

## Original Article

# Pulse dose of oral itraconazole is effective in the treatment of onychomycosis

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**Abstract** *Background* Onychomycosis is a recalcitrant disease of the nails caused by dermatophytes, yeasts, and molds.

*Objective* To see the efficacy of pulse dose of oral itraconazole in the treatment of onychomycosis.

*Patients and methods* It was an open clinical trial which was carried out for a period of 2 years from March 2009 to February 2011, in the outpatient department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU) Dhaka, Bangladesh. Thirty patients with onychomycosis were recruited purposively. 30 patients of onychomycosis were treated with oral itraconazole 400 mg/day, seven days a month for three months.

*Results* Mean age of the respondents was  $36.57 \pm 14.01$  years and male to female ratio was 1:1. Among the patients, 36.7% cases had involvement of toenails and 63.3% cases had involvement of fingernails. In 6.7% cases onychomycosis was mild, 80.0% cases moderate and in 13.3% cases severe. Three months after treatment with itraconazole, improvement was found in 66.7% cases and marked improvement in 33.3%. Before treatment, culture was found positive in 30% cases and three months after treatment, culture became negative in 66.7% cases.

*Conclusions* Monthly one week cycle of oral itraconazole 400 mg daily for 3 months is effective therapeutic option for onychomycosis.

### Key words

Pulse dose, oral itraconazole, onychomycosis.

## Introduction

Onychomycosis is a chronic infection of the nail predominantly caused by anthropophilic dermatophytes and, to a lesser extent, by yeasts (*Candida* spp.), and non-dermatophyte molds. It affects 2.7% to 13% of the adult population.<sup>1,2</sup> It represents 30% of all mycotic infections of the skin.<sup>3,4</sup> Therapeutic options have been limited and the results are disappointing, especially for onychomycosis of the toenails. Successful treatment of

onychomycosis has been a challenge for dermatologists. Traditional agents like griseofulvin have a narrow spectrum, require a longer duration of therapy, and have a high relapse rate.<sup>5</sup> Ketoconazole, although much more effective, carries risk of hepatotoxicity that limits its widespread use. The agents most commonly used for the treatment of onychomycosis are fluconazole, itraconazole and terbinafine. These agents have better pharmacokinetic profiles, like prompt penetration of the nail and nail bed, persistence in the nail for months even after stopping therapy, and fewer adverse reactions.<sup>6,7,8</sup>

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The persistence of itraconazole in keratinous tissue and its fast elimination from plasma are important factors for the potential intermittent treatment of onychomycosis. Better results with higher doses but with shorter duration of therapy are explained by its pharmacokinetic properties.<sup>7</sup>

Itraconazole is a triazole antifungal, inhibiting fungal lanosterol 14 $\alpha$ -demethylase, an essential enzyme in ergosterol synthesis. Of all the oral antifungal agents, this triazole has the broadest *in vitro* spectrum of activity, which includes activity against dermatophytes, *Candida* species as well as some moulds.<sup>9</sup> It is a highly lipophilic drug with a high affinity for keratinous tissues, in which the concentration is several times greater than that obtained in plasma. Itraconazole exerts a lasting inhibitory effect, probably because of high and long-lasting levels in the epidermis.<sup>10</sup>

However, itraconazole is a costly drug, and long periods of treatment may lead to serious side-effects. Considering these issues and lack of such studies in Bangladesh we carried out this study.

### Patients and methods

It was an open clinical trial which was carried out for a period of 2 years from March, 2009 to February, 2011, in the outpatient department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU) Dhaka, Bangladesh. Purposive type of non-probability sampling technique was followed to recruit 30 patients of onychomycosis in finger- or toenails (confirmed by microscopy or culture), of both sexes,  $\geq 18$  years old who gave informed consent to be included in the study. Exclusion criteria were unwilling to participate in the study, pregnant or breast-feeding women, pre-existing renal or hepatic disease, poor-compliance to drug regimen, hypersensitivity

to imidazole derivatives and treatment with systemic and topical antifungal treatments within last 3 months and 1 month, respectively, before commencement of the study. In each patient, a complete history was taken, general physical, systemic and dermatological examination was done. Nail specimens were sent for direct microscopic examination and fungal culture.

In eligible patients, itraconazole was given 400 mg per day after meal for 7 days a month, with three monthly cycles. The clinical response to treatment was monitored by observation of infected and normal areas on the patient's target nail. Nail signs like discoloration, onycholysis, thickening of the nail plate and paronychia inflammation were assessed on a four-point scale (0, absent; 1, mild; 2, moderate; and 3, severe). At the end of the treatment period, overall assessments of efficacy and tolerability were made. The follow-up investigations were performed 3 months after the end of treatment, when the patients were re-examined both clinically and mycologically.

Adverse events were evaluated with the use of standardized questions. The following hematological and biochemical laboratory parameters were evaluated at baseline before therapy and again every month: CBC, levels of ALT, bilirubin, creatinine, uric acid, cholesterol and triglycerides.

Data were analyzed by computer with the help of SPSS 15 software package. Statistical analysis was done by using appropriate test where applicable. Statistical significance was set at 0.05 level and confidence interval at 95% level.

### Outcome measure

The overall effectiveness of the treatment was assessed on the basis of the combined clinical

and mycological outcomes. The efficacy was divided into four classes: *completely cured*, mycologically cured and free from clinical signs; *marked improvement*, mycologically cured, growth of more than 8 mm of unaffected nail and effective index more than 70%; *improvement*, mycologically cured, growth of 4-8 mm of unaffected nail and effective index more than 30%; *failure*, no mycological cure or growth of less than 4 mm of unaffected nail, effective index less than 30% or discontinuation because of adverse events. Effective index was calculated as follows:

Effective index =  $\frac{\text{sum of scores at the beginning} - \text{sum of scores at end}}{\text{sum of scores at the beginning}} \times 100$

To evaluate the mycological efficacy, two concepts were recommended: *elimination*, negative on microscopy and culture; *non-elimination*, positive on microscopy and/or culture for fungi.

Photographs of lesions and clinical assessment at baseline and follow-up visit were taken for subsequent assessment and further compare.

## Result

Mean age of the respondents was  $36.57 \pm 14.01$  years with a range of 14 to 67 years. Among them 26.7% patients were  $\leq 25$  years old, 23.3% were 25-35 years old, 23.3% were 35-45 years old, 13.3% were 45-55 years old and 13.3% were  $\geq 55$  years old. Males and females were equal, 50.0% each. On the basis of occupation, 33.3% were service holder and 33.3% were house wives, 30.0% student and 3.3% were retired person.

Among the patients, 36.7% cases had involvement of toenails and 63.3% cases had involvement of fingernails. In 6.7% cases onychomycosis was mild, 80.0% cases

moderate and in 13.3% cases severe. Onycholysis was absent in 63.3%, mild in 30.0%, moderate and severe in 3.3%. Nail thickening was absent in 26.7%, mild in 26.7%, moderate in 33.3% and severe in 13.3%.

Three months after treatment improvement was found in 66.7% cases and marked improvement in 33.3%. Before treatment culture was found positive only in 30% cases. Three months after treatment culture was found negative in 66.7% cases (**Table 1**).

No clinical, hematological or biochemical side effects were noted in any patient.

## Discussion

In our study, age of the patients was  $36.57 \pm 14.01$  years with a range of 14 to 67 years. Among them 26.7% patients were  $\leq 25$  years old, 23.3% were 25-35 years old, 23.3% were 35-45 years old, 13.3% were 45-55 years old and 13.3% were  $> 55$  years old. These findings are not similar to other studies. Several studies had shown that the prevalence of onychomycosis increases with age. In a Finnish study 200 subjects suffering from onychomycosis almost 24% aged 70 years or older.<sup>11</sup> Similarly, 28.1% of the members of the Ohio cohort aged 60 years or older had onychomycosis, versus 1.1% and 2.9% were aged 10 to 18 years and 19 to 30 years, respectively.<sup>12</sup>

Three months after treatment with itraconazole, improvement was found in 66.7% cases and marked improvement in 33.3%. Three months before treatment culture was found positive in 30% cases and negative in 70% cases. Three months after treatment culture was found negative in 66.7% cases and positive in 33.3% cases (**Table 1**).

Mishra *et al.*<sup>13</sup> conducted a randomized single-



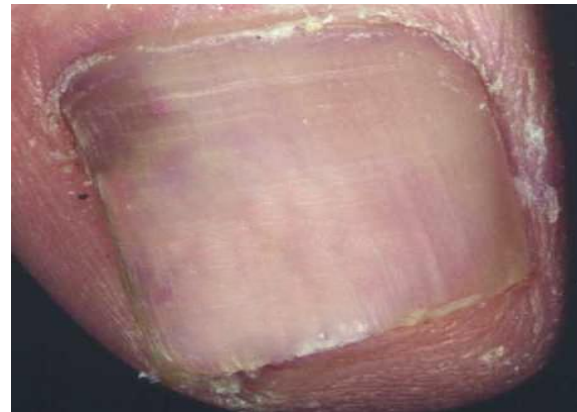
**Figure 1a** Fingernail disease before treatment.



**Figure 1b** 3 months after treatment.



**Figure 2a** Toenail onychomycosis before treatment.



**Figure 2b** Toenail after three months of treatment.

**Table 1** Distribution of the patients by mycological response.

	Before treatment N (%)	After treatment N (%)
Positive	9 (30%)	3 (33.3%)
Negative	21 (70%)	27 (66.7%)
Total	30 (100%)	30 (100%)

blind comparative study on itraconazole pulse vs. terbinafine pulse therapy in 120 patients of onychomycosis. The patients were evaluated at 4-weekly intervals till sixteen weeks and then at 24, 36 and 48 weeks. They observed a clinical cure rate of 82% and mycological cure rate of 90% in the group of patients treated with itraconazole while the group with terbinafine showed clinical and mycological cure rates of 79% and 87%, respectively. This difference was not statistically significant. They concluded that both oral itraconazole and terbinafine are effective in the treatment of onychomycosis when administered in the pulse dosage form.<sup>13</sup>

De Doncker *et al.*<sup>14</sup> used itraconazole intermittently in a dose of 400 mg daily for 1 week monthly for 2 and 3 months in the treatment of onychomycosis and reported cure rates of around 95%.

In a placebo-controlled study by Odom *et al.*<sup>15</sup> a significantly greater proportion of itraconazole-treated patients (dose of 200 mg twice daily) than placebo-treated patients achieved clinical success (77% vs 0%) after two months therapy. Yet in another study by De Backer *et al.*<sup>16</sup> 58.1% of patients were clinically totally cured or had only minimal residual symptoms after 200 mg daily itraconazole for 12 weeks. Our results are closer to this study.

Similarly, in the study by Wu *et al.*<sup>17</sup> at the end of 3-month treatment improvement was found in 23.8% cases, marked improvement in 54.8% and complete cure in 19.1% patients. Six months after treatment improvement was found in 26.2% cases, marked improvement in

40.5% and complete cure in 28.6% cases.

## Conclusion

From the findings of the study, we conclude that monthly one week cycle of oral itraconazole 400 mg daily for 3 months is effective therapeutic option for onychomycosis. Future studies should be more comparative, randomized studies with a greater number of patients to confirm the efficacy of the drug.

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