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Clinical and pharmacokinetic investigations of oral terbinafine in patients with tinea unguium

Klinische und pharmakokinetische Untersuchungen zur oralen Terbinafin-Therapie an Patienten mit Tinea unguium

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Schlüsselwörter. Tinea unguium, antimykotische Chemotherapie, Terbinafin, Pharmakokinetik, Nagel, Haare, Plasma.

Summary. A clinical trial of once-daily administration of a 125-mg tablet of terbinafine, an oral antimycotic agent, was performed on patients with tinea unguium to evaluate its efficacy, safety, possible side-effects and its incorporation into nails and hair. Thirty-four patients were recruited into the study. For the statistical analysis, one of these patients was used only for the safety rating. Accordingly, 33 patients were used for the efficacy rating, and all 34 patients were employed for the safety rating. The efficacy rating in the overall efficacy evaluation was 90.9% (30/33). No adverse effects, including abnormal changes in laboratory test values, were observed. A pharmacokinetic study revealed that terbinafine was detected in the nail tissue at and after week 2. It reached 0.78 ng mg^{-1} at the end of week 12 and remained at almost the same level thereafter. Terbinafine was also detected in hair at and after week 23. The average value was 3.14 ng mg^{-1}. The plasma concentration of the drug reached a steady state (280.3 ng ml^{-1}) at approximately week 10, and no tendency to further accumulation was noted. These results confirm the favourable incorporation of terbinafine into nail and hair. On the basis of these results, it was concluded that the drug demonstrates excellent efficacy and satisfactory safety in patients with tinea unguium. The pharmacokinetic investigation also demonstrated its excellent treatment efficacy.

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Zusammenfassung. Mit einer Dosis von 125 mg Terbinafin täglich oral wurde bei Patienten mit Tinea unguium eine klinische Studie durchgeführt, um Wirksamkeit, Sicherheit, mögliche Nebenwirkungen und den Einbau des Antimykotikums in Nagel und Haare zu bewerten. In die Studie wurden 34 Patienten einbezogen. Davon bildeten 33 Situationen die Grundlage der Wirksamkeitsanalyse, und alle 34 gingen in die Sicherheitsbewertung ein. Die Wirksamkeitsrate lag bei 90,9% (30/33). Es wurden keine Nebenwirkungen und keine ungewöhnlichen Veränderungen von Labor-Testwerten festgestellt. Die pharmakokinetischen Erhebungen zeigten, daß Terbinafin ab der zweiten Woche im Nagelgewebe nachgewiesen werden konnte. Am Ende der 12. Woche erreichte Terbinafin eine Konzentration von 0,78 ng/mg und hielt sich anschließend fast auf dem gleichen Wert. Ab der 23. Woche wurde Terbinafin im Haar in einer Durchschnittskonzentration von 3,14 ng/mg gefunden. Die Terbinafin-Plasmakonzentration erreichte den Plateauwert von 280,3 ng/ml ab ca. der zehnten Woche; eine Tendenz zu weiterer Akkumulation wurde nicht beobachtet. Terbinafin zeigte somit sehr gute Wirksamkeit und zufriedenstellende Sicherheit in der Anwendung bei Patienten mit Tinea unguium. Die Ergebnisse der pharmakokinetischen Untersuchungen bestätigen den bevorzugten Einbau von Terbinafin in Nägel und Haare.

Introduction

Terbinafine is a new synthetic antifungal agent of the allylamine class [1]. The drug exerts its antifun-

gal effect by inhibiting the enzyme squalene epoxidase, a key enzyme in ergosterol biosynthesis in fungi [2–4], and thus in the lipid metabolic pathway of fungi. Further, it has a wide spectrum of activity against pathogenic fungi *in vitro* and, in particular, it is fungicidal against dermatophytes [5–9]. Outstanding treatment results have been obtained in several clinical trials of the drug performed in Japan, in which patients with superficial dermatomycoses were treated [10–12].

Unless sufficient drug can be incorporated into tissues where pathogenic fungi are present, an antifungal agent cannot be effective. It is worthwhile investigating the incorporation of a drug into tissue in order to demonstrate its efficacy.

The results of pharmacokinetic investigations in healthy volunteers and in patients with superficial dermatomycoses so far reveal no problematic accumulation [10, 13, 14]. In those studies, however, the steady state of the drug in plasma could not be confirmed. In the treatment of tinea unguium, long-term administration may be required, and it is necessary to confirm the drug's pharmacokinetics during long-term administration. We investigated the efficacy and safety of once-daily administration of one 125-mg tablet of terbinafine, as well as its accumulation in nails and incorporation into hair in patients with tinea unguium. The following results were obtained.

Patients and study methods

Subjects

Among the patients with tinea unguium who consulted the Dermatology Clinic of Kitasato University and the Dermatology Clinic of Toshiba Hospital during the period from December 1991 to April 1993, those in whom the presence of fungi was proven by direct microscopy and/or culture were selected for the study.

The infected nails used for study were fingernails or the first to third toenails. Each nail was divided into 10 parts, and was considered for the study if three or more of its parts were turbid.

General outline of the trial

The study was performed according to the rules of the Declaration of Helsinki, and the trial plan proper was approved by the ethical committees of each of the participating institutes. Enrolment was based on written informed consent.

Treatment

One 125-mg tablet of terbinafine, supplied by Sandoz Yakuhin K.K., was orally administered to each patient once daily after breakfast. The administration had to be continued until sufficient drug efficacy could be obtained for the evaluation, i.e. for about 24 weeks.

Exclusion criteria and concomitant drugs

Individuals of non-Japanese nationality, those ≤ 19 years or ≥ 76 years, those who had used other antimycotic agents (including topical and oral forms) within a week before the study, those with serious systemic disease or serious renal or hepatic disorders, those whose liver function tests were apparently abnormal, those who were pregnant, lactating or possibly pregnant, and those who were judged unsuitable for the study by the physician in charge, were excluded from the study.

During the study period, antimycotic agents other than terbinafine, oral steroids, etc., which were considered to affect the efficacy evaluation of terbinafine, were prohibited from being used concomitantly. Further, concomitant use of rifampicin and cimetidine was prohibited because they might affect the metabolism of terbinafine.

Clinical and mycological evaluation

Each patient was observed on the day after the start of treatment, at the end of weeks 2, 4, 6, 8 and 10 of treatment and once every 4 weeks from week 12 of treatment onwards. The following time lag was accepted for each observation day: 2 days for week 2, 3 days for weeks 4 and 6, 4 days for weeks 8 and 10, and 7 days for week 12 onwards.

Before the start of treatment, a mycological test was performed using material from the affected part to judge the presence or absence of fungi, and the causal fungi were isolated and identified. On each observation day (except on the day after the start of treatment), the affected part was examined by direct microscopy of KOH specimens, or clinical material from the affected part was cultured. Clinical findings observed were the turbidity and thickening of the affected part on each observation day (exclusive of the day after the start of treatment). An illustration of the lesion and the turbidity were recorded, and the thickening of the affected part was judged as asymptomatic, mild, moderate or severe.

Regularity of drug intake during the study period was investigated and classified into four grades: the patient takes the drug as instructed; the patient sometimes forgets to take the drug; more than half of the drug given is left unused;

the patient does not take any drug at all. Subjective symptoms and abnormal changes in laboratory findings whose relation to the test medication could not be denied were handled as adverse events, and the symptoms, sites, severity, date of onset, progress, subsequent treatment, date of disappearance, relation to the test medication, etc., were recorded. The severity of each adverse event was evaluated using three grades: mild (it was possible to continue the test medication without any treatment); moderate (it was possible to continue the test medication with some treatment); and severe (it was necessary to withdraw the test medication). The relationship with the test medication was evaluated using four grades (related, possibly related, unknown or not related).

The date of appearance, symptoms, severity, treatment and progress of both complications and adventitious disease were investigated in detail.

The following laboratory tests were carried out on the day before the initiation of treatment and on each examination day (exclusive of the day after the start of treatment):

(1) haematology: RBC, haemoglobin, haematocrit, WBC and differential leucocyte count;
(2) blood biochemistry: total protein, albumin, total bilirubin, direct bilirubin, GOT, GPT, gamma-GTP, ALP, LDH, A/G, total cholesterol, triglycerides, BUN, uric acid, creatinine, Na, K, Cl, Ca and CPK;
(3) urinalysis: pH, protein, sugar and specific gravity;
(4) ophthalmological tests: visual acuity, intraocular pressure, naevus, media, ocular fundus and visual field.

When a clinically significant abnormal change was noted, the item was followed up and the relationship with the test medication was investigated. Further, ophthalmological tests were carried out on the patients who gave consent for the tests, on the first day and at the end of week 24 of treatment.

Efficacy evaluation

The final mycological efficacy (direct microscopy) was evaluated as positive (+) or negative (−) for fungal elements. The final evaluation of clinical findings compared the turbidity of the affected nail at the start of the study and at the end of the study. Evaluation was carried out using the five-grade criterion of markedly improved, improved, slightly improved, unchanged and aggravated (Table 1).

The physician in charge evaluated the overall efficacy using five grades (markedly effective, effective, slightly effective, ineffective, or aggravated) in considering the final evaluation of the clinical findings.

The safety rating included adverse events and laboratory test values. It was classified into the following four grades: the drug is safe; the drug is almost safe (it was possible to continue the study without any treatment); there are small problems with drug safety (it was possible to continue the drug with some treatment); and there are definitely problems with drug safety (the study had to be discontinued). Discontinued cases and dropouts were evaluated on the last day of treatment.

Assay of drug levels

Nail plates were sampled from patients on the first day of treatment and every 4 weeks thereafter. These samples were divided into normal ones and infected ones, placed in glass vessels and kept at −20 °C. Hair was sampled 24 weeks after the

Table 1. Final evaluation of clinical findings

Evaluation	Turbidity at the first examination							
	3	4	5	6	7	8	9	10
	Remaining turbidity							
Markedly improved	Within 16 weeks 0	Within 20 weeks 0	Within 20 weeks 0	Within 24 weeks 0	Within 24 weeks 0–1	Within 24 weeks 0–2	Within 24 weeks 0–3	Within 24 weeks 0–4
Moderately improved	Between weeks 17 and 24 0	Between weeks 21 and 24 0–1	Between weeks 21 and 24 0–2	During week 24 1–3	During week 24 2–4	During week 24 3–5	During week 24 4–6	During week 24 5–7
Slightly improved	During week 24 1–2	During week 24 2–3	During week 24 3–4	During week 24 4–5	During week 24 5–6	During week 24 6–7	During week 24 7–8	During week 24 8–9
Unchanged	Turbidity has not changed							
Aggravated	Turbidity has increased							

start of the study. It was plucked out as close to the hair root as possible, put into polyethylene bags and kept at −20 °C.

Blood was sampled from patients on the first day of treatment and thereafter on each observation day to assay plasma levels of the metabolite. On the day of blood sampling, the drug was administered to patients after the physician in charge's consultation and after blood had been sampled. A blood sample of 8 ml was drawn into a heparinized glass tube and immediately centrifuged to separate the plasma. It was also kept at −20 °C. The level of the drug metabolite was measured in accordance with the high-performance liquid chromatography method developed by Sandoz Pharma [15, 16].

The levels of drug in the nail plates, hair and plasma were examined at the New Drug Development Research Center, Sandoz Yakuhin K.K., and Japan Clinical Laboratories.

Results

Cases employed for evaluation and background of cases

A total of 34 patients were used for the study. One of the 34 patients, who withdrew consent during week 4 of treatment, was used only for the safety rating because the duration of administration was too short for the efficacy evaluation. Another patient, in whom the drug intake from week 18 of treatment onwards was less than half, was used for all the evaluations because the patient had taken the drug as instructed until week 18 of treatment. Consequently, the efficacy of the drug was evaluated in 33 patients and the safety was rated in 34 patients.

The 34 patients used for the safety rating comprised 19 male and 15 female patients, ranging in age from 20 to 75 years (average 52.0 years). The causal fungi was in 14 cases *Trichophyton rubrum* and in two cases *Trichophyton mentagrophytes* var. *interdigitale*; in 18 cases we were unable to isolate the causal agent (Table 2).

Clinical evaluation

Efficacy. The negative ratings for fungi in fingernails and toenails were 100% (5/5) and 88.9% (24/27), respectively, or 90.6% (29/32) combined (Table 3). One patient with tinea pedis was excluded from the evaluation because he had not undergone mycological testing.

The ratio of turbidity was 8.21 on the average at the start of treatment, but improved to 2.70 at the end of week 24. Similar improvement was noted in the thickening as well (Figs. 1 and 2).

Table 2. Patients' background

Sex	
Male	19 (55.9)
Female	15 (44.1)
Age (years)	
<30	3 (8.8)
30–<40	2 (5.9)
40–<50	9 (26.5)
50–<60	10 (29.4)
60–<70	7 (20.6)
70–<80	3 (8.8)
Mean±standard deviation	52.0±13.5
Range	20.0–75.0
Median	53.0
Infected nail	
Fingernail	5 (14.7)
Toenail	29 (85.3)
Causal fungus	
T. rubrum	14 (41.2)
T. mentagrophytes	2 (5.9)
Failed in culture	18 (52.9)
Duration of disease	
<1 year	2 (5.9)
1–<5 years	9 (26.5)
5–<10 years	10 (29.4)
>10 years	13 (38.2)
Mean±standard deviation	102.2±81.3 months
Range	6.0 months to 30 years
Median	7 years
Total	34

( ): %.

Table 3. Mycological efficacy (direct microscopy)

Infected nail	Number of cases	No. negative (%)	No. positive
Fingernail	5	5 (100)	0
Toenail	27	24 (88.9)	3
Total	32	29 (90.6)	3

Subsequent progress in turbidity was investigated in patients who completed, discontinued or dropped out of the study (Table 4). It was possible to follow 27 of the 34 patients. One patient who had taken griseofulvin after the final observation day was excluded, and final evaluation was made on 26 cases. Those twenty-six patients were divided into two groups, i.e. those in whom turbidity still remained at the final observation and those in whom turbidity had disappeared by the final observation. In the former group, increases or decreases in turbidity were investigated, while relapses or reinfections were investigated in the latter group.

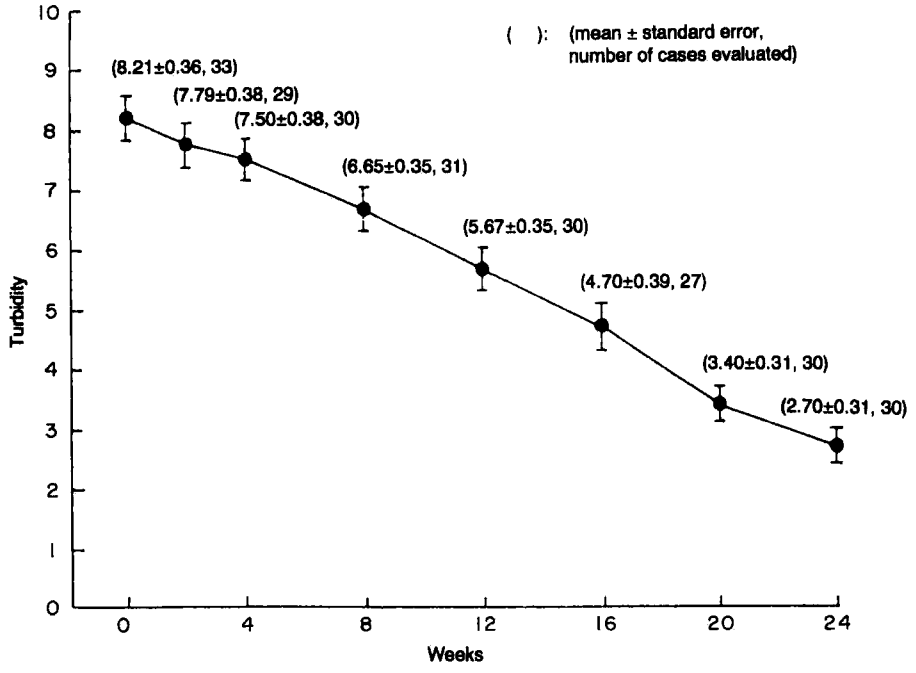

Figure 1. Changes in turbidity. Mean ± standard error and number of patients evaluated are given in parentheses.

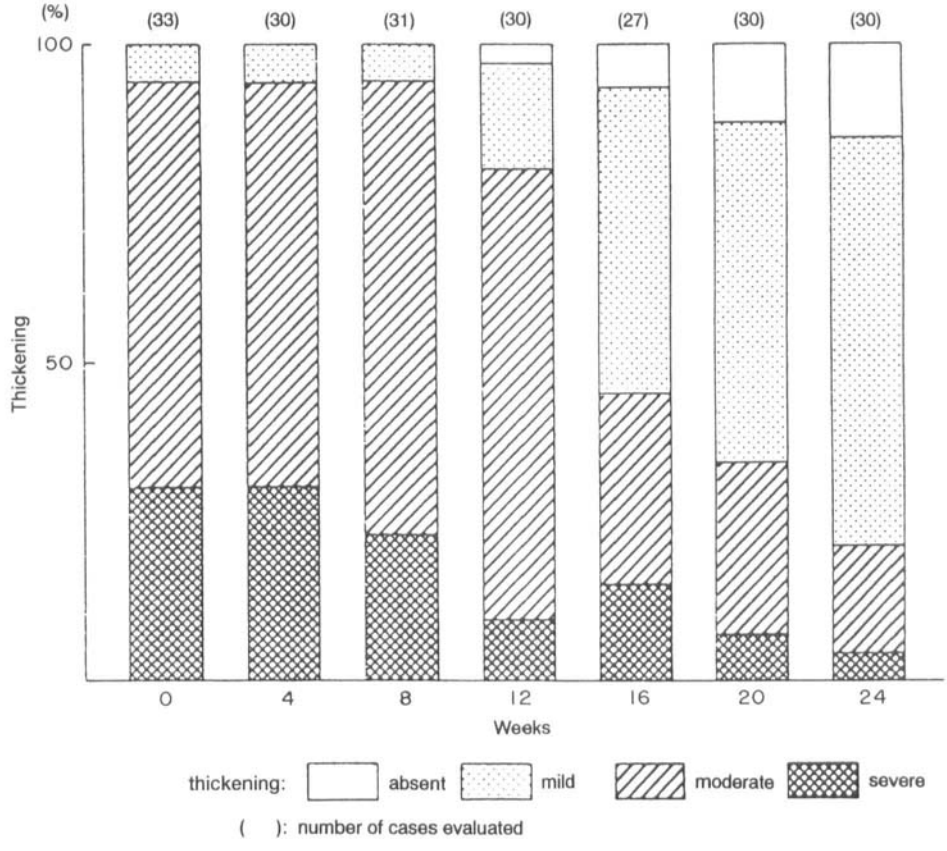

Figure 2. Changes in thickening of affected sites. Number of patients evaluated is given in parentheses. Thickening: □, absent; ▨, mild; ▨, moderate; ▩, severe.

The number of patients in whom turbidity still remained at the final observation was 17, and the average duration of terbinafine administration was 29.8 weeks. The average duration between the final observation and the follow-up observation in these patients was 11.9 weeks. Among them, the number of those in whom turbidity was decreased, unchanged and increased was 7, 9 and 1 respect-

Table 4. Changes in turbidity after final observation

Turbidity at the final observation	Changes in turbidity	Duration between final administration and follow-up observation						Number of cases
		≦4 weeks	5 weeks to ≦8 weeks	9 weeks to ≦12 weeks	13 weeks to ≦16 weeks	17 weeks to ≦20 weeks	21 weeks to ≦24 weeks	25 weeks ≦or longer	
1 or more	Decreased	1	1	0	4	0	0	1 (38 weeks)	7
	Unchanged	2	2	3	2	0	0	0	9
	Increased	0	0	0	0	1	0	0	1
	Subtotal	3	3	3	6	1	0	1	17
0 (no sign of turbidity)	Unchanged	0	0	1	2	0	1	4 (28–44 weeks)	8
	Increased	0	1	0	0	0	0	0	1
	Subtotal	0	1	1	2	0	1	4	9
Total		3	4	4	8	1	1	5	26

ively. The number of those in whom turbidity had disappeared by the final observation was 9, and the average duration of terbinafine administration was 40.4 weeks. The average duration between the final observation and the follow-up observation in these patients was 24 weeks. Among them, the number of those in whom relapse or reinfection was not noted and the scores of the ratio of turbidity remained '0' was 8; relapse was noted in one patient.

In the final evaluation of the clinical findings, the improvement ratings in fingernails and toenails were 80.0% (4/5) and 92.9% (26/28), respectively, or 90.9% (30/33) combined (Table 5).

In the final overall efficacy evaluation, in which the final evaluation of clinical findings was taken into account, the efficacy ratings in fingernails and in toenails were 80.0% (4/5) and 92.9% (26/28), respectively, or 90.9% (30/33) combined (Table 6).

The efficacy of terbinafine in patients to whom griseofulvin had previously been administered was investigated. Among 33 patients in whom the efficacy of terbinafine was evaluated, a history of griseofulvin treatment was noted in six patients. The efficacy of griseofulvin was evaluated in these six patients. The cases rated as ineffective, effective and unknown numbered 3, 1 and 2 respectively. Those in whom griseofulvin was evaluated as ineffective had received griseofulvin for 12 weeks or longer in the past, and the efficacy of terbinafine was evaluated as effective in these patients.

Safety. Adverse events and abnormal changes in laboratory findings were not noted during the treatment period. In eight patients, ophthalmological tests were performed at the start and at the end of week 24 of treatment; the eight patients comprised four male and four female patients, ranging in age from 26 to 75 years. No abnormal ophthalmological findings due to terbinafine was noted.

The safety of the drug was demonstrated in all 34 patients used in the safety evaluation.

Pharmacokinetics

The levels of terbinafine in the nail plates, hair and plasma were scored in the same manner as the weekly changes in clinical findings. Four of 34 patients were excluded from the evaluation of terbinafine levels in the nail plates. In two of the four patients, it was impossible to assay the level of terbinafine because the quantity of the sample collected was insufficient; in the remaining two patients, it was impossible for some reason to collect the nail samples for the assay from the end of week 4 of treatment. Further, the data on one

Table 5. Final evaluation of clinical findings (cumulative percentage in parentheses)

Infected nail	Number of cases	Markedly improved	Improved	Slightly improved	Unchanged	Aggravated
Fingernail	5	4 (80.0)	0 (80.0)	1	0	0
Toenail	28	13 (46.4)	13 (92.9)	2	0	0
Total	33	17 (51.5)	13 (90.9)	3	0	0

Table 6. Overall efficacy evaluation (cumulative percentage in parentheses)

Infected nail	Number of cases	Markedly effective	Effective	Slightly effective	Ineffective	Aggravated
Fingernail	5	4 (80.0)	0 (80.0)	1	0	0
Toenail	28	13 (46.4)	13 (92.9)	2	0	0
Total	33	17 (51.5)	13 (90.9)	3	0	0

patient from week 18 of treatment onwards were excluded from evaluation because the drug intake from week 18 onwards in this case was less than half.

Terbinafine was detected in the infected nails of 27 of 30 patients between weeks 2 and 21 of treatment. Terbinafine was also detected in another three patients, but the amount detected in each case was less than the quantitation limit (0.2 ng mg^{-1}). The level of terbinafine gradually increased, reached 0.78 ng mg^{-1} during week 12 of treatment, and remained at almost the same level thereafter. The level of terbinafine in normal nails was similar to that in the infected ones (Fig. 3).

Hair was sampled in 31 of 34 patients during the treatment period. Among the 31 patients, one patient, in whom drug intake from week 18 onwards was less than half, and another patient, from whom not enough sample for the assay was collected, were excluded from the evaluation. In one of the 29 patients, terbinafine was detected but the amount detected was less than the quantitation limit (0.2 ng mg^{-1}). The hair in these 29 cases was sampled between weeks 23 and 32 of treatment, and the level of terbinafine detected

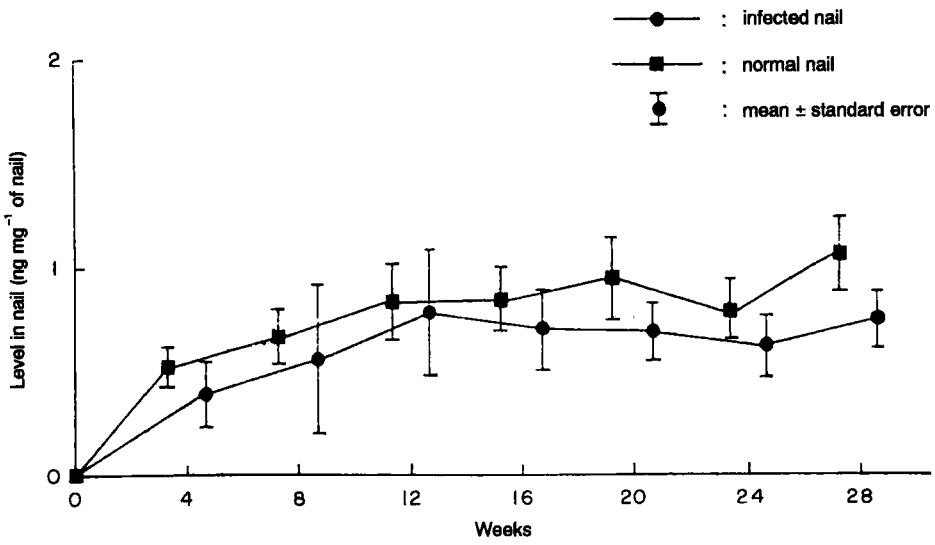

Figure 3. Changes in terbinafine levels in nails. —●—, Infected nail; —■—, normal nail; ⊕, mean ± standard error.

was 3.14 ± 0.34 ng mg^{-1}. The quantitation limit of terbinafine in plasma was 2 ng ml^{-1}.

Data on three of the 34 patients were excluded from evaluation because the patients were administered the test drug immediately before blood sampling on each observation day from the start to the end of the treatment period. One of these three patients was the one in whom drug intake from week 18 onwards was less than half. The level of terbinafine gradually increased until week 10 of treatment, and reached 280.3 ± 40.4 ng ml^{-1} during week 10. It remained at almost the same level from week 10 onwards with some individual differences (Fig. 4).

The values were compared in five patients who were 65 years or older (aged) and in those patients who were less than 65 years old (non-aged). Individual differences were noted in the aged patients, but the changes in values were similar to those of the non-aged patients.

Discussion

The overall efficacy rate of terbinafine in tinea unguium in this study was 90.9%. This result is in accordance with the result of a previous study [12]. Incorporation of the drug into nail plates was detected in the distal nail plate of some patients as early as week 2 of treatment. The level of terbinafine gradually increased, reached 0.78 ng mg^{-1} at week 12, and was then considered to have reached a steady state. Since the drug levels in normal and infected nails were similar, it was considered that destruction of the nail plate tissue by dermatophytes did not greatly affect terbinafine incorporation into the nail plate. Finlay [17] performed a 48-week clinical trial of terbinafine at a daily dose of 250 mg, in which terbinafine incorporation into the nail plate in patients with tinea unguium was investigated. In their study 0.25–0.55 ng mg^{-1} terbinafine was detected in the distal nail plates between weeks 3 and 18 of treatment. In our study, although the daily dose was less, the level of terbinafine detected in nail was comparatively higher.

It was considered, therefore, that the results of both studies show favourable incorporation of the drug into the nail plates. The amount of terbinafine incorporation into the nail plate and minimum inhibitory concentrations (MICs) [5] for dermatophytes were compared. The former was 10 times greater than the MICs at week 4 of treatment and 20 times greater at week 12, by which time the level of terbinafine was considered to have reached a steady state. This excellent incorporation of terbinafine into the nail plate was considered to underlie the high effectiveness level obtained in this study.

The level of terbinafine in hair was assayed between weeks 23 and 32 of treatment, during which time the terbinafine in plasma was considered to have reached a steady state. The level detected was 3.14 ± 0.34 ng mg^{-1}, proving that terbinafine incorporation in hair further exceeded the range of MICs [5] against dermatophytes. This result suggested that terbinafine is very effective in the treatment of tinea capitis, kerion celsi, tinea barbae and others dermatophytoses.

Subsequent progress was investigated in 26 patients who completed, discontinued or dropped out of the study. Among 17 patients in whom

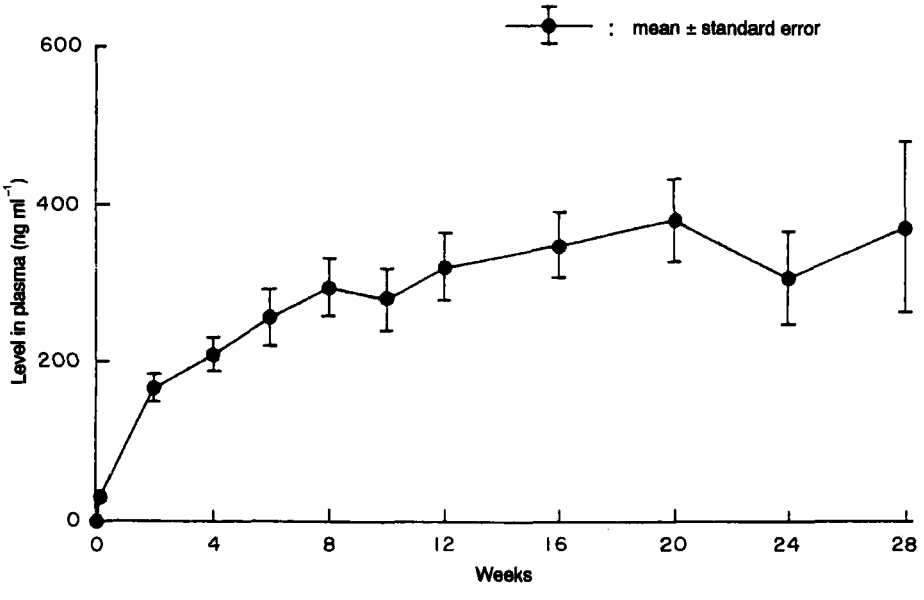

Figure 4. Changes in terbinafine levels in plasma ⊣⊢, mean ± standard error.

turbidity was observed at the final observation, those in whom turbidity was decreased, unchanged and increased numbered 7, 9 and 1 respectively. Turbidity later disappeared in five of the seven patients in whom it had been decreased. Turbidity was again observed in one of the nine in whom it had not been noted at the final observation.

A characteristic of terbinafine is that it demonstrates both antibacterial and fungicidal activity [9] against dermatophytes both *in vitro*. It is suggested that, if a drug is fungicidal, its incorporation into the nail plate may make it possible to shorten the treatment period. Previous clinical studies of terbinafine in patients with tinea unguium were thus performed in a short period.

Goodfield [18] performed a 12-week clinical trial of terbinafine in 112 patients with tinea unguium, in which the patients received a daily dose of 250 mg of terbinafine or a placebo. Follow-up was carried out 36 weeks after the completion of terbinafine administration. They obtained negative ratings for fungi in toenails and fingernails at 12 weeks after the completion of administration in 29% (14/48) and 71% (5/7), respectively, while the negative ratings for fungi in toenails and fingernails followed up at 36 weeks after the completion of administration were 82% (37/45) and 71% (5/7) respectively.

Although the daily dose in our study differed from that used by Goodfield [18], it was presumed that improvements in turbidity, even after the completion of administration, were due to the fungicidal activity of terbinafine.

The ophthalmological test, performed in eight patients before and at week 24 of treatment, revealed no test drug-induced abnormal findings. The ophthalmological test was included in this study because abnormal changes had been noted in the retina of *Cynomolgus* monkeys in a toxicity study in which multiple doses of terbinafine was given to the monkeys for 32 weeks (unpublished data, Sandoz Pharma). This abnormal finding occurred at doses 60 and 120 times greater than those used in previous clinical studies in Japan. The abnormalities almost completely disappeared during the recovery period, which lasted 13 weeks after the completion of drug administration. On the basis of this report, ophthalmological tests were carried out in both England and The Netherlands during a clinical study in which terbinafine was administered at a daily dose of 250 mg to patients with tinea unguium (unpublished data, Sandoz Pharma). However, no abnormal finding possibly related to terbinafine was noted in either study.

The level of drug in plasma (mean value) gradually increased until week 10 of treatment, and it was considered to reach the steady state during week 10. At the steady state, the drug concentration in plasma fluctuated around a value 10 times greater than the value on the day after the start of treatment. Although the data on each patient demonstrated individual differences, changes in the drug concentration in plasma were similar. It is generally considered that the pharmacokinetics of a drug varies in aged patients, probably as a result of weakened physiological function, but the pharmacokinetic changes in terbinafine in aged and non-aged patients were similar in this study. It was thus deemed that age hardly affected terbinafine's pharmacokinetics. These results prove that there was no terbinafine accumulation during long-term administration and that it is a highly safe drug.

In three of the six patients who had previously been given 12 weeks' griseofulvin treatment, griseofulvin was rated as ineffective. Terbinafine was considered to be effective in these three patients. Griseofulvin has been used for more than 30 years and cases of griseofulvin resistance have been reported [19, 20]. Although the number of cases in this study was not sufficient to draw definite conclusions, the efficacy of terbinafine in the treatment of griseofulvin-resistant tinea unguium can be expected.

As griseofulvin is fungistatic rather than fungicidal against dermatophytes, griseofulvin treatment should be continued until dermatophyte-invaded nail plates grow fully; this takes 6 months in fingernails and more than a year in toenails. It is highly likely that relapse will occur if viable organisms remain in the nail. In contrast, terbinafine demonstrated excellent efficacy in the treatment of tinea unguium in a 24-week treatment regimen. It also alleviated clinical findings even after the completion of administration. These results were deemed to indicate the advantage of terbinafine in the treatment of tinea unguium.

Griseofulvin induces adverse events such as headache and gastrointestinal disorders, and occasional photohypersensitive dermatitis, which make it difficult to continue treatment. In this study, terbinafine induced no adverse events, and its safety also proved to be satisfactory. It is suggested that terbinafine is a useful drug in the treatment of tinea unguium.

Conclusions

Terbinafine showed excellent efficacy and safety in the treatment of tinea unguium. The pharmacokinetic investigations also demonstrated satisfactory treatment results. Terbinafine is effective at a

dose of one 125-mg tablet once daily. Since long-term administration is required in the treatment of tinea unguium, patient compliance is important. On the basis of our study, it is concluded that terbinafine is effective in the treatment of tinea unguium.

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