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Original Research Article

The Outcome of Systemic Administration of Itraconazole, Fluconazole and Terbinafine in Different Groups of Patients Treated for Skin Infection: A Randomised Control Study

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Abstract

Aim: The aim of the present study to compare the outcome of systemic administration of itraconazole, fluconazole and terbinafine in different groups of patients treated for skin infection.

Methods: A randomised control study was conducted in the Department of Pharmacology, ICARE Institute of Medical Sciences and Research & Dr. Bidhan Chandra Roy, Hospital, Haldia, West Bengal, India, for 24 months. A total of 300 patients were selected for the study. 3 groups were made (group A, group B, group C) under which each 100 patients were assigned. All consenting patients with different types of superficial fungal infections like tinea corporis, tinea cruris, tinea pedis, tinea barbae, tinea manuum, tinea faciei were included in the study. Only those patients who were diagnosed de novo for superficial fungal infections were considered for the study. Itraconazole 100 mg od for 14 days was given for group A, terbinafine 250 mg od for 14 days was administered to the group B, fluconazole 150 mg was given once in every 3 days for 6 weeks. All patients in group A and group B were asked to come back for follow up after 15 days, group C patients were asked to come after 6 weeks.

Results: The response to treatment was found statistically significant ($p<0.05$) with various antifungal molecules. Response to itraconazole and terbinafine was good in majority of patients (72% and 42% respectively) while it was poor in 15% of the patients for fluconazole. the clinical response observed with various antifungal molecules. Peripheral spread was present in 19% cases with itraconazole, while it was present in 60% and 70% with terbinafine and fluconazole, respectively. The distribution of peripheral spread was statistically significant ($p<0.05$) with various antifungal molecules. Increased erythema was present in 12%, 61% and 82% of the cases with itraconazole, terbinafine and fluconazole respectively. Similarly, increased scaling was present in 22%, 38% and 77% of the cases with itraconazole, terbinafine and fluconazole, respectively. Spread to other body sites was present in 30%, 52% and 77% of the cases with itraconazole, terbinafine and fluconazole, respectively. Chi Square test was 63.68; $p<0.001$, therefore it was highly significant

Conclusion: Itraconazole was the most superior antifungal drug in terms of clinical remission. This was closely followed by terbinafine in terms of drug being effective in superficial fungal infection patients.

Keywords: antifungal drug, itraconazole, terbinafine, fluconazole

Introduction

Dermatophytic infections are the most common fungal infections affecting 20%–25% population globally[1]. The hot and humid climate in India favors dermatophytosis[2]. Terbinafine is considered to be a first-line drug for the treatment of tinea corporis and tinea cruris due to its favorable mycological and pharmacokinetic profile[3]. It acts by inhibiting the enzyme squalene epoxidase, thereby inhibiting ergosterol synthesis[4]. In the past, the drug was consistently effective against dermatophytosis with cure rates of >90% achieved at doses of 250 mg once a day for 2 weeks[3,4]

Recently, there has been an increase in the incidence of terbinafine resistance with increasing numbers of clinical failures and relapses[5,6]. One of the principal mechanisms of antifungal resistance is a decrease in effective drug concentration[7]. Terbinafine was reported to be efficacious and safe in dermatophytosis with fewer failure rates at higher doses of 500 mg/day[8]. Itraconazole is another antifungal drug which acts by inhibiting cytochrome P450-dependent enzyme, hence interfering with demethylation of lanosterol to ergosterol. It has shown good results in the treatment of dermatophytosis at doses of 100 mg once a day for 2 weeks and with 200 mg once a day for 7 days[9,10]. Because of frequent relapses at short intervals, some physicians have used it in doses of 200 mg once a day for prolonged periods[11]. It has been observed recently that there has been widespread resistance to various antifungal agents used in conventional dose with an increase in relapse rates prompting a need to find an effective first-line antifungal drug and appropriate dosage and duration schedule to achieve maximum results with fewer relapses.

This study was done to compare the outcome of systemic administration of itraconazole, fluconazole and terbinafine in different groups of patients treated for superficial fungal infections under close clinical examination at regular follow up intervals and to find out the most effective drug in terms of clinical remission and absence of relapse.

Materials and Methods

A randomised control study was conducted in the Department of Pharmacology, ICARE Institute of Medical Sciences and Research & Dr. Bidhan Chandra Roy, Hospital, Haldia, West Bengal, India, for 24 months. after taking the approval of the protocol review committee and institutional ethics committee.

Methodology

A total of 300 patients were selected for the study. 3 groups were made (group A, group B, group C) under which each 100 patients were assigned. All consenting patients with different types of superficial fungal infections like tinea corporis, tinea cruris, tinea pedis, tinea barbae, tinea manuum, tinea faciei were included in the study. Only those patients who were diagnosed de novo for superficial fungal infections were considered for the study. Patients in the age group of 18 to 62 years were included in the study. The pregnant and lactating women, patients with underlying immunosuppression, patients unwilling for a regular follow up, patients with relapse and

recurrent cases of tinea infections were excluded from this study.

Investigations

All the patients were mainly diagnosed based on clinical examination. But for confirmation scales from the lesions were examined using 10% KOH (potassium hydroxide) under a microscope. Presence of hyphae and fungal spores was considered as confirmation of the diagnosis of dermatophytic infection.

Itraconazole 100 mg od for 14 days was given for group A, terbinafine 250 mg od for 14 days was administered to the group B, fluconazole 150 mg was given once in every 3 days for 6 weeks. All patients in group A and group B were asked to come back for follow up after 15 days, group C patients were asked to come after 6 weeks.

Along with oral antifungals patients were also given various topical cream and ointment formulations like luliconazole, amrolfine, ketoconazole. Dusting powder was prescribed especially to the patients with lesions in intertriginous areas. For symptomatic treatment antihistamines were given.

Statistical Analysis

Chi-square ($\chi 2$) test was used for association between two categorical variables. If the p-value was <0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analyzed using SPSS software v.21 (IBM statistics, Chicago, USA) and Microsoft office 2007. All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean ±standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation.

Results

Good response indicated complete resolution of lesions. Moderate response meant partially resolved lesions with persistence of scaly, erythematous, itchy patches. Poor response indicated no improvement in the lesions.

Table 1 shows the association between response to treatment with various antifungal molecules. The response to treatment was found statistically significant ($p<0.05$) with various antifungal molecules. Response to itraconazole and terbinafine was good in majority of patients (72% and 42% respectively) while it was poor in 15% of the patients for fluconazole.

In the group A patients 1.5:1 ratio for males to females was seen, while in group B a ratio of 1.22:1 was found. Patients in group C were found to have a ratio of 2.33:1. We observed that there was a slight predominance of male patients over female patients who visited the outpatient department for consultation. Hence the total ratio was 1.4:1.

Table 3 shows the clinical response observed with various antifungal molecules. Peripheral spread was present in 19% cases with itraconazole, while it was present in 60% and 70% with terbinafine and fluconazole, respectively. The distribution of peripheral spread was statistically significant ($p<0.05$) with various antifungal molecules. The variation in the proportions of other clinical responses like erythema, scaling and spread to other body sites was also found to be statistically significant with various antifungal molecules. Increased erythema was present in 12%, 61% and 82% of the cases with itraconazole, terbinafine and fluconazole respectively. Similarly, increased scaling was present in 22%, 38% and 77% of the cases with itraconazole, terbinafine and fluconazole, respectively. Spread to other body sites was present in 30%, 52% and 77%

of the cases with itraconazole, terbinafine and fluconazole, respectively.

Most of the patients who responded very well to the drug had a residual post inflammatory hyperpigmentation atthe end of the study of 2 weeks

Table 1: Response to treatment with various antifungal molecules

Drug	**Good N (%)**	**Moderate N (%)**	**Poor N (%)**	**Total**
Itraconazole	72 (72)	16 (16)	12 (12)	100
Terbinafine	42 (42)	26 (26)	32 (32)	100
Fluconazole	15 (15)	30 (30)	55 (55)	100

Table 2: Ratio of male and female patients enrolled for the study

Drugs	**Male**	**Female**	**Ratio**
Itraconazole	60	40	1.5:1
Terbinafine	45	55	1.22:1
Fluconazole	70	30	2.33:1
Total	175	125	1.4:1

Table 3: Clinical response observed.

Parameter		**Itraconazole N (%)**	**Terbinafine N (%)**	**Fluconazole N (%)**	Chi-**square**	P-value
Peripheral spread	Present	19 (19)	60 (60)	70 (70)	63.68	p<0.001
	Absent	81 (81)	40 (40)	30 (30)		
Erythema	Increased	12 (12)	61 (61)	82 (82)	87.69	p<0.001
	Decreased	88 (88)	39 (39)	18 (18)		
Scaling	Increased	22 (22)	38 (38)	77(77)	61.78	p<0.001
	Decreased	78 (78)	62 (62)	23 (23)		
Spread to other Body sites	Present	30 (30)	52 (52)	77(77)	29.39	p<0.001
	Absent	70 (70)	48 (48)	23 (23)		

Discussion

Tinea infections are superficial fungal infections caused by three species of fungi: Trichophyton, Microsporum and Epidermophyton, collectively known as dermatophytes. Commonly these infections are named for thebody part affected including tinea corporis (general skin), tinea cruris (groin) and tinea pedis (feet). Tinea capitis refers to a dermatophyte infection of the head, tinea barbae affects the beard area, tinea manuum is limited to the hands and tinea unguium infects the nails. These names do not distinguish between species (for example, tinea capitis may be caused by Trichophyton or Microsporum genera)[12].

If the tinea lesions are smaller in size and limited to a very small body surface area, usually topical therapy alone is advised. Though there are no fixed consensus regarding this. Systemic therapy is normally required when the infected areas are large, macerated with a secondary infection, or in immunocompromised individuals[13]. Tinea infections that remain untreated can cause significant morbidity and predispose to

complications including cellulitis and ulcers on the feet and alopecia on the scalp, hence the pressing need for a systemically highly effective drug[14].

This is an oral synthetic dioxolanetriazole 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. Absorption from the gastrointestinal tract is improved if the drug is given with food or under acidic conditions. Itraconazole is generally well tolerated with minor adverse effects of nausea, headache and abdominal pain being reported in a few patients. Itraconazole concentrations are reduced following concomitant administration of phenytoin, rifampicin, antacids and H2 antagonists. Itraconazole can cause gastric upset, headache, taste alteration and jaundice. Rarely, it can cause hypokalemia, torsade's de pointes and heart failure. De-doncker et al pointed out that increasing resistance

against terbinafine has led them to consider oral itraconazole currently as an important drug for treatment of such widespread dermatophytosis[15].

This is an oral or topical synthetic allylamine compound that inhibits the action of squalene epoxidase, a crucial enzyme in the formation of ergosterol, leading to membrane disruption and cell death. The drug is well absorbed and is strongly lipophilic, being concentrated in the dermis, epidermis and adipose tissue. Terbinafine is metabolised by the liver and the inactive metabolites are excreted in the urine. The most common side effects with terbinafine are gastric upset, headache, altered taste, altered liver function tests and rash. Rarely, it can cause blood dyscrasias and hepatitis[16].

Fluconazole is an oral synthetic bistriazole compound that functions in much the same way as itraconazole. Absorption of fluconazole is not dependent on acid conditions and is also unaffected by food intake. Minor adverse effects such as nausea and vomiting occurring ina few patients[17]

A 2017 Cochrane review showed that terbinafine is superior to fluconazole and itraconazole for both clinical and mycological cure of onychomycosis[14]. Randomized clinical trials by Elly J W et al found that newer agents such as terbinafine and fluconazole have equal effectiveness and safety and shorter treatment courses. Oral terbinafine is first line therapy for tinea capitis and onychomycosis because of its tolerability, high cure rate, and low cost[18]. In a study by Sahoo et al they claim that both terbinafine (250-500 mg/day for 2–6 weeks) and itraconazole (100- 200 mg/day for 2–4 weeks) appear to be effective, but they remain dubious about appropriate dose and duration of administration of a single drug which can produce mycologic cure and prevent recurrence[19].

Trial by Bhatia et al revealed similar results like our study. Itraconazole has higher clinical and mycological cure rates as compared to terbinafine. Although the cost of terbinafine is lower, the failure rate is higher and the duration of treatment required is longer. Therefore, itraconazole seems to be superior to terbinafine in the treatment of tinea corporis and tinea cruris[16].

In contrast to our study Wing field et al found significant remission in the terbinafine and griseofulvin groups, lasting up to 8 weeks after cessation of therapy. Whereas fluconazole group experienced no significant remission and remission was of short duration in the itraconazole group[20].

Observations similar to our study were made in Nepal by Shakya et al which showed that itraconazole has high cure rate and less failure

rate without side effects in comparision to terbinafine[21].

Also, in contrast to our study where we found itraconazole to be most efficacious drug, a study by Sultana et al in Bangladesh found more number of patients to be resistant to itraconazole, followed by fluconazole. Least drug resistance was found with terbinafine[22].

We had parallel findings with a study by Singh et al who found that itraconazole is the most effective drug, followed by fluconazole (daily), terbinafine and then griseofulvin in chronic and chronic relapsing dermatophytosis in India[23].

In a study done on a patient with long term recurrent tinea corporis by Ardeshna et al isotretinoin(20 mg/day) was combined with itraconazole (200 mg/day). This led to complete clearance of the lesions without any further relapses. Here also we can note that itraconazole was used as the last resort after using all the other orallyavailable drugs[24].

Preventive measures to keep fungal infections at bay should be adhered to by all the patients. Measures such as wearing loose, cotton garments, sharing of bed linen, towels and clothes to be avoided. Regular washing of towels and bed linen in hot water separately, followed by sun drying & ironing, taking regular showers, wearing clothes only after thoroughly drying the body, non occlusive footwear should be used. Dusting, wet mopping or vacuuming the house followed by cleaning with detergent so as to reduce the spore load in the immediate environment[25].

Conclusion

The present study concluded that itraconazole was the most superior antifungal drug interms of clinical remission. This was closely followed by terbinafine in terms of drug being effective in superficial fungal infection patients. Fluconazole was the least effective drug based on the parameters defined in our study.

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