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The treatment of tinea pedis with oral ketoconazole

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Thirty cases of tinea pedis were treated with the new broad spectrum antimycotic agent ketoconazole. Ketoconazole is the soluble dibasic imidazole compound which can be taken by oral route. There were 26 cases that completed the study. The patients consisted of 18 males and 8 females with an average age of 36 years. Sixteen cases (61.6%) had chronic relapsing infection. Ten cases (38.4%) had acute infection. The most common dermatophyte isolated from this study was Trichophyton rubrum (50%). The over all cure rate was 84.6%. The cure rate in the chronic relapsing group and acutely infected group were 81.2% and 90% respectively. The majority of cases (63.3%) improved clinically after 2 weeks of treatment. KOH examination was negative after 4-8 weeks. No serious adverse effect was noted except nausea in 2 cases and elevated serum cholesterol in one case. There were no significant changes of hepatic enzyme levels before and after the study.

**นภคณ นพคุณ, มงคล ถ้ายองเสถียร. การรักษาเชื้อราที่เท้าด้วย Ketoconazole. จุฬาลงกรณ์
เวชสาร 2528 มกราคม; 29 (3) : 353 - 360**

ผู้ป่วย 30 รายที่เป็นเชื้อราที่เท้า ได้รับการรักษาด้วยยาต่อต้านเชื้อราชนิดใหม่ คือ ketoconazole โดยให้รับประทานในขนาด 200-400 มิลลิกรัม ต่อวัน นาน 4 ถึง 12 สัปดาห์ ยาตัวนี้เป็นยาที่มีฤทธิ์ต่อต้านเชื้อราอย่างกว้างขวาง สามารถห้ามการเจริญเติบโตของเชื้อราชนิดต่าง ๆ ได้ มีผู้ป่วยที่ได้รับการรักษาและติดตามผลจนครบกำหนดทั้งสิ้น 26 ราย เป็นผู้ชาย 18 ราย และหญิง 8 ราย อายุเฉลี่ยประมาณ 36 ปี ผู้ป่วย 16 ราย (61.6%) เป็นเชื้อราที่เท้าชนิดเรื้อรัง อีก 10 ราย (38.4%) เป็นเชื้อราที่เท้าเป็นครั้งแรก เชื้อราที่ตรวจพบมากที่สุดคือ Trichophyton rubrum (50%)

ผลการรักษาปรากฏว่าผู้ป่วยหายจากโรค (KOH preparation ให้ผลลบและเพาะเชื้อราไม่ขึ้น) 84.6% ของผู้ป่วยทั้งหมด อัตราการรักษาในผู้ป่วยเชื้อราที่เท้าชนิดเรื้อรัง และผู้ป่วยที่เป็นเชื้อราที่เท้าเป็นครั้งแรกเท่ากับ 81.2% และ 90% ตามลำดับ ส่วนใหญ่ผู้ป่วยมีอาการดีขึ้นภายใน 2 สัปดาห์หลังได้รับยา แต่ KOH preparation จะให้ผลลบ หลังจากรักษานาน 4-8 สัปดาห์ ผู้ป่วยหนึ่งรายต้องหยุดยาหลังจากรับประทานยาได้ 4 สัปดาห์ เนื่องจากมีระดับ cholesterol ในเลือดเพิ่มขึ้น ผู้ป่วยสองรายมีอาการคลื่นไส้ หลังรับประทานยา ผู้ป่วยนอกนั้น ไม่มีผลข้างเคียงที่ร้ายแรงจนต้องหยุดการรักษา ระดับน้ำย่อยของตับก่อนและหลังรักษา ไม่เปลี่ยนแปลง

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Tinea pedis or foot ringworm is the commonest dermatophyte infection.⁽¹⁾ Three anthropophilic species, *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Epidermophyton floccosum* are together responsible for causing tinea pedis throughout the world.⁽¹⁾ Among these three species, *Trichophyton rubrum* is the commonest (60 %).⁽²⁾ As a rule, Tinea pedis is very sensitive to topical antifungal therapy, but in a long-standing, chronic case with extensive involvement of the feet, topical treatment is not so effective, especially if caused by *Trichophyton rubrum*, and systemic therapy may be indicated.⁽³⁾ Griseofulvin is the wellknown oral systemic antifungal drug which has been used for a long time. The resistance of *Trichophyton rubrum* to griseofulvin had been reported, and griseofulvin became less effective in the treatment of dermatophyte infection especially tinea pedis.^(2,3) Ketoconazole is the new broad spectrum antifungal drug which is effective against dermatophytes, tinea versicolor, candida

species and some deep mycoses.^(4,5)

It can be used as an alternative oral treatment for dermatophytosis. It is the soluble dibasic imidazole compound which can be taken orally.⁽⁵⁾ We wanted to study the effectiveness of oral ketoconazole and its adverse effects in the treatment of tinea pedis in the patients attending the skin clinic at Chulalongkorn hospital.

Materials and method

Thirty patients with dermatophyte infection of either one or both feet seen at the skin clinic, Chulalongkorn hospital were recruited for this study, under the following criteria.

(1) To have dermatophyte infection on either one or both feet confirmed by positive KOH preparation for fungi.

(2) No treatment with either topical or systemic antifungal agents at least two weeks before admission into the study.

Patients were not eligible if they were under 18 years old, were pregnant, had significant onychomycosis or had history of the following diseases : hepato-

cellular dysfunctions, renal disorder, diabetes, hypercholesterol or hyperlipidemia and any blood diseases.

Upon entry into the study, the patients were given one 200 mg tablet of ketoconazole (Nizoral), daily with meal. The duration of therapy was a minimum of 28 days and a maximum of 12 weeks. After 28 days, for any patients who showed no clinical improvement or KOH preparation was still positive, the dosage was increased to 2 tablets per day until the end of the study.

The prestudy evaluation included; clinical assessment of the lesions, KOH examination of sample from lesions, culture of tissue samples for fungi (in Mycosel media). Complete blood count with differential, urine examination, blood urea nitrogen, serum creatinine, blood sugar, serum cholesterol and liver function tests were performed on every patient prior to administration of the drug.

Patients were asked to return to the clinic every two weeks during the study for KOH examination, clinical assessment

of the disease, response to the treatment and to report adverse effects. Clinical assessment was carried out by observing the following signs and symptoms; desquamation, exudation or incrustation, vesiculation or pustules, fissures, maceration, erythema, inflammation and subjective complaints. Severity of the above signs and symptoms was graded by attending physicians by the following; 0 = negative, 1 = moderate and 2 = severe.

Method of evaluation

Patients were considered cured if all the lesions had disappeared and the KOH examinations gave negative results and the cultures were negative.

Patients were considered improved if there were mild residual lesions (erythema, desquamation), but KOH preparation was negative.

Failure of treatment is considered if there were no clinical improvement after 12 weeks of treatment, were deterioration or side effects.

Therapy was discontinued if

(1) The patient was cured.

(2) The patient had minimal residual disease, but KOH was negative.

(3) No improvement after 12 weeks.

(4) There were adverse clinical effects or laboratory abnormalities.

Clinical assessment, KOH examination, culture and blood examinations for CBC, urine analysis, blood sugar, blood urea nitrogen, serum creatinine, serum cholesterol and liver function test were repeated at the completion of therapy.

Results

There were a total 26 cases treated with ketoconazole who completed the study. Of the 4 cases who dropped out, one had elevated serum cholesterol after 4 weeks of treatment, one wanted to stop the treatment after 6 weeks with minimal response, the other 2 cases did not return to follow up after initiation of clinical trial.

Characteristic of the patients

Of the 26 cases who completed the clinical trial, there were

18 males and 8 females. Age varied from 18 to 54 years, with an average of 36 years. Concerning the distribution of the lesions, 21 cases (80.7 %) had bilateral tinea pedis. The remaining 5 cases (19.3 %) had unilateral involvement.

16 cases (61.6 %) had chronic relapsing infection with a duration varying from one month to 10 years. 10 cases (38.4 %) had tinea pedis for the first time.

In the chronic relapsing group, all of the patients had been treated with one or combination of many antimycotic agents such as whitfield ointment, tolnaftate, imidazole compounds and griseofulvin.

In the group that had infection for the first time the duration of infection varied from 10 days to one month. 5 cases had been previously treated with one of the above antimycotic agents, without improvement. One case had been treated with griseofulvin without response. 4 cases had never had treatment before.

Results of the culture

The organisms cultured from

the lesions are shown in table I.

Table 1

Organisms	relapsed group (16 cases)	First-time infection (10 cases)
T. rubrum	8	5
T. mentagrophytes	4	1
E. floccosum	1	2
Contaminants	3	1
No growth	-	1

There was no significant difference in causative dermatophytes between the two groups. T. rubrum was the commonest dermatophyte found from the lesions in this study. In the relapsing group, there were slightly higher numbers of T. mentagrophytes than the first-timers.

Results of the treatment

Of the 26 cases, there were 22 cases (84.6%) who had been cured with oral ketoconazole (negative KOH preparation and culture).

There were 4 cases (15.4%) who failed to respond to oral ketoconazole therapy after 12 weeks of trial.

In the cured group, there were 2 cases that did not respond to treatment with ketoconazole 200 mg per day after 4 weeks, and the dosage had to be increased to 400 mg for two more weeks. Clinical improvements were noted at the 2nd week of treatment in 14 cases, the 4th week of treatment in 6 cases and the 6th week of treatment in 2 cases.

KOH examination and culture were negative after 2 weeks in 1 case, after 4 weeks in 7 cases, 6 weeks in 6 cases, 8 in 6 cases and at 12th weeks in 2 cases.

Of the non-responding group (4 cases or 15.4%), one case did not improve despite increasing

the dosage to 400 mg per day. This patient had had tinea pedis off and on for 7 years and had been treated with many antimycotic agents. The dermatophytes cultured from his lesions was *T. rubrum*. One case had *T. mentagrophytes* infection and had had tinea pedis for 4 years. One case failed to respond to griseofulvin before entering this study. The culture yielded *T. rubrum* and he did not respond to oral ketoconazole either. The last patient had *T. rubrum* infection without previous treatment and failed to respond to ketoconazole.

When we looked at the different cure rates between the relapsed and non-relapsed group, these were 13 out of 16 (81.2 %) in the relapsed group, and 9 out of 10 (90 %) in the non-relapsed group.

Adverse effect

No serious adverse effects of ketoconazole were noted in this clinical trial. There were 2 cases who experienced nausea after taking ketoconazole tablets, but gradually improved and there was no need to discontinue the

medication. There was one case who had elevated serum cholesterol after 4 weeks of 200 mg ketoconazole once a day therapy. When the drug was discontinued the serum cholesterol level returned to normal.

The remaining cases had no significant changes in any of the blood chemistry done before or after treatment, especially in the liver function tests.

Discussion

From this study, oral ketoconazole is very effective against tinea pedis. As expected, the cure rate of non-relapsed group is higher (90 %) than the relapsed group which was more difficult to treat. However, the cure rate of relapsed group was significantly high (81.2 %). Most of the treated cases (63.3 %) improved within 2 weeks, but the KOH examination became negative after 4 to 8 weeks of the treatment in most cases (86.4 %). These findings suggested that the treatment with ketoconazole had to be long enough, at least 4 to 8 weeks, to cure tinea pedis.

The most common dermatophyte isolated from this study was *Trichophyton rubrum* (50 %) , similar to other reports ⁽²⁾. *Tinea pedis* due to *Trichophyton rubrum* was extremely difficult to eradicate ^(1,2,5). Resistance of *T. rubrum* to griseofulvin had been reported ⁽³⁾. From this study, there were only 3 cases out of 15 cases infected with *T. rubrum* that did not respond to ketoconazole. So ketoconazole seemed to be effective against *Trichophyton rubrum* caused tinea pedis ^(4,5).

Approximately 10 % of patients treated with ketoconazole (most for weeks or months) have shown adverse reactions that include nausea, vomiting, headache, dizziness, constipation, diarrhea, somnolence, nervousness and pruritus. Nausea and pruritus are the most frequent adverse reactions ⁽⁵⁾. The gastrointestinal symptoms may usually be avoided by taking ketoconazole immediately before a meal. The most notable adverse effects are elevations of hepatic enzyme levels ^(6,7), hepatitis ^(8,9) and gynecomastia.

None of our patients had any

significant adverse effects that required discontinuation of the drug. Two patients claimed to have nausea which disappeared when ketoconazole was taken immediately before meals. None of the patients had significant changes in hepatic enzyme levels after the treatment. Only one case had elevated serum cholesterol, but returned to normal after discontinuing the drug.

However, because of the reported potential adverse effects, especially liver dysfunction and hepatitis, and because the drug is relatively new, one should be very cautious when administering this drug against dermatophytosis. It should be used only when indicated, such as in infections that are resistant to griseofulvin, in chronic recurrent tinea pedis which resists conventional therapy, or in systemic infections.

In the administration of ketoconazole, especially in its prolonged use (over weeks and months), one should watch the patient closely for any adverse effect. Pre and post treatment

laboratory evaluations including a complete blood count and differential, a serum cholesterol

and liver function tests should be done in every case.

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