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Bifonazole (Mycospor® cream) in the treatment of moccasin-type tinea pedis. Comparison between combination therapy of bifonazole cream + 10% urea ointment (Urepearl®) and occlusive dressing therapy with the same agents

Bifonazol (Mycospor® Creme) in der Behandlung der Tinea pedis vom Mokassintyp. Vergleich zwischen Kombinationstherapie mit Bifonazol-Creme + 10% Harnstoffsalbe (Urepearl®) und Okklusivverbandtherapie mit den selben Substanzen

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Key words. Tinea pedis, moccasin-type, antimycotic chemotherapy, bifonazole, combination therapy, urea ointment, occlusive dressing.

Schlüsselwörter. Tinea pedis, Mokassin-Typ, antimykotische Chemotherapie, Bifonazol, Kombinationstherapie, Harnstoffsalbe, Okklusionsverband.

Summary. Moccasin-type tinea pedis(MTTP) is a hardly curable superficial dermatomycosis primarily characterized by hyperkeratosis of the sole. In this study, we compared the usefulness of combination therapy of bifonazole (Mycospor® cream) + 10% urea ointment (Urepearl®) (overlapping application group = group I) with occlusive dressing therapy with the same agents (group II) in the treatment of MTTP, and obtained the following results.

(1) The clinical improvement rate (percentage of "marked improvement" and "moderate improvement") was 60.4% in group I and 83.3% in group II.

(2) The mycological eradication rate was 48.7% in group I and 82.1% in group II after 4 weeks of treatment and 90.9 and 96.9%, after 12 weeks of treatment, respectively.

(3) The clinical utility rate (percentage of "very beneficial" and "beneficial") was 83.3% in group I and 93.8% in group II.

These results indicate the superiority of both combination therapy of bifonazole + 10% urea ointment (overlapping application group) and occlusive dressing therapy with the same agents in terms of efficacy and safety for the treatment of MTTP, and suggest that they can be recommended for treatment of patients for whom it is difficult to use oral antimycotic agents or for patients who fail to respond to oral medications alone.

Zusammenfassung. Bei der hyperkeratotischen Form der Tinea pedis handelt es sich um eine hauptsächlich in der Hornhautschicht proliferierende, schwer heilbare Dermatomykose. In der vorliegenden Studie haben wir eine Behandlung der hyperkeratotischen Form der Tinea pedis mit Bifonazol (Mycospor® Creme) und einer 10% Harnstoffsalbe (Urepearl®) durchgeführt und die Patienten in eine Kombinationsgruppe (Gruppe I) und eine mit Okklusivverbänden behandelte Gruppe (Gruppe II) unterteilt. Beim Wirksamkeits-Vergleich der einzelnen Behandlungsformen wurden die folgenden Ergebnisse erhalten:

(1) Die Besserungsrate betrug 60.4% in Gruppe I und 83.3% in Gruppe II.

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(2) Die Eliminationsrate der Fungi nach 4 Wochen betrug 48.7% in Gruppe I und 82.1% in Gruppe II. Nach 12 Wochen betrug dieses Verhältnis 90.9% in Gruppe I und 96.9% in Gruppe II.

(3) Die Nützlichkeitsrate (Fälle, die als "besser" eingestuft wurden oder "nützlich") betrug 83.3% in Gruppe I und 93.8% in Gruppe II.

Diese Ergebnisse deuten darauf hin, daß sowohl eine Kombinationsbehandlung der hyperkeratotischen Form der Tinea pedis mit Bifonazol-Creme und einer 10% Harnstoffsalbe (Gruppe mit gleichzeitiger Applikation) als auch die Behandlung mit Okklusivverband eine hervorragende Nützlichkeit und Sicherheit aufweisen. Bei Patienten, bei denen eine systemische Behandlung mit Antimykotika nicht möglich ist oder bei denen durch die orale Behandlung allein kein ausreichender Behandlungserfolg erzielt werden kann, sollte diese Therapie bevorzugt eingesetzt werden.

Introduction

The term of moccasin-type tinea pedis (MTTP) is often used carelessly for tinea pedis mainly consisting of hyperkeratosis of the sole in Japan [1–5]. In Europe and USA, tinea pedis showing a tendency toward hyperkeratosis without any marked inflammatory symptoms over a long-term period and showing little response to treatment with topical agents has been reported as moccasin-type or hyperkeratotic type tinea pedis [6–8].

In this study, we compared the usefulness of combination therapy of bifonazole (Mycospor® cream) + urea ointment (overlapping application group = group I) with occlusive dressing therapy with the same agents (group II) in the treatment of MTTP as a refractory superficial cutaneous mycosis at eight medical centres.

Study methods

Study sites

A joint research team (representative coordinator: Prof. S. Nishiyama of Kitasato University at the time of study) was organized by eight medical centres including Kitasato University Hospital and other dermatological centres and the study was conducted over a period from December 1992 to the end of September 1993 in accordance with good clinical practice (GCP) after its clinical and ethical appropriateness had been reviewed and approved by the Clinical Trial Review Board set up at each study site.

Target disorder

Participants were selected from tinea patients who were seen at the above-mentioned eight study sites using the criteria: aged between 20 and 75 years, with an established diagnosis of MTTP in both feet (tinea pedis primarily characterized by hyperkeratosis without small blisters) in whom the presence of fungi was demonstrated by direct microscopic examination or culture.

However, patients fulfilling any of the following criteria were excluded from this study: contact dermatitis or purulent infection as a complication at the test region; oral steroid therapy; serious systemic disease; use of an antimycotic agent (topical or oral) within 2 weeks before the study; pregnancy, breast-feeding or possible pregnancy; other reasons considered by the physicians in charge to render the patient unsuitable for this study.

Patient informed consent

Prior to the study start, the physicians in charge obtained verbal or written consent to participate in the study from every patient based on his or her own free will after the physicians in charge fully informed, as specified in GCP, the patients themselves or their family members of the study purpose and method, expected benefits and potential adverse reactions and availability of other therapies and obtained their understanding that the patients would not suffer from any disadvantage even if they prematurely withdrew from the study or declined the offer to participate in the study.

Test drugs

The test drugs were Mycospor® (Bayer Yakuhin, Osaka, Japan) cream: 1% bifonazole cream and Urepearl® (Otsuka Pharmaceutical Co, Tokyo, Japan) or Pastaron® (Sato Pharmaceutical Co, Tokyo, Japan): 10% urea ointment

Administration method and duration of treatment

Administration method. In general, patients took a bath every day, and applied the study drugs to the affected region once a day within 10 min after bathing. Using the envelope technique, patients were instructed to apply bifonazole (Mycospor® cream) together with urea ointment to one foot (group I: overlapping application group) and bifonazole (Mycospor® cream) together with urea ointment by means of overlapping application followed by wearing of occlusive dressing before

retiring to the other foot (group II: occlusive dressing group).

Duration of treatment. The treatment period was 12 weeks. However, the physicians in charge could discontinue the study at their own discretion for a patient who suffered any development of adverse reactions or aggravation of symptoms or was cured of the disorder in the middle of study. For patients in whom no benefits had been achieved by the end of the administration period specified, administration could be further continued to collect reference data for evaluation of clinical utility.

Concomitant drugs. As a general rule, concomitant use of antimycotic agents other than the study drugs was not allowed during the study. In addition, the use of other drugs such as steroids and antihistamines that might affect the evaluation of the study drugs was also prohibited.

However, if fissures occurred on the heel and others, then application of white petroleum jelly to that region alone was exceptionally allowed. If any concomitant drugs were used for some unavoidable reasons to treat complications or incidental diseases including such an exceptional case as above, then the drug name, administration method, dosage, duration of treatment and reasons for use were to be recorded in the investigation record.

Days of observation and items of investigation. Normally, observations were made after 2 weeks (14 ± 2 days) of treatment, 4 weeks (28 ± 3 days) of treatment, 8 weeks (56 ± 3 days) of treatment, and 12 weeks (84 ± 3 days) of treatment. In addition, investigation and evaluation of the following items were made, at the sixth week (42 ± 3 days) and tenth week (70 ± 3 days), if possible.

Mycological investigation. Prior to the study start, the presence of fungi was confirmed by direct microscopic examination or culture, and the pathogen was separated and identified. Furthermore, direct microscopic examination was made on specimens collected from several lesions on each day of observation in order to confirm the presence (+) or absence (−) of the pathogen.

Clinical symptoms. On each observation day, investigations were made for hyperkeratosis, scales, redness, fissures and itching; their extent was assessed in the following four grades: 0, no symptoms; 1, mild symptoms; 2, moderate symptoms; 3, severe symptoms.

Adverse reactions. On each observation day, assessment was made for subjective and objective symptoms by assessing their extent and causal association with the study drugs using the four grades defined below.

Adverse reactions were defined as subjective or objective symptoms and abnormal variations of laboratory values which causal association with the study drugs could not be denied. They were checked as closely as possible including those which were extremely mild. If any adverse reaction was seen, investigations were made on its type, region of onset, extent, day of occurrence, progress/treatment, day of disappearance and causal association with the study drugs.

Standards for evaluation of adverse reactions: 0 (none), none; 1 (mild), requiring no special treatment and permitting continued treatment; 2 (moderate), requiring some treatment but permitting continued treatment; 3 (severe), severe enough to require discontinuation of the trial.

Causal association with the study drugs: 1, deniable; 2, unknown; 3, probable; 4, definite.

Complications and incidental diseases. For complications or incidental diseases which newly occurred during the trial, investigations were made on the time of development, their type, extent, treatment/outcome.

Laboratory tests. Whenever possible, the following tests were conducted before the treatment started and on each observation day. In addition, if any abnormal variation of clinical significance was found, it was followed-up to investigate whether there was any causal association with the study drugs.

(1) Haematology in general: erythrocyte count, haemoglobin, haematocrit, white cell count, white cell differential, platelet count.

(2) Blood biochemistry: total protein, albumin, total bilirubin, direct bilirubin, glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT) γ-GPT, ALP, total cholesterol, neutral fat, urea nitrogen, uric acid, creatinine, Na, K, Cl, CPK.

(3) Urinalysis: pH, protein, glucose, urobilinogen.

Assessment of efficacy

Evaluation/assessment was made for the following items at the end of administration. If the disorder was almost completely or completely cured during the treatment, evaluation was made at that time.

Assessment of mycological efficacy. Assessment was made in the two grades of positive (+) and negative (−).

Assessment of overall dermatological symptoms. Assessment was made in the following five grades:

1, marked improvement: the dermatological manifestations were completely or almost completely resolved; 2, moderate improvement: the dermatological manifestations were considerably improved; 3, slight improvement: the dermatological manifestations were slightly improved; 4, no change: the dermatological manifestations remained unchanged; 5, aggravation: the dermatological manifestations were aggravated.

Assessment of overall efficacy. Based on mycological efficacy and assessment of overall dermatological symptoms, overall efficacy was rated as shown in Table 1.

Assessment of safety. The safety of the test drug was rated as follows based on adverse reactions and laboratory tests: 1, safe; 2, almost safe; 3, safety questionable; 4, unsafe.

Assessment of clinical utility. On the final day of the study, the clinical utility of the test drug was rated using the criteria listed below, based on the clinical improvement and safety ratings: 1, very beneficial; 2, beneficial; 3, slightly beneficial; 4, not beneficial; 5, Noxious.

Handling of dropouts/discontinuations

For patients who discontinued the trial or dropped out of it in the middle for the reasons below, every possible effort was made to record the dates of dropout/discontinuation, reasons, treatment and outcome along with assessment of various items for evaluation at that time. For patients who ceased to return to the study sites during the trial, the reason and the outcome were investigated as closely as possible.

Patients who fell under any of the following categories were regarded as dropouts, for whom only safety was evaluated: 1, patients who did not return after the first presentation; 2, patients for whom the trial was discontinued due to adverse reactions; 3, patients who needed to use antihistamines; 4, patients who did not meet the specified frequency of application of the study drugs; 5, patients who ceased to return to the study site in the middle of treatment; 6, patients who did not return on the final evaluation day; 7, patients whose consent was withdrawn by patients themselves or by their family members; 8, patients in whom the physicians in charge considered further continuation of the trial difficult.

Patients falling under category 1 were handled in the same way as cases of exclusion, and those falling under category 2 were subjected to evaluation of safety and clinical utility only. Patients falling under categories 5 to 8 were analysed as much as possible to collect reference data for clinical utility.

Handling of cases

Handling of cases of protocol violation and discontinuations/dropouts was discussed and settled at the coordination meeting.

Results

Composition of evaluatable subjects

This trial involved 73 cases of MTTP in both feet. Some of them were found to have deviated from the rules specified in the trial contract or discontinued/dropped out in the middle of the trial, and thus subjected to the case review meeting at which discussions were made concerning how such cases should be handled. It was decided that those who were excluded from evaluation of efficacy, safety and clinical utility should be classified as unevaluable cases but included in analysis of final evaluation. Accordingly efficacy was evaluated in 48 cases, safety in 69 cases and clinical utility in 48 cases.

Subjects

There were 22 men and 26 women with a mean age of 56.0 years (range: 21–79 years). The pathogens could be identified in 14 feet in group I (*Trichophyton rubrum* in 13 feet and *Trichophyton mentagrophytes* in one foot) and in 15 feet in group II (*T. rubrum* in 14 feet and *T. mentagrophytes* in one foot). The scores for MTTP and those for

Table 1. Overall efficacy criteria

Final dermatological improvement ratings	Negative	Positve
Marked improvement	1 Marked efficacy	3 Slight efficacy
Moderate improvement	2 Moderate efficacy	3 Slight efficacy
Slight improvement	2 Moderate efficacy	3 Slight efficacy
No change	4 No efficacy	4 No efficacy
Aggravation	5 Aggravation	5 Aggravation

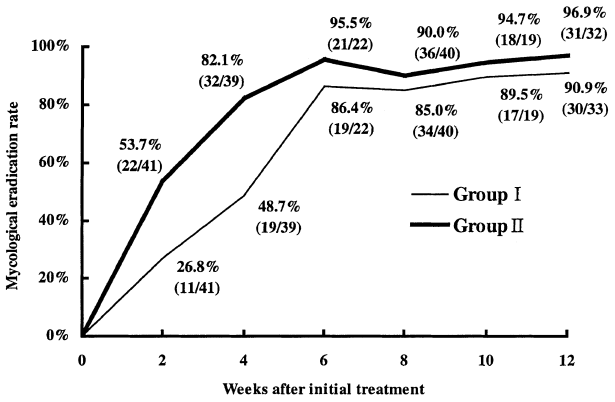

Figure 1. Changes in mycological eradication rate.

individual dermatological symptoms before initial treatment showed no significant difference between the two groups (Table 2).

Clinical results

Assessment of mycological efficacy. The final mycological eradication rate was 93.8% (45 of 48) in group I versus 95.8% (46 of 48) in group II (Table 3). The percentage elimination of pathogens in patients evaluated at each week of observation was 26.8 and 53.7% after 2 weeks of treatment, 48.7 and 82.1% after 4 weeks of treatment, 85.0 and 90.0% after 8 weeks of treatment, and 90.9 and 96.9% after 12 weeks of treatment, respectively (Fig. 1).

Overall assessment of dermatological symptoms. Figure 2 shows how the scores for moccasin-type tinea pedis as a whole and those for individual dermatological symptoms changed over time in each treatment group.

The final improvement rate of dermatological symptoms (the rate of "marked improvement" + "moderate improvement") was 60.4% (29 of 48) in group I and 83.3% (40 of 48) in group II, without any significant difference between the two groups, but the improvement rate of "marked improvement" or higher was 10.4% (five of 48) in group I and 47.9% (23 of 48) in group II, the latter being demonstrated to be significantly better than the former by the Wilcoxon test ($P<0.001$) (Table 4).

The improvement rate of dermatological symptoms in patients evaluated at each week of observation was 9.5% in group I and 33.3% in group II after 2 weeks of treatment, 25.0 and 60.0% after 4 weeks of treatment, 55.0 and 75.0% after 8 weeks of treatment, and 57.6 and 81.3% after 12 weeks of treatment (Fig. 3).

Assessment of overall clinical efficacy. Table 5 shows the final overall clinical efficacy assessment based on the final mycological efficacy and final dermatological clinical symptoms. The efficacy rate (the rate of "Marked efficacy" + "Moderate efficacy") on the day of final overall assessment was 93.8% (45 of 48) in group I and 93.8% (45 of 48) in

Table 2. Subjects

Item				
Sex	Male		22	
	Female		26	
Age (yrs)	Range		21–79	
	Mean ± SD		65 ± 11.4	
		group	I	II
Causative fungi (feet)	*T. rubrum*		13	14
	T. mentagrophytes		1	1
	Negative culture		24	23
Score for MTTP (Mean ± SD)	Hyperkeratinization		2.35 ± 0.56	2.35 ± 0.60
	Scaling		2.33 ± 0.56	2.33 ± 0.60
	Redness		1.38 ± 0.62	1.44 ± 0.63
	Fissure		2.03 ± 0.72	2.07 ± 0.78
	Itching		1.88 ± 0.59	1.85 ± 0.66
	Statistical analysis		NS	

Table 3. Mycological efficacy

Group	No. of feet	Eradicated	Persisted	Eradication rate	Statistical analysis
Group I	48	45	3	93.8%	NS
Group II	48	46	2	95.8%	

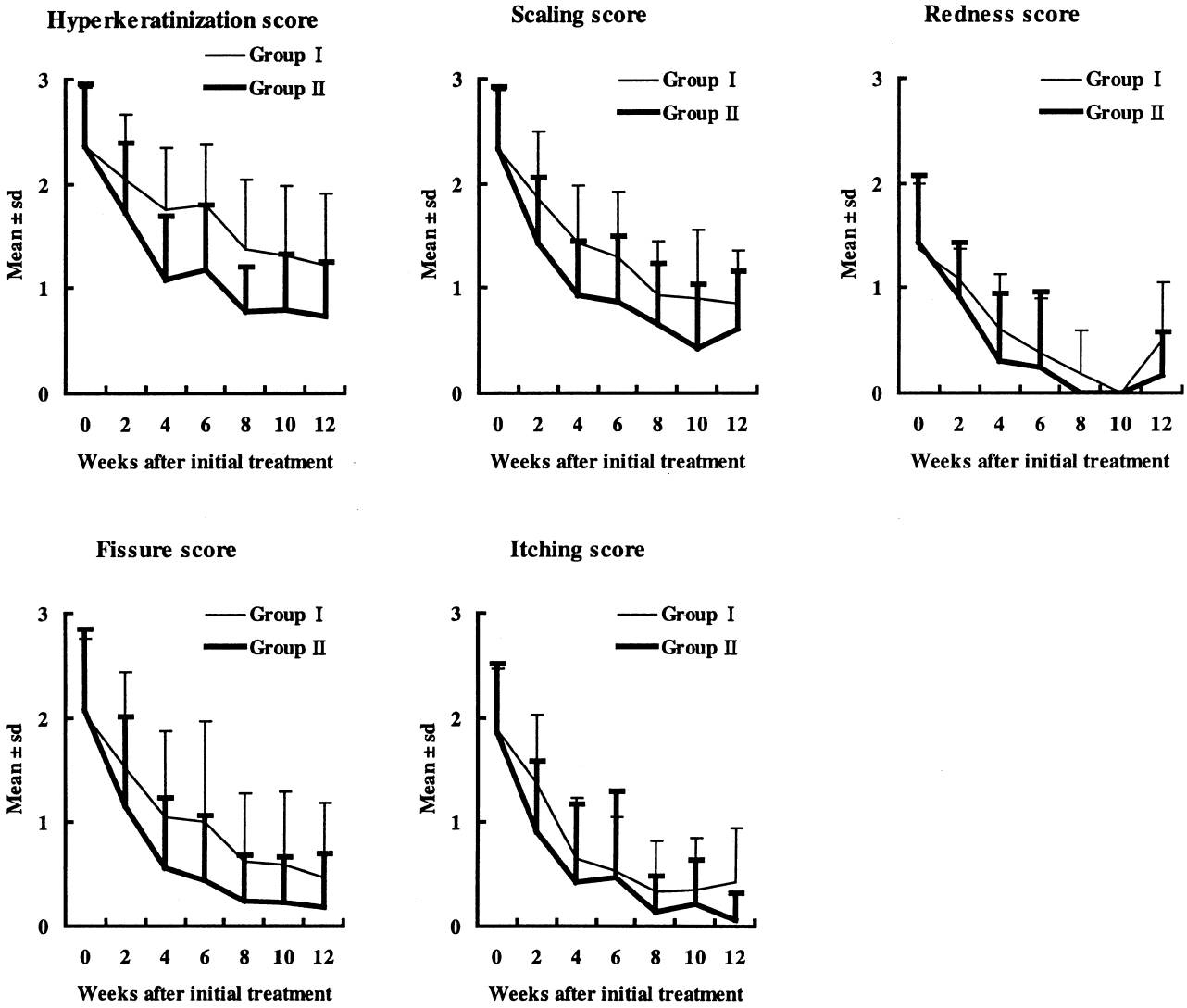

Figure 2. Changes in the improvement score in skin symptoms after treatment.

Table 4. Final improvement rate of dermatological symptoms

Group	No. of feet	Marked improvement	Moderate improvement	Slightly improvement	No change	Aggravation	Improvement rate	Statistical analysis
Group I	48	5	24	19	0	0	60.4%	Wilcoxon
Group II	48	23	17	6	0	2	83.3%	$P=0.0002$***

group II without any significant difference being noted between the two groups. However, the rate of "Marked efficacy" was 10.4% (five of 48) in group I and 47.9% (23 of 48) in group II, which was demonstrated to be significantly higher ($P<0.001$) than the former by the Wilcoxon test.

Safety assessment

Adverse reactions (subjective/objective symptoms). Out of the total 130 feet (65 cases) evaluated for safety, no adverse reactions were found in group I whereas they were found in three feet in group II. There were three feet in which the trial had to be discontinued, and itching and newly generated small blisters were the most common symptoms of adverse reactions. There were three occurrences of adverse reactions in which the causal association was considered definite or probable, but none of them was serious; they disappeared or resolved with discontinuation of treatment.

Abnormal variations of laboratory data. There was no case in which any abnormal variation of laboratory data was observed. The incidence of adverse reactions (including those with abnormal variations of

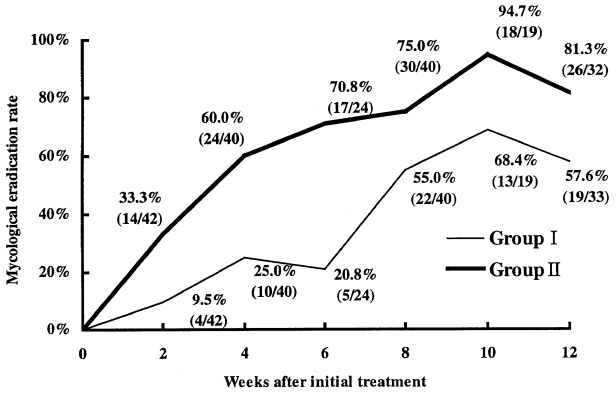

Figure 3. Changes in improvement rate.

laboratory data) was 0% (none of 65) in group I and 4.6% (three of 65) in group II.

Clinical utility

Assessment of clinical utility is summarized in Table 6. The usefulness rate (the rate of "very beneficial" + "beneficial") on the day of final overall assessment was 83.3% (40 of 48) in group I and 93.8% (45 of 48) in group II without any significant difference being noted between the two groups. However, as far as the rate of "very beneficial" was concerned, it was 8.3% (four of 48) in group I and 47.9% (23 of 48) in group II, which was demonstrated to be significantly higher ($P<0.001$) than the former by the Wilcoxon test.

Discussion

It is generally believed that MTTP is very difficult to cure by topical therapy using antimycotic agents for topical use alone because they are prevented from infiltrating into lesions, and hence in Japan the disorder has been commonly treated with oral administration of griseofulvin, which is currently being replaced by itraconazole [1]. However, oral administration of antimycotic agents is not feasible in all patients because they may be associated with gastrointestinal disorder or liver dysfunction in addition to the problem of concomitant drugs. In such cases, it often becomes necessary to apply antimycotic agents for topical use.

Bifonazole is an antimycotic agent of the imidazole series developed by Bayer in Germany, having a broad antimycotic spectrum against pathogenic fungi [9, 10].

In guinea-pigs with experimentally infected dermatophytosis, bifonazole was found to have a retention time of as long as 36–48 h within the horny layer. When compared with clotrimazole and miconazole, bifonazole proved to have an anti-infective action which persisted about twice as long. It was also reported that bifonazole has a better penetration and retention within the horny layer [9].

Furthermore, a permeability study using human abdominal skin demonstrated that bifonazole cream penetrated into the horny layer of the epidermis, the prickle-cell layer and the reticular layer of corium at concentrations of 200–1000 $\mu g\,cm^{-3}$, 20 $\mu g\,cm^{-3}$ and 2–3 $\mu g\,cm^{-3}$, respectively, which were far above the MIC against dermatophyte [11].

In this study, we compared the usefulness of combination therapy of bifonazole cream having such characteristics + 10% urea ointment (group I) with occlusive dressing therapy with the same agents (group II) in the treatment of 73 patients with MTTP, both being applied once a day over a period of 12 weeks.

As a result, the final improvement rate of dermatological symptoms (the rate of "marked improvement" + "moderate improvement") was 60.4% (29 of 48) in group I and 83.3% (40 of 48)

Table 5. Overall clinical efficacy

Group	No. of feet	Marked efficacy	Moderate efficacy	Slight efficacy	No efficacy	Aggravation	Efficacy rate	Statistical analysis
Group I	48	5	40	3	0	0	93.8%	Wilcoxon
Group II	48	23	22	1	0	2	93.8%	$P=0.0005$***

Table 6. Usefulness

Group	No. of feet	Very beneficial	Beneficial	Slightly beneficial	No	Noxious rate	Usefulness analysis	Statistical
Group I	48	4	36	8	0	0	83.3%	Wilcoxon
Group II	48	23	22	1	0	2	93.8%	$P=0.0000$***

in group II without any significant difference, but the improvement rate of "marked improvement" or higher was 10.4% (five of 48) in group I and 47.9% (23 of 48) in group II, the latter being demonstrated to be significantly better than the former by the Wilcoxon test ($P<0.001$).

The improvement rate of dermatological symptoms in patients evaluated at each week of observation was 9.5% in group I and 33.3% in group II after 2 weeks of treatment, 25.0 and 60.0% after 4 weeks of treatment, 55.0 and 75.0% after 8 weeks of treatment, and 57.6 and 81.3% after 12 weeks of treatment.

In this study, the mycological effect was assessed by the results of direct microscopic examination. This method is common in Japanese clinical study. There is the report which explains there are no significant differences in the result between direct microscopic examination and culture [12]. The final mycological efficacy (the percentage elimination of pathogen) was 93.8% (45 of 48) in group I and 95.8% in group II. Furthermore, the mycological efficacy (the percentage elimination of pathogen) in patients evaluated at each week of observation was 26.8% in group I and 53.7% in group II after 2 weeks of treatment, 48.7 and 82.1% after 4 weeks of treatment, 85.0 and 90.0% after 8 weeks of treatment, and 90.9 and 96.9% after 12 weeks of treatment. The response rate (the rate of "marked efficacy" + "moderate efficacy") on the day of final overall assessment was 93.8% in group I and 93.8% in group II without any significant difference between the two groups, However, the rate of "marked efficacy" was 10.4% (five of 48) in group I and 47.9% (23 of 48) in group II, which was demonstrated to be significantly higher ($P<0.001$) than the former by the Wilcoxon test.

In addition, itching and newly generated small blisters were found in an extremely small number of patients in group II, a finding suggesting that more careful caution should be exercised when ODT therapy is practised under an environmental condition such as summer during which patients are more liable to feel stuffy. Finally we are planning to prepare a mixture of an antimycotic agent and urea ointment in order to study its usefulness as well as its distribution into the horny layer.

Conclusion

Both of the combination therapy of bifonazole (Mycospor® cream) + 10% urea ointment (Urepearl®) and the occlusive dressing therapy with the same agents were found to be highly useful, which suggests that they can be recommended for patients for whom it is difficult to use oral antimycotic agents or for patients who fail to respond to oral medications alone.

We are planning to make further studies on distribution of this drug into the horny layer by means of simple application, combined use with urea ointment, or occlusive dressing therapy.

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