keratinophilic[9]. It is effective against dermatophytes but less effective in candida species. It acts by inhibiting Squalene epoxidase, an enzyme in the formation of fungal cell membrane which leads to fungal cell death[10] (fungicidal).Both topical and oral forms are available for therapeutic purpose.

In general, due to poor compliance of our patients, they may not adhere to prolonged oral medication. They should receive oral antifungal agents which are more safer with a short course of therapy. Hence, this study is undertaken to compare the safety of Terbinafine and Griseofulvin in patients with tinea corporisin the Tertiary Care Hospital, Madurai.

AIM AND OBJECTIVES

.To compare the safety of terbinafine and griseofulvin in tinea

corporis patients in tertiary care hospital, Madurai.

MATERIALS AND METHOD

STUDY CENTRE

Institute of Pharmacology, Madurai Medical College, Madurai. Department of Dermatology, Government Rajaji Hospital Madurai

COLLABORATING DEPARTMENTS

Department of Bio Chemistry, Madurai Medical College, Madurai. Institute of Microbiology, Madurai Medical College, Madurai.

STUDY DESIGN:

An open label Single center Prospective Comparative Clinical study

STUDY PERIOD:

This study was conducted for a period of one year.

SAMPLE SIZE:

Total: 60 patients
Group I (30 patients) : Oral Tab.Terbinafine 250mg/day for 4 week.
Group II (30 patients) : Oral Tab. Griseofulvin 10mg/kg/ day for 4 weeks

ETHICAL APPROVAL

Ethical clearance was obtained from the Institutional ethical committee, Government Rajaji Hospital, Madurai.

INFORMED CONSENT

Written informed consent both in Tamil and English were obtained from all the patients. They were personally explained, dated and signed in duplicate by both patient and the investigator.

SELECTION OF THE STUDY GROUP

Patients with Tinea corporis infection attending the Outpatient Department of Dermatology, Government Rajaji Hospital were selected for the study according to the inclusion and exclusion criteria

INCLUSION CRITERIA:

Age: From 18 to 45 years.
Sex: Both male and female

- New patients with fungal infection involving body region (>10cm in size)
- Patients with potassium hydroxide preparation positive for fungal elements on direct microscopy.

EXCLUSION CRITERIA:

- Patients with negative KOH preparation for fungal elements.
- Patients treated with topical antifungal agents within past 2 weeks.
- Patients treated with systemic antifungal agents within past 30 days.
- Patients with elevated liver enzymes and H/O active liver disease.
- Patients with Diabetes mellitus, HIV/AIDS
- Patients on immunosuppressant drugs
- Patients taking oral corticosteroids
- Pregnant and lactating women,Children.
- Patients with history of hypersensitivity to any other drugs.
- Patients who are lost for follow up

DISCONTINUATION CRITERIA

Patients were permitted to discontinue from the study, once they were decided to do so. Patients when found to develop other illness or worsening of existing illness or with non-compliance of the drugs were excluded from the study.

WORKUP BEFORE THERAPY

After selecting the patient, a detailed clinical record was prepared including age, sex, address, occupation, family history, duration of the disease, size and extent of lesion, history of pervious drug intake. An inquiry about associated co morbidities like Diabetes Mellitus HIV/AIDS, Malignancies, and Immunosuppressive therapy were recorded.

Then all the patients were subjected for local and systemic examinations in detail. After that, all patients were tested for necessary investigations which include Complete Hemogram, Liver function test, Renal function test and Fungal test – KOH mount. Diagnosis was based on clinical features, KOH preparation on direct microscopy, and culture on Sabouraud's agar.

METHODOLOGY

After obtaining informed consent in oral and written format, about sixty patients attending the Outpatient Department of Dermatology, Govt. Rajaji Hospital, Madurai, were selected as per the inclusion and exclusion criteria mentioned above. They were allocated into two groups of thirty each. The two groups were compared and evaluated are as follows:

GROUP 1: 30 patients in this group were treated with tablet terbinafine at a dose of 250mg/day at morning time after breakfast for 4 weeks

GROUP 2 : 30 patients in this group were given tablet griseofulvin at a dose of 500mg/day in two divided doses after meals for 4 weeks.

FOLLOW UP AND EVALUATION

Patients were followed at the end of every week
The safety of the drugs was also assessed by means of any adverse effects. Patients were examined clinically and inquired about any side effects like. Blood samples drawn for haematological and biochemical profile at baseline and at the end of 2nd and 4th weeks

a. Headache
b. Nausea, vomiting
c. Diarrhoea
d. Heartburns
e. Flatulence
f. Dry mouth
g. Peripheral neuritis
h. Fatigue & mental confusion
i. Syncope
j. Blurred vision
k. Photosensitivity
l. Erythema / rash
m. Augmentation of effects of alcohol

If any patient found to have adverse effect, he/she will be excluded from the study. The results were tabulated and analyzed statistically.

Statistical Method:

All the data were recorded and tabulated and statistics was proceeded with student's t
test. The information collected regarding all the selected cases were recorded. Data analysis was done with the help of computer by using SPSS software and Sigma Stat 3.5 version . Using this software, percentage, mean, standard deviation and 'p' value were calculated through Student's't' test for all the parameters . P value of < 0.05 was taken as significant

RESULTS & DISCUSSION

Superficial fungal infections caused by dermatophytes are clinically classified on the basis of the location of the lesions on the body. In tropical and sub-tropical countries including India, tinea infection is one of the important public health problem where the growth of fungi is promoted by heat and moisture[9] skin infections such as tinea corporis are predominantly seen in middle age patients.

Health education to create awareness is one of the essential tool in the prevention of dermatophytosis. If they are affected with such infection, they should promptly be treated with appropriate

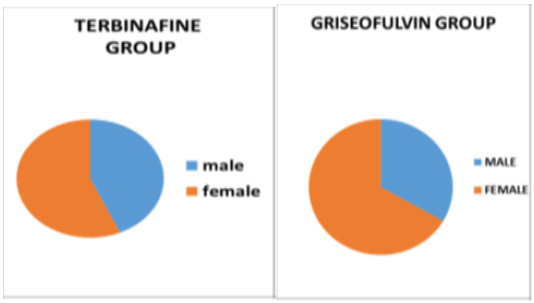
therapy either topical or systemic, depending upon the extension of the lesion.Employing proper and timely treatment will help to cut the chain of spread and thereby reduce the burden of the disease.

Oral griseofulvin and ketoconazole have been used to treat extensive lesions for many years. But due to the development of side effects like hepatotoxicity and androgen abnormalities the use of ketoconazole is restricted nowadays. The first orally active, systemic antifungal agent used in the treatment of dermatophytosis was Griseofulvin. It is fungistatic and bioavailability of griseofulvin is poor. It should be taken with high-fat meals and as ultrafine crystalline preparations to enhance adequate absorption from the gastrointestinal tract. Griseofulvin induces hepatic cytochrome P450 activity. The rate of metabolism of a number of drugs are increased by griseofulvin. In chronic alcoholics, griseofulvin potentiates the intoxicating effects of alcohol. Relapses are more common . Multiple doses should be taken daily. The most common adverse effect encountered is intolerable headache Eventhough tolerance develops to this adverse effect, many patients will not accept the fact and they will skip over to some other drugs. Abnormal blood parameters such as transient leucopenia especially neutropenia will be seen in some of the patients. So, the overall compliance of the patient will be less.

Terbinafine is a fungicidal agent active against most of the dermatophytes. Single daily dose of 250 mg for 2 – 4 weeks is highly curative and obtained high compliance among all the patients when compared with multiple doses of griseofulvin. Food does not cause any change in absorption. Apart from gastrointestinal tract disturbances there is no serious adverse effects commonly encountered with terbinafine. The relapse / recurrence are very much minimal with this drug when compared with other agents. There are no serious drug interactions.

Our present study has observed that out of 60 patients diagnosed for dermatophytosis, 23(38.3%) were male and 37(61.6%) were female with M: F ratio of 0.62: 1. (figure 1)We have also observed that 88 % of tinea corporis occurred during the age of 26 to 45.

Figure 1
Gender Distribution among Terbinafine and Griseofulvin Groups



In our present study, the most common causative organism isolated after culture report was T. rubrum, 34 cases (56.6%) followed by T. mentagrophyte, 14cases (23.3 %) T. tonsurans, 8 cases (13.3 %), M.canis, 4 cases (6.6 %) and. In a study conducted by Venkatesan et al, the major causative organism isolated was T. rubrum (69.6%), followed by T. mentagrophyte (28.2%) and M.gypseum (2.2%) from tinea corporis patients.12

On analysing the biochemical parameters of patients in both the groups, there are no abnormality seen in renal as well as liver function tests. There are slight variations in the complete haemogram as seen in patients of Group 2 which is shown as decrease in the haemoglobin level, total leucocyte count and neutropenia.(Table 1 to 6)

Table No: 1
Distribution of mean Hb values among Terbinafine andGriseofulvin Groups

	GROUP 1		GROUP 2			
	Mean	SD	Mean	SD	p value	significance
Baseline	12.277	1.617	12.387	1.226	0.437	Not significant
2nd week after treatment	12.453	1.523	11.85	1.083	0.005	Significant
4th week after treatment	12.36	1.385	11.033	1.254	<0.001	Significant

Table No: 2
Distribution of mean Total WBC Count values amongTerbinafine and Griseofulvin Groups

	GROUP 1		GROUP 2			
	Mean	SD	Mean	SD	p value	significance
Baseline	7073.333	1768.095	6953.333	1467.753	0.449	Not significant
2nd week after treatment	7143.333	1769.216	6026.667	1238.724	<0.001	Significant
4th week after treatment	7263.333	1798.176	5876.667	1220.707	<0.001	Significant

Table No: 3
Distribution of mean polymorph Count values among Terbinafine and Griseofulvin Groups

	GROUP 1		GROUP 2			
	Mean	SD	Mean	SD	p value	significance
Baseline	53.633	8.52	52.867	6.383	0.449	Not significant
2nd week after treatment	53.333	7.716	47.4	6.891	0.003	Significant
4th week after treatment	53.467	8.245	41.667	6.666	<0.001	Significant

Table No: 4
Distribution of mean Urea values among Terbinafine and Griseofulvin Groups

	GROUP 1		GROUP 2			
	Mean	SD	Mean	SD	p value	significance
Baseline	20.067	5.078	21.833	5.187	0.188	Not significant
2nd week after treatment	20.4	3.276	21.533	2.623	0.144	Not Significant
4th week after treatment	20.5	2.739	21.267	2.164	0.234	Not Significant

Table No: 5
Distribution of mean Serum creatinine values among Terbinafine and Griseofulvin Groups

	GROUP 1		GROUP 2			
	Mean	SD	Mean	SD	p value	significance
Baseline	0.863	0.133	0.827	0.174	0.362	Not significant
2nd week after treatment	0.747	0.157	0.727	0.202	0.67	Not Significant
4th week after treatment	0.863	0.133	0.73	0.256	0.064	Not Significant

Table No: 6

Distribution of mean Serum Alkaline Phosphatase values among Terbinafine and Griseofulvin Groups

	GROUP 1		GROUP 2			
	Mean	SD	Mean	SD	p value	significance
Baseline	52.367	12.45	56.533	15.145	0.249	Not Significant
2nd week after treatment	52.267	10.385	55.1	12.675	0.348	Not Significant
4th week after treatment	51.933	10.661	56.7	12.943	0.125	Not Significant

Figure No: 2

Distribution of mean SGOT, SGPT values among Terbinafine(group1) and Griseofulvin (group2)

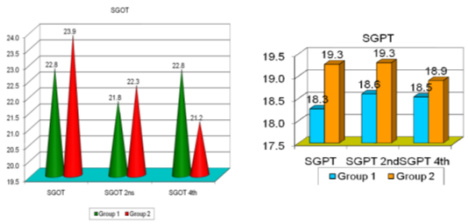


Table No: 7

Distribution of Adverse Drug Reactions among Terbinafine and Griseofulvin Groups

Adverse Drug Reactions	Terbinafine group 1	Griseofulvin group 2
Head ache	0	20
Vomiting	3	6
Diarrhoea	0	0
Heart burns	4	7
Flatulence	0	0
Dry mouth	0	0
Peripheral neuritis	0	4
Fatigue and mental confusion	0	0
Syncope	0	0
Blurred vision	0	0
Photosensitivity	0	5
Erythema/rash	0	2

Terbinafine is reported to be superior to griseofulvin in several studies.In our study, griseofulvin treated patients have experienced more adverse effects such as headache 66.6%, vomiting 20%, peripheral neuritis13.3%, photosensitivity16.6% heartburns 23.3%, and rashes 6.6%. Apart from gastro intestinal disturbances such as vomiting 10%, heartburns13.3%, no other serious adverse effects occurred in terbinafine group of patients.(Table 8)

Terbinafine is most commonly used in the treatment of dermatophytosis now-adays. It requires shorter duration of therapy with better tolerability, and is more effective than griseofulvin. Patient's compliance is also good with terbinafine due to a short duration of therapy such as 2 to 4 weeks. 7This is very much useful in the management of chronic and recurrent infections and also in source reduction on community basis.

Hence, from this study we can infer that terbinafine seems to be more safer than griseofulvin

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