A Comparison of the Efficacy between Two Itraconazole Generic Products and the Innovative Itraconazole in the Treatment of Tinea Pedis

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Background: *Treatment of tinea pedis with conventional oral antifungal agents produces poor response rates. Itraconazole is a broad-spectrum, orally active antifungal agent with pronounced antimycotic activity. However treatment cost of itraconazole is problematical in developing countries.*
Objectives: *To study the efficacy of the 1-pulse dosing regimen of two generic products of itraconazole (Itracon® and Itra®) in comparison with the innovative product (Sporal®) for the treatment of tinea pedis.*
Material and Method: *The study was a double-blind randomized controlled trial. One hundred and thirty-three patients with tinea pedis were treated with Itracon®, Itra® or Sporal® 200 mg twice daily for 1 week. Clinical and mycological examinations were performed at baseline and at the follow-up visits (taking place at 1, 2, 4 and 12 weeks after the medication administration).*
Results: *Fifty-four, sixty-one and eighteen patients were randomized to Sporal®, Itracon® and Itra® treatment group respectively. Mycological cure rate and clinical response rates were not significantly different among the three groups. Moreover, there were also no statistically significant differences with regard to relapse rate. During treatment, no serious adverse events were recorded in any groups.*
Conclusion: *The present study demonstrated that the efficacy of the original and generic itraconazole is not significantly different in the treatment of tinea pedis by the pulse regimen.*

Keywords: *Itraconazole, T. pedis, Dermatophytes, Hendersonula*

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Tinea pedis is the most frequent dermatophytosis. Treatment of tinea pedis is variable and quite different because of the recurrence. In general, good outcomes can be obtained with some topical treatments[1,2]. The conventional oral antifungal agents usually produces poor response rates[3], however the modern antifungal agents like itraconazole and terbinafine, lead to a better result and contribute to reducing the length of treatment[4-6].

Itraconazole is a triazole antifungal agent that has a broad activity spectrum, favorable pharmacokinetic, well tolerated and associated with a safety profile. The clinical and animal infection studies have demonstrated its efficacy in a wide range of superficial fungal infections including difficult-to-treat dermatophytoses and onychomycoses. Furthermore, intermittent (pulse) treatment regimens that allow similar efficacy with lower overall drug exposure, have proven to be effective[7-11]. The original capsule formulation of itraconazole may lead to variability in absorption and the plasma concentration. For the treatment of superficial fungal infections, this is not a problem because itraconazole accumulates at the infection site, making consistently high plasma concentrations unnecessary - a characteristic that has been exploited in the development of a pulse regimen[12]. Nevertheless, the treatment cost of imported original itraconazole is still problematical in developing countries including Thailand. To help alleviate this problem, one strategy of the National Drug Policy is to promote the usage of locally made generic

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products[13]. If generic products have equivalent efficacy or better than the branded formulations, its cost advantage would be attractive for its use.

Material and Method

Study design

A randomized double-blind comparative trial of three products of itraconazole was conducted in outpatients attending the Dermatology Department, King Chulalongkorn Memorial Hospital.

Drugs

Itraconazole 100 mg capsules used in the present study were from three sources: the innovative product, Sporal® (Janssen-Cilag Thailand Ltd.), two generic products of itraconazole, Itracon® (Unison laboratories Co., Ltd.) and Itra® (Macrophar Co., Ltd.). Twenty-eight capsules of each were put into a non-transparent enclosed sachet by randomization method.

Patients

The present study included the patients that had clinical and mycological tinea pedis, without onychomycosis. They also need to stop using the topical antifungal agents 30 days and stop using the systemic antifungal agents 2 months prior to the study. Patients with contraindication conditions or chronic processes were excluded (like congestive heart failure[14], gastric and liver disorders[15], immunosuppression[16], etc.), as well as women of childbearing age, pregnant and lactating women[17]. Patients with known hypersensitivity to itraconazole or taking drugs with known interactions were also excluded[18].

Study visits and efficacy assessments

Before drug administration, the major clinical signs and symptoms were evaluated such as itching, burning, pain, erythema, scaling, maceration and fissuring. Tinea pedis was confirmed through direct examinations with potassium hydroxide (KOH) and the isolation of the causal agent in the usual Sabouraud dextrose agar and Mycosel agar (Sabouraud media + chloramphenicol & cycloheximide). Treatment consisted of the oral administration of 200 mg twice daily of Sporal®, Itracon® or Itra® for 7 days; this is equivalent to one pulse of itraconazole. Clinical and mycological exams (KOH) were also conducted at every follow-up visits that were scheduled at 1, 2, 4 and 12 weeks after medical administration. The assessment within the first 4 weeks was defined as follows:

• Complete cure: No clinical signs and symptoms and also negative KOH.

• Mycologic cure: Negative KOH but lesion is still present.

• Not cure: Clinically present as well as positive KOH.

At twelfth week, the assessment of relapse rate was done. The side effects were also evaluated. In case of a serious adverse reaction, medication would be discontinued.

Statistical analysis

The characteristic data of the patients, the culture report between the 3 groups of Itra, Itracen and Sporal respectively as well as the clinical efficacy results at four weeks and twelve weeks of the follow-up were analyzed by descriptive statistics: mean $\pm$ SD and response percentage rate. To compare the difference of means between the three groups were analyzed by analysis of variance. To compare the difference between percentage rate were analyzed by Chi-square test. A p-value of 0.05 or less was considered statistically significant.

Results

The study initially included 140 patients, 133 of them completed all the phases of the study and met all the criteria. There were 97 males and 36 females; the youngest patient was 16 years old, the oldest was 84, mean age was 42.9 years. Table 1 summarizes most of the demographic data. There were no statistically significant differences between the three groups with regard to age, sex, education, income and disease duration.

According to the clinical classification, 42 (31.6%) cases had the interdigital (intertriginous) type, 41 (30.8%) cases had the hyperkeratotic type (moccasin-type) and 35 (26.3%) had vesiculobullous type of tinea pedis; the rest of them, 15 (11.3%), had both interdigital and hyperkeratotic types. From the etiologic standpoint, *T. mentagrophytes* was the most common organism and found in 40/133 patients (30.1%) followed by *T. rubrum*, found in 28/133 patients (21.1%) (Table 2).

Table 3 shows the clinical efficacy results of all three groups. In four weeks, there was complete cure in 73 cases (54.9%), mycological cure (cure with residual lesion) in 44 cases (33.1%) and no cure in 16 cases (12.0%). The final result of the follow-up, in twelve weeks, was no cure in 14 cases (10.5%) and relapsed 13 cases (9.8%). There was no statistically significant difference between the two generic

Table 1. Characteristic of the patients in three groups

	Itra (n = 18)	Itracon (n = 61)	Sporal (n = 54)	p value
Age (yr) (mean ± SD)	46.8±19.0	41.6±14.2	43.1±15.2	0.3
Sex				
Male	13 (72.2%)	42 (68.9%)	42 (77.8%)	0.56
Female	5 (27.8%)	19 (31.2%)	12 (22.2%)	
Education				
Elementary or under	8 (44.4%)	16 (26.2%)	14 (26.0%)	0.62
High school	3 (16.7%)	15 (24.6%)	16 (29.6%)	
Vocational	0 (0%)	10 (16.4%)	8 (14.8%)	
Graduate or above	7 (38.9%)	20 (32.8%)	16 (29.6%)	
Income/family/month(Baht)				
<5000	5 (27.8%)	3 (4.9%)	5 (9.3%)	0.045
5000-10000	4 (22.2%)	7 (11.5%)	9 (16.7%)	
10001-20000	2 (11.1%)	14 (23.0%)	18 (33.3%)	
>20000	7 (38.9%)	36 (59.0%)	20 (37.0%)	
No answer*	0 (0%)	1 (1.6%)	2 (3.7%)	
Disease duration(mo)				
Mean ± SD	62.4±112.4	59.3±80.7	61.3±123.2	0.37
Range	0.5-480	0.5-360	0.25-600	
Clinical manifestation				
Interdigital type	5 (27.8%)	17 (27.9%)	20 (37.0%)	0.39
Hyperkeratotic type	6 (33.3%)	20 (32.8%)	15 (27.8%)	
Vesiculobullous type	3 (16.7%)	20 (32.8%)	12 (22.2%)	
Combination	4 (22.2%)	4 (6.6%)	7 (13.0%)	

* due to patients were the priests

Table 2. The isolation of the causal agents

Culture report	Drug			Total (n = 133)
	Itra (n = 18)	Itracon (n = 61)	Sporal (n = 54)	
T. mentagrophytes	5 (27.8%)	23 (37.7%)	12 (22.2%)	40 (30.1%)
T. rubrum	4 (22.2%)	14 (23.0%)	10 (18.5%)	28 (21.1%)
Candida sp.	2 (11.1%)	5 (8.2%)	6 (11.1%)	13 (9.8%)
Hendersonula sp.	2 (11.1%)	3 (4.9%)	1 (1.9%)	6 (4.5%)
Scopulariopsis sp.	0 (0%)	2 (3.2%)	1 (1.9%)	3 (2.3%)
Cladosporium sp.	0 (0%)	0 (0%)	2 (3.7%)	2 (1.5%)
E. floccosum	0 (0%)	0 (0%)	1 (1.9%)	1 (0.8%)
Trichosporon	1 (5.6%)	0 (0%)	0 (0%)	1 (0.8%)
fusarium sp.	0 (0%)	0 (0%)	1 (1.9%)	1 (0.8%)
No growth	3 (16.7%)	13 (21.3%)	20 (37.0%)	36 (27.1%)
Not done	1 (5.6%)	1 (1.6%)	0 (0%)	2 (1.5%)

χ^2 p = 0.21

products of itraconazole (Itracon® and Itra®) and the innovative product (Sporal®) at both follow-up visits.

Concerning adverse events, 5 cases were reported (0.037%). One case of Sporal and one case of Itra group had mild headache; the other three who had moderate dyspepsia and nausea were from each group. None of the 5 cases needed to discontinue the medication and were therefore evaluated for treatment efficacy.

Table 3. The result of the evaluation at 4 and 12 weeks of follow-up.

	At 4 week			p value	At 12 week			p value
	Complete cure	Mycologic cure	Not cure		Cure	Relapse	Not cure	
Itra	11 (61.1%)	6 (33.3%)	1 (5.6%)	0.695#	14 (77.8%)	3 (16.7%)	1 (5.6%)	0.510#
Itracon	35 (57.4%)	16 (26.2%)	10 (16.4%)	0.199#	46 (75.4%)	6 (9.8%)	9 (14.8%)	0.386#
Sporal	27 (50.0%)	22 (40.7%)	5 (9.3%)		46 (85.2%)	4 (7.4%)	4 (7.4%)	
Total	73 (54.9%)	44 (33.1%)	16 (12.0%)		106 (79.7%)	13 (9.8%)	14 (10.5%)	

compare to sporal

Discussion

Itraconazole can be used to treat tinea pedis in three different ways: 100 mg/day for 4 weeks; 200 mg/day for 2 weeks or the pulse regimen in the present study, using 400 mg/day for one week. All three regimens resulted in a similar cumulative dose with a total of 2.8 g of itraconazole. However, other studies have reported even better results with the latter regimen. For instance, in a multicenter trial Gupta et al[7] obtained the following cure rates: 67% with the first regimen, 65% with the second one, and 85% with the third. The latter outcome is very similar to what the authors obtained in three products in the present study and is comparable to what other authors have reported[8-11].

Itraconazole is a triazole derivative with a high affinity for keratinized tissues. It is mostly excreted through the sebaceous glands and moderately by the sweat glands. It is important to emphasize that the stratum corneum in the palms and soles is 30-50 times thicker, without any sebaceous excretion and only a limited sweat excretion. This is why at higher doses, itraconazole reaches higher concentrations in the stratum corneum and, according to its pharmacokinetics, at such concentrations it behaves like a "reservoir" drug whose levels continue to increase even after the treatment has been discontinued. In fact, the present study showed that a clinical and mycologic cure rate of only 51% was obtained at the end of the second week; however, by the fourth week it had increased to 88%, reflecting the influence of the incorporation of the itraconazole into the basal cells of the epidermis and migration during the normal turnover of keratinocytes (keratopoiesis)[7,19,20].

The cure rate at 12 weeks follow-up was 106 patients (79.7%) compared to 117 patients (88.0%) at 4 weeks follow-up; this decrease in the cure rate of all three groups is believed to be the increase in the follow-up period allows re-infection or relapse. It is important to point out that one of the exclusion criteria was onychomycosis, because a single pulse of itraconazole (one week) is insufficient to cure onychomycosis and the latter would, therefore, represent a source of reinfection of patients. The innovative itraconazole, Sporal®, showed to have a lower relapse rate (7.4%) than the generic products (16.7% in the Itra® group and 9.8% in the Itracon® group), however this difference was not statistically significant.

Concerning the aetiology (Table 2), a predominance of *T. mentagrophytes* was observed (30.1%), followed by *T. rubrum* (21.1%). This is consistent with the causal agents reported in the literature [21-26]. Cases of *C. albicans* were 13 (9.8%) in the present study, are relatively frequent. However, since itraconazole is a broad-spectrum agent and is also effective against *Candida*-type of yeast, this makes no difference from the therapeutic viewpoint.

It is important to stress that the authors' efficacy results in comparison to the generic and the innovative products are preliminary as a double-blinded clinical trial. In the bioequivalence studies[27], Kaewvichit et al showed two generic products of itraconazole were not bioequivalent to Sporal® capsules. However, this conclusion related specifically to unchanged itraconazole. Since itraconazole is extensively metabolized in the liver to the active form, hydroxy-itraconazole, a bioequivalence study of this active metabolite should be performed, then it can determine the overall therapeutic effects.

Overall the three drugs used in the present study were safe, since only 5 cases with side effects attributable to itraconazole were reported (0.037%). All of them were minor and did not require discontinuation of the medication. Not only did the number of side effects not increase when pulse therapy with itraconazole was used, but their number even decreased when compared with continuous therapy. In a recent review of this dosage, adverse effects were reported in only 5% of cases, with the most important ones being: nausea, abdominal pain, headache and dyspepsia[28]. Side effects reported in the present

study were mild headache in two cases and dyspepsia and nausea in three cases.

Conclusion

The present study demonstrated that the treatment of tinea pedis with one pulse of generic itraconazole or the original one, showed no statistically significant difference in clinical and mycologic cure rates at 4 and 12 weeks follow-up. The authors' evaluation indicates that these products are effective and well tolerated and can be recommended as a low-cost alternative product for the treatment of tinea pedis.

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การเปรียบเทียบประสิทธิภาพยาอิทราโคนาโซลต้นแบบและยาสามัญในการรักษาโรคกลากที่เท้า

เสาวณีย์ ห่อหริตานนท์, เจนจิรา ชัยชโลธรกุล, วัณณศรี สินธุภัค

ที่มา: *การรักษาโรคกลากที่เท้าด้วยยารับประทานต้านเชื้อราแต่เดิมมีประสิทธิภาพไม่ดีนัก อิทราโคนาโซลเป็นยาต้านเชื้อราที่ออกฤทธิ์กว้างและให้ผลการรักษาที่ดี อย่างไรก็ตามราคายาที่แพงยังเป็นปัญหาในประเทศกำลังพัฒนา*

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบประสิทธิภาพของยาอิทราโคนาโซลต้นแบบ (Sporal®) และยาสามัญ 2 ชนิด อิทราคอน (Itracon®) และ อิทรา (Itra®) ในการรักษาโรคกลากที่เท้าด้วยวิธีให้ยาขนาดสูงเพียง 1 สัปดาห์*

วัสดุและวิธีการ: *เป็นการศึกษาแบบปิดสองทางที่มีกลุ่มควบคุม และการสุ่มตัวอย่าง ใช้ผู้ป่วยที่เป็นโรคกลากที่เท้า 133 คน โดยผู้ป่วยจะได้รับยาอิทราคอน อิทรา และ สปอรัล ขนาด 200 มิลลิกรัม วันละ 2 ครั้ง เป็นเวลา 1 สัปดาห์ มีการตรวจบันทึกลักษณะทางคลินิกและผลการตรวจทางห้องปฏิบัติการเชื้อราก่อนรับประทานยา ในสัปดาห์ที่ 1, 2, 4 และ 12 หลังได้รับยา*

ผลการศึกษา: *ผู้ป่วยที่ได้รับยาอิทราคอน อิทรา และสปอรัล, มีจำนวน 61, 18 และ 54 ราย ตามลำดับ ผลการรักษาทางคลินิกและการตรวจทางห้องปฏิบัติการเชื้อราไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ นอกจากนั้นยังไม่มีความแตกต่างทางสถิติในแง่ของการกลับเป็นซ้ำ และไม่พบผล ข้างเคียงที่รุนแรงระหว่างการศึกษา*

สรุป: *จากการศึกษาพบว่าประสิทธิภาพของยาต้นแบบและยาสามัญในการรักษาโรคกลากที่เท้าด้วยวิธีการให้ยาแบบขนาดสูง 1 สัปดาห์ ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ*