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Oral Ketoconazole as an Alternative to Griseofulvin in Recalcitrant Dermatophyte Infections and Onychomycosis

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In an open study 58 patients with chronic dermatophytosis mainly caused by Trichophyton rubrum and five patients with Tinea capitis were treated with ketoconazole. The indications were ineffectiveness of or side effects to griseofulvin. Response to treatment varied from 1 week in scalp infections to 11 weeks in toe-nail lesions. Dermatophytosis of hands and feet were cured in 25%, marked improvement observed in further 30%. Toe- and finger-nail infections were cured in 20% and 43%, respectively, and marked improvement seen in further 36% and 14%, respectively. All scalp infections were cured without relapse. Recurrence of infections before 6 months after treatment was seen in 55–60% of hand and foot lesions and 33–38% of finger and toe-nail infections. In a double-blind study 20 patients with onychomycosis caused by T.rubrum the efficacy of ketoconazole was compared to that of griseofulvin. Cure rates in the griseofulvin group were 25% for finger-nails and zero for toe-nails, while 50% and 57% experienced marked improvement. In the ketoconazole group, 25% of finger-nail infections were cured and 75% markedly improved, while the corresponding figures for toe-nails were 11% and 89%, respectively. Adverse reactions to ketoconazole were seen in 29 (46%) of the patients in the open study and in 2 (20%) in the double-blind study and comprised mainly minor complaints. Side effects caused discontinuation in 12 patients, in two of whom due to toxic hepatitis. *Key words: Ketoconazole; Griseofulvin; Dermatophytosis.* (Received June 13, 1984.)

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Ketoconazole, an oral broad-spectrum antimycotic, has been found effective against several systemic and superficial mycoses (1). Like miconazole, clotrimazole and econazole, ketoconazole is an imidazole derivative. The mechanism of action is an inhibitory effect on the synthesis of ergosterol, which is a permeability regulator normally present in the membranes of fungal cells (2).

This paper reports partly on an open study of the efficacy of the drug in the treatment of patients with dermatophytosis resistant to or showing side effects to griseofulvin and partly of a double-blind study, where ketoconazole was compared to griseofulvin in the treatment of onychomycosis.

PATIENTS

Open study

The criteria for inclusion in the study was i) indication for systemic treatment, due to wide spread lesions or scalp infection, ii) unresponsiveness to griseofulvin, viz. no satisfactory improvement after at least three months on 500–1000 mg d.d. of microsize griseofulvin, or iii) side effects to griseofulvin. Thirtyeight males and 19 females with chronic tinea of the hands, feet, nails or glabrous skin were included in the study. Chronicity was defined as clinical signs of mycologically proven lesions for more than two years. The mean duration for these patients was 12 years (range 2 to 50 years). In addition, ketoconazole was given to five patients with tinea capitis ± kerion.

Table I. *Review of dermatophytes, clinical diagnosis, patients and indication for ketoconazole*

Dermatophyte	Location	♂	♀	Age mean (range)	Indication: Unresponsive to griseofulvin	Indication: Side effects to griseofulvin
T.rubrum	Tinea pedis	2	1	47.6 (39–59)	3	0
	Tinea pedis and manus	5	0	44.8 (40–58)	4	1
	Tinea pedis and unguium	7	8	42.2 (22–67)	11	4
	Tinea pedis, manus and unguium	10	1	45.1 (33–76)	10	1
	Onychomycosis	11	5	46.2 (24–73)	12	4
	Tinea pedis, manus, corporis cruris and unguium.	3	2	40.4 (17–73)	2	3
T.mentagrophytes	Onychomycosis	1		56	1	0
T.violaceum	Tinea pedis and unguium		1	63	1	0
E.floccosum	Tinea pedis	1		30	1	0
M.canis	Tinea capitis (Kerion)		2	31 (6–56)	2	0
M.audouini	Tinea capitis		1	8	1	0
T.verrucosum	Tinea capitis (Kerion)	1	1	6 (3–9)	0	2
Total, n=63		41	22		48	15
Per cent		65	35		76.2	23.8

The average duration of previous griseofulvin treatment in the chronic group was 2.5 years (range ¼–8 years) and in the tinea capitis group seven months (3–10 months). Side effects to griseofulvin had been severe enough to cause cessation of treatment in fifteen patients (Table I).

Double-blind study

Included in this study were 18 males and two females with onychomycosis caused by dermatophytes severe enough to indicate systemic treatment. The age range was 14 to 66 years (mean 42 years) and the duration of the nail infection from 1 to 30 years (mean 9.3 years). Fifteen patients had received prior treatment with griseofulvin for less than three months without side effects.

METHODS

Mycological examination including KOH preparation and Sabouraud–cycloheximide–chloramphenicol agar cultures was performed initially to establish the diagnosis, every second months, at the end of the treatment period and at the follow-up visits.

Table II. *Responsiveness to ketoconazole therapy assessed by body region*

Body region	n	Cured n	Cured %	Markedly improved n	Markedly improved %	Improved n	Improved %	Unchanged n	Unchanged %	Relapse 6 months +	Relapse 6 months –	Unknown
Hands	21	5	24	6	29	7	33	1	5	3	1	1
Feet	42	11	26	13	31	9	22	3	7	6	4	1
Fingernails	7	3	43	1	14	0		1	14	1	2	0
Toenails	47	9	20	17	36	10	21	1	2	3	5	1
Scalp	5	5	100	0		0		0		0	0	0

Laboratory tests including haemoglobin, leucocyte count, platelet estimate, creatinine, cholesterol and alanin-aminotransferase (ALAT) were assayed prior to treatment, every two weeks for two months, and then monthly during the treatment period.

Treatment

In the open study treatment was initiated at 50–100 mg ketoconazole per day in children below 10 years and 200 mg in adults. The tablets were taken with a meal once a day. If improvement was not obtained after one to six months, the dose was increased to maximum 400 mg per day. The treatment was continued until clinical and/or mycological sure and did not exceed 12 months.

In the double-blind study, patients with culturally proven dermatophyte infection of the nails received griseofulvin or ketoconazole on a randomized basis. Identically numbered bottles contained tablets of either 500 mg microsize griseofulvin or 200 mg ketoconazole. Every patient receive one tablet daily at breakfast. If no improvement occurred during 2–4 months the medication was doubled. Treatment was continued until clinical and mycological cure, but no longer than one year.

Response to treatment was evaluated by clinical examination and KOH examination and culture monthly. Cure of skin infection and onychomycosis was defined as complete absence of clinical lesions and negative microscopy and culture. Marked improvement was the score given to clinically almost cured lesions with positive KOH preparation and negative culture. Improvement was defined as the response in patients, who had obtained a tolerable condition with at least 50% improvement as compared to the baseline condition. Clinical improvement of the nail infection included measurable decrease of the area involved, brittleness, subungual hyperkeratosis and onycholysis. At each visit the involved zone of each nail was shaded on a figure in the record.

RESULTS

Open study

Number and species of isolated dermatophytes as well as the clinical manifestations of dermatophytosis are summarizad in Table I. The response to ketoconazole was assessed by body region (Table II). The cure rates for skin lesions of hands and feet were similar and made up 25%. Marked improvement was observed in further 29% (hands) and 31% (feet) respectively, while 6% did not respond. Response to treatment was observed in 77% of the toe-nail infections, but only 20% was cured. Finger-nail infections were cured in 43% of the cases. The number of this group of patients, however, was small. All scalp infections were cured and without relapse. Response to treatment was observed earlier in the scalp infections i.e. mean one week, later in the chronic lesions of palms and soles i.e. mean 6–7 weeks, in finger-nail infections after mean 8 weeks and in toe-nail lesions i.e. mean 11 weeks. The duration of treatment until cure did not vary much from region to region and was 7.2 months on the average. Relapse of infection in those patients who had been assessed as cured was observed during the six month follow-up period. Mainly lesions of hands and feet had regressed (60% and 55%, respectively) versus 33% of finger-nail infections and 38% of toe-nail infections.

Duration of treatment

Until improvment		Until cure		Unevaluable due to side effects	
Range (months)	Mean (weeks)	Range (months)	Mean (months)	*n*	%
¼–4	7	4–11	7	2	9
¼–4	6	3–12	8	6	14
1–3	8	4–6	5	2	29
½–9	11	6–11	8	10	21
½–1	1	4–11	8	0	

Twelve (29%) of 42 patients with chromic T. rubrum infection previously non responsive to griseofulvin were cured and 20 (48%) improved. An increased dose (400 mg d.d.) was considered necessary in around half of these patients. At follow-up visits during 6 months, six of the cured patients showed relapse, predominantly of the skin lesions. Four of thirteen patients, in whom side effects to griseofulvin had indicated ketoconazole, were cured, but one relapsed during the six month follow-up. Other four of this group showed side effects to ketoconazole severe enough to cause discontinuation of treatment.

Four patients (6%) did not respond to ketoconazole. After five months on ketoconazole 200 mg daily two of these had their dose increased to 400 mg d.d. for 10 months without efficacy. Sensitivity testing was not performed.

Adverse reactions

A total of 29 patients (46%) showed adverse reactions (Table III), which in 11 patients caused discontinuation of treatment. Ketoconazole-associated hepatic dysfunction was asymptomatic in 4 patients and revealed by raised liver enzyme levels, which did not cause cessation of treatment. Symptomatic hepatic reaction after 3-4 months of treatment occurred in two patients, i.e. a 68-year-old woman (3) and a 48-year-old man (4), as previously reported.

Double-blind study

Ten patients, 9 males and 1 female, age range 14–65 years (mean 40.5 years) were treated with ketoconazole. Six had isolated toe-nail infection and four both toe- and finger-nail involvement. Trichophyton rubrum was isolated from all patients. Oral daily dose was one tablet = 200 mg ketoconazole to all patients. One patient had to discontinue treatment after two months due to side effects. The remaining were treated for 8–12 months (average 10.6). Griseofulvin was given to nine males and one female, age range 28–66 years (mean 44.8). Two had finger-nail infection only, five isolated toe-nail lesions and three combined finger- and toe-nail involvement. T.rubrum was the only cause of infection in this group. Two patients had an oral daily dose of 1 tablet = 500 mg during their entire treatment period, while eight had the dose doubled after two or four months due to lack of

Table III. *Side effects to ketoconazole in 63 patients with dermatophytosis*

Symtom	Number of patients	%	Number of patients who discontinued treatment due to side effect
Gastro-intestinal discomfort	17	27	2
Dizziness	8	13	6
Headache	6	10	None
Transient liver enzyme raise ALAT 40–100 units/l	4	6	None
Nausea	3	5	None
Hepatitis	2	3	2
Eye symptoms	1	1.6	1
Loss of taste	1	1.6	None
Weight gain	1	1.6	None
Heat	1	1.6	None
> one symptom	10	16	6
Total number of patients with side effects	29	46	11

improvement. Two patients stopped treatment after three and four months, respectively, due to side effects and three after six and eight months because of unresponsiveness in spite of double dose. Five patients were treated for 12 months.

The final clinical and mycological response to ketoconazole versus griseofulvin is shown in Table IV. Nine patients on ketoconazole and eight patients on griseofulvin were evaluable. All patient with toe-nail infection in the ketoconazole group responded to treatment with either clinical cure (11%) or marked improvement (89%). All finger-nail lesions were clinically healed, but only one was cured showing negative direct microscopy. In the griseofulvin group clinial cure was obtained in one patient with combined toe- and finger nail infection but only of the finger-nails. Six patients experienced marked improvement of either finger (50%) or toe-nails (57%). A total of three nail infections did not respond at all. Thus, the clinical response concerning toe-nail infections (cure + marked improvement) seemed in favour of ketoconazole ($p=0.06$ n.s.), whereas no differences in efficacy between griseofulvin and ketoconazole was observed in the treatment of finger-nail lesions.

Adverse reactions

In the ketoconazole group, slight dizziness was reported by one patient. In another patient, elevated liver enzymes without subjective complaints were demonstrated after two weeks of treatment. After four weeks the elevation exceeded 100 units, which was the indication for stop of treatment. In the griseofulvin group, two patients stopped treatment after three and four month due to headache, dizziness and gastrointestinal discomfort, respectively.

DISCUSSION

In previous studies, ketoconazole has been described as a safe and effective drug against dermatophytosis. Cure rates between 63 and 83% in glabrous skin infections and onychomycosis (5) have been reported. However, in 20 patients with chronic tinea of skin and nails Robertson et al. (6) only found clinical and mycological cure in 30% and in 67% of these relapse occurred after 5 months. The latter findings correspond well with the results of the present study. Similar results were found in a previous double-blind study (7) of 34 patients with tinea of the glabrous skin in which cure rates were 33% for ketoconazole and

Table IV. *Efficacy of Ketoconazole as compared with griseofulvin in the treatment of onychomycosis caused by T.rubrum*

		Patients with toe-nail infection		Mycology result		Patients with finger-nail infection		Mycology result	
Drug	Response	*n*	%	Pos.	Neg.	*n*	%	Pos.	Neg.
Ketoconazole	No change	0	0	0	0	0	0	0	0
	Improvement	0	0	0	0	0	0	0	0
	Marked improvement	8	89	8	0	3	75	3	0
	Cure	1	11	0	1	1	25	0	1
Griseofulvin	No change	3	43	3	0	0	0	0	0
	Improvement	0	0	0	0	1	25	1	0
	Marked improvement	4	57	4	0	2	50	2	0
	Cure	0	0	0	0	1	25	0	1

28% fo griseofulvin. Most encouraging in the present open study was the efficacy on finger-nail infection, while the results of the double-blind study were not able to confirm that the effect of ketoconazole is actually better than that of griseofulvin.

The follow-up period of six months revealed that, in spite of clinical and mycological cure, relapse of T.rubrum infection of the nails occurred in 33%, and of the skin of hands and feet in 60% and 55%, respectively. All tinea capitis patients were cured for good, which might be due to a better excretion of the drug in hair follicles than in the skin of palms and soles, or differences in sensitivity of species in vitro. Moreover, tinea capitis caused by zoophilic species has a tendency to heal spontaneously. Ketoconazole seemed to be of value in griseofulvin resistant cases of T.rubrum, 77% of these cases responding to the new drug. The number of patients with adverse reactions was substantial, especially in the open study. Most symptoms were harmless, but the symptomatic hepatic reactions caused several months of discomfort for two patients. It is noteworthy that four (33%) of 12 patients with griseofulvin intolerance also developed side efects to ketoconazole, and in all four cases severe enough to cause cessation of therapy. In the remaining 51 patients adverse reactions were observed in 25, but only seven (13%) discontinued the treatment. By now, ketoconazole offers the only alternative to griseofulvin in the treatment of severe, chronic or resistant dermatophytosis. Even though most patients in the open study responded well to long term treatment with ketoconazole, the cure rates were moderate and the frequency of relapses considerable. In the treatment of onychomycosis of the toe-nails there was a borderline significant tendency to a better response to ketoconazole than to griseofulvin, only not a better cure rate. More extensive studies are necessary to confirm if this finding is real or due to chance.

By now, toxic hepatitis due to long-term treatment with ketoconazole has been reported in more than 90 cases, 33 of whom have been carefully analysed (8). The mechanism of injury is presumed to be a metabolic idiosyncracy. Recently, anaphylactic reactions to the drug have been described (9). In addition, an inhibitory though transient effect on the testosterone synthesis has been demonstrated (10). Thus, it is essential to stress the importance of careful clinical and laboratory control when using ketoconazole in this group of patients. As long-term treatment is needed, the accordingly increased risk of a severe potentially life threatening condition must be balanced against the benefits anticipated in what is a benign though troublesome skin disease (11).

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