

Original Research Article

A comparative study of efficacy of oral itraconazole, terbinafine and fluconazole: a clinical trial

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Received: 09 February 2021

Revised: 12 March 2021

Accepted: 15 March 2021

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ABSTRACT

Background: Keeping in view the rising number of cases of dermatophyte infections and also poor response to topical drugs, this study was conducted with the intention to arrive at a conclusion regarding the best available systemic drug.

Methods: A total of 270 patients were selected for the study. 90 patients were assigned to each group under itraconazole, terbinafine & fluconazole.

Results: It was found that itraconazole was the most effective drug which led to a considerable decrease in erythema, peripheral spread, scaling and spread to other body sites. Next drug to be the most effective was terbinafine, which was followed by fluconazole.

Conclusions: We finally arrived at a conclusion that itraconazole is the most effective drug for all types of superficial fungal infections. It was followed by terbinafine & fluconazole in terms of drug effectiveness. Hence in this study we advocate the use of itraconazole as first line of drug in all patients of tinea infections.

Keywords: Itraconazole, Terbinafine, Tinea

INTRODUCTION

In the recent times in our country, owing to its hot and humid tropical nature there has been a phenomenal upsurge in the cases of fungal infections leading to reconsider tinea infections being endemic in nature to our nation. Not only has the number of new cases of dermatophytosis on the rise but also a humungous number of patients are experiencing a great degree of relapses and recurrences. Making us, the dermatologists to look for causes like drug resistance, poor drug compliance, inadequate therapy and topical steroid abuse as the potential causes for such a trend. Other pre-

disposing factors for dermatophyte infections like diabetes mellitus, poor personal hygiene, immune-suppression, atopy and corticosteroid abuse should be kept in mind during treatment.

Dermatophytosis (superficial fungus infection) are the most common infective dermatoses seen globally. According to WHO the prevalence rate of superficial mycosis has been found to be 20%-25%. We conducted this trial primarily with objective of studying the efficacy of various systemic drugs and their therapeutic response in all types of dermatophytic infections. Diagnosis is usually based on history and clinical appearance plus

direct microscopy of a potassium hydroxide preparation.¹ 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.

Preventative measures of tinea infections include practicing good personal hygiene, keeping the skin dry and cool at all times and avoiding sharing towels, clothing or hair accessories with infected individuals.²

METHODS

Type of study

This study was a randomised control study. A total of 270 patients were selected for the study. 3 groups were made (group A, group B, group C) under which each 90 patients were assigned. This randomized comparative study was done over a period of 7 months from June 2020 to December 2020 at outpatient department of skin & venereal diseases, Al-Ameen medical college and hospital.

Inclusion criteria

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 60 years were included in the study.

Exclusion criteria

The excluding patients were those who were pregnant and lactating women, patients with underlying immunosuppression, patients unwilling for a regular follow up, patients with relapse and recurrent cases of tinea infections.

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 (χ^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.23 (IBM statistics, Chicago, USA) and microsoft office 2007. All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean \pm standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation.

RESULTS

Chi Square test was 65.43; $p < 0.001$, therefore it was highly significant.

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 (72.2% and 42.2% respectively) while it was poor in 16.7% of the patients for fluconazole.

In the group A patients 1.72:1 ratio for males to females was seen, while in group B a ratio of 1:1.04 was found. Patients in group C were found to have a ratio of 2.91:1. 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 1.64:1.

Table 2 shows the clinical response observed with various antifungal molecules. Peripheral spread was present in 20% cases with itraconazole, while it was present in 62.2% and 71.1% 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 13.3%, 58.9% and 81.1% of the cases with itraconazole, terbinafine and fluconazole respectively. Similarly, increased scaling was present in

21.1%, 36.7% and 76.7% of the cases with itraconazole, terbinafine and fluconazole, respectively. Spread to other body sites was present in 31.1%, 52.2% and 76.7% 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 at the end of the study of 2 weeks.

Table 1: Response to treatment with various antifungal molecules.

	Good N (%)	Moderate N (%)	Poor N (%)	Total
Itraconazole	65 (72.2)	15 (16.7)	10 (11.1)	90
Terbinafine	38 (42.2)	25 (27.8)	27 (30)	90
Fluconazole	15 (16.7)	28 (31.1)	47 (52.2)	90

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

	Male	Female	Ratio
Itraconazole	57	33	1.72:1
Terbinafine	44	46	1:1.04
Fluconazole	67	23	2.91:1
Total	168	102	1.64:1

Table 3: Clinical response observed.

		Itraconazole N (%)	Terbinafine N (%)	Fluconazole N (%)	Chi square	P value	Significance
Peripheral spread	Present	18 (20)	56 (62.2)	64 (71.1)	65.84	p<0.001	highly significant
	Absent	72 (80)	34 (37.8)	16 (28.9)			
Erythema	Increased	12 (13.3)	53 (58.9)	73 (81.1)	85.99	p<0.001	highly significant
	Decreased	78 (86.7)	37 (41.1)	17 (18.9)			
Scaling	Increased	19 (21.1)	33 (36.7)	69 (76.7)	59.78	p<0.001	highly significant
	Decreased	71 (78.9)	57 (63.3)	21 (23.3)			
Spread to other body sites	Present	28 (31.1)	47 (52.2)	69 (76.7)	30.31	p<0.001	highly significant
	Absent	52 (68.9)	43 (47.8)	21 (23.3)			

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 the body 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).¹

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.² 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.³

Itraconazole

This is an oral synthetic dioxolane 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. 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, torsades 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.⁴

Terbinafine

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.⁵

Fluconazole

Fluconazole is an oral synthetic bis-triazole 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 in a few patients.⁶

A 2017 Cochrane review showed that terbinafine is superior to fluconazole and itraconazole for both clinical and mycological cure of onychomycosis.³

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.⁷

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.⁸

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.⁵

In contrast to our study Wingfield 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.⁹

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 comparison to terbinafine.¹⁰

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.¹¹

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.¹²

In a study done on a patient with long term recurrent tinea corporis by Ardesna 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 orally available drugs.¹³

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.¹⁴

CONCLUSION

From the above study conducted, we concluded that 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. Fluconazole was the least effective drug based on the parameters defined in our study.

ACKNOWLEDGEMENTS

We would like to thank Dr. Mohd Shannawaz for all the statistical analysis.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

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Cite this article as: Koregol SC, Naik SR, Hosthota A, Koregol AC. A comparative study of efficacy of oral itraconazole, terbinafine and fluconazole: a clinical trial. *Int J Res Dermatol* 2021;7:435-9.