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# Therapeutic Efficacy of Topically Applied KP-103 against Experimental Tinea Unguium in Guinea Pigs in Comparison with Amorolfine and Terbinafine

Yoshiyuki Tatsumi,[1]* Mamoru Yokoo,[1] Hisato Senda,[1] and Kazuaki Kakehi[2]

*Central Research Laboratories, Kaken Pharmaceutical Co., Ltd., Shinomiya, Yamashina-ku, Kyoto-city, Kyoto 607-8042,[1] and Faculty of Pharmaceutical Sciences of Kinki University, Kowakae, Higashi-Osaka-shi, Osaka 557-0818,[2] Japan*

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**The therapeutic efficacy of KP-103, a novel topical triazole, in a guinea pig tinea unguium model was investigated. Experimental tinea unguium and tinea pedis were produced by inoculation of *Trichophyton mentagrophytes* SM-110 between the toes of the hind paw of guinea pigs. One percent solution (0.1 ml) of KP-103, amorolfine, or terbinafine was topically applied to the nails and whole sole of an infected foot once daily for 30 consecutive days, and terbinafine was also orally administered at a daily dose of 40 mg/kg of body weight for 30 consecutive days, starting on day 60 postinfection. The fungal burdens of nails and plantar skin were assessed using a new method, which makes it possible to recover infecting fungi by removing a carryover of the drug remaining in the treated tissues into the culture medium. Topically applied KP-103 inhibited the development of nail collapse, significantly reduced the fungal burden of the nails, and sterilized the infected plantar skin. On the other hand, topical amorolfine and topical or oral terbinafine were ineffective for tinea unguium, although these drugs eradicated or reduced the fungal burden of plantar skin. The in vitro activities of amorolfine and terbinafine against *T. mentagrophytes* SM-110 were 8- and 32-fold, respectively, decreased by the addition of 5% keratin to Sabouraud dextrose broth medium. In contrast, the activity of KP-103 was not affected by keratin because its keratin affinity is lower than those of the reference drugs, suggesting that KP-103 largely exists in the nails as an active form that was not bound to keratin and diffuses in the nail without being trapped by keratin. The effectiveness of KP-103 against tinea unguium is probably due to its favorable pharmacokinetic properties in the nails together with its potent antifungal activity.**

Among dermatophytoses, tinea unguium is the most resistant to the treatment of antifungal drugs. At present, the oral antifungal agents griseofulvin (10), terbinafine (12), and itraconazole (9) are available for the treatment of tinea unguium because antifungal agents are generally ineffective when applied topically (13, 23). The treatment of tinea unguium has improved following the introduction of terbinafine and itraconazole. However, some 20% of patients fail to benefit from therapy (20). The main reason for the treatment failure was suggested to be inadequate compliance for the usual long-period treatment of 6 to 12 months with these oral drugs (20). In addition, the long-period oral treatment can lead to severe systemic adverse effects or interactions with other systemic drugs being taken by the patients (5, 6), which interrupt the therapy. Therefore, there is a clear need for new antifungal drugs that can be administered topically to reduce the risk of side effects or that achieve complete cure in a shorter treatment period than the existing oral antifungal drugs to improve compliance. Two topical antifungal drugs, amorolfine (8) and ciclopirox (7), are available in nail lacquer formulations containing concentrations of 5 and 8%, respectively, and are used for the treatment of tinea unguium. However, complete cure cannot be expected in every case (13).

When terbinafine was orally administered to healthy individuals at a daily dose of 250 mg for 28 days, a concentration 10- to 1,000-fold higher than MICs for dermatophytes was achieved in nails and persisted for up to 4 months after stopping treatment (3). Nevertheless, a long-period treatment over 3 months does not lead to cure rates above 80% for toenails (31), and relapse often occurs after treatment (4, 21, 30). Presumably because oral antifungal drugs cannot remove fungi from nails before nails are turned over, the pace of response of tinea unguium seems to be a function of the nail growth rate. It is likely that the low fungicidal effect for tinea unguium is related to pharmacokinetic problems of oral antifungal drugs in the nails (20). Indeed, many antifungal agents are strongly bound to keratin, which not only reduces their antifungal potency but also may restrict their penetration into the nails (22, 24, 25).

We reported that KP-103, a novel topical triazole antimycotic, is highly effective in treating and preventing relapse in guinea pig models of tinea pedis and tinea corporis (16, 24–26), and its effectiveness is presumably because KP-103 has lower keratin affinity than the existing antifungal drugs and is largely retained as an active form that is not bound to keratin in the horny layer (25).

In the present study, to predict the potency of antifungal activity of KP-103 in the nails, we examined the influence of keratin on its in vitro antidermatophyte activity and its affinity

* Corresponding author. Mailing address: Central Research Laboratories, Kaken Pharmaceutical Co., Ltd., 14 Minamikawara-cho, Shinomiya, Yamashina-ku, Kyoto-city, Kyoto 607-8042, Japan. Phone: 81-75-594-0787. Fax: 81-75-594-0790. E-mail: tatsumi_yoshiyuki@kaken.co.jp.

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to keratin compared with those of amorolfine and terbinafine. Moreover, we evaluated the therapeutic effect of KP-103 for guinea pigs with tinea unguium and plantar tinea pedis caused by *Trichophyton mentagrophytes* in comparison with the two reference drugs. Their therapeutic efficacies were assessed using the new method that we recently reported (26), which permits the precise recovery of fungi from the treated tissues by removal of a carryover of the drug remaining in the skin tissues into the culture media.

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## MATERIALS AND METHODS

**Antifungal agents.** KP-103, amorolfine, and terbinafine hydrochloride were synthesized at the Central Research Laboratories, Kaken Pharmaceutical Co., Ltd., Kyoto, Japan.

**Media.** Sabouraud dextrose broth (SDB) and Sabouraud dextrose agar (SDA) were purchased from Difco Laboratories, Detroit, Mich. Potato dextrose agar was purchased from Nissui Seiyaku, Tokyo, Japan. The morpholinepropanesulfonic acid (MOPS)-buffered RPMI 1640 agar medium (pH 7.0), which contained liquid RPMI 1640 medium supplemented with L-glutamine (Nissui), 2% sodium bicarbonate, 0.165 M MOPS, and 1.6% agar, was used.

**Test organism.** Clinical isolates of *T. mentagrophytes* SM-110 and KD-04 were supplied by S. Fujita, Niigata University School of Medicine, Niigata, Japan, and H. Takahashi, Teikyo University School of Medicine, Tokyo, Japan, respectively. *Candida kefyr* JCM 1167 was purchased from The Institute of Physical and Chemical Research, Saitama, Japan.

**In vitro study. (i) In vitro antidermatophyte activity in the presence of keratin.** MICs for *T. mentagrophytes* KD-04 were determined by the following method. Ten microliters of twofold serial dilutions of the drugs solubilized in dimethyl sulfoxide (DMSO) was dispensed into a tube containing 1 ml of SDB medium containing 50 mg of defatted-keratin powder. Each tube was seeded with $10^6$ microconidia of *T. mentagrophytes* SM-110 and then incubated at 30°C for 7 days. For reference, the same test was also run in SDB without keratin powder. The MICs were defined as the lowest drug concentrations that inhibited visible growth of the fungi.

**(ii) Affinity to keratin.** The affinities of the test drugs to keratin powder were determined by a slight modification of the method of Uchida et al. (29). A 100-μl sample of the drug solution prepared in DMSO at a concentration of 1 mg/ml was dispensed into 9.9 ml of saline containing 5% defatted-keratin powder. After shaking at 37°C for 1 h (75 rpm), the mixture was centrifuged at 3,000 × *g* for 5 min, and two 100-μl portions of the supernatant were taken to determine the rate of binding of drug to keratin. The precipitate (the drug-bound keratin) was washed 10 times by shaking (75 rpm) in 10 ml of saline at 37°C for 10 min. After each washing, the mixture was then centrifuged at 3,000 × *g* for 5 min, and two 100-μl samples were taken from the supernatant to determine the rate of release of the drug from keratin.

To determine the drug concentration in the sample solution using bioassay, standard curves were constructed. All drugs tested were dissolved in DMSO at a concentration of 1 mg/ml, serially diluted twofold with DMSO, and then diluted 1:100 with saline. Bioassay was performed in MOPS-buffered RPMI 1640 agar medium containing *C. kefyr* JCM 1167 ($2 \times 10^4$ cells/ml) for KP-103 and SDA and potato dextrose agar containing *T. mentagrophytes* KD-04 ($1 \times 10^4$ conidia/ml) for amorolfine and terbinafine, respectively. Assay plates were prepared in duplicate. Wells (8 mm in diameter) were cut in the agar. Aliquots (100 μl) of samples and standards were dispensed into the wells and incubated at 30°C for 3 days. Diameters of zones of inhibition were measured with a vernier caliper to the nearest 0.01 mm. Standard curves relating the zone diameter to the concentration of the drugs were prepared on a semilogarithmic graph and were linear over the range of 0.039 to 10 μg/ml for KP-103 and terbinafine and 0.156 to 10 μg/ml for amorolfine, with $\gamma^2$ being >0.99.

**In vivo efficacy. (i) Animals.** Male Hartley strain guinea pigs weighing 370 to 420 g were used in the study. The experiments were performed with groups of five animals.

**(ii) Preparation of inocula.** Arthrospores of *T. mentagrophytes* SM-110 were prepared by the method described previously (24–26). The arthrospores were collected and suspended in saline containing 0.05% Tween 80. The suspension was homogenized with a glass homogenizer, filtered through gauze, and then adjusted to give a concentration of $10^8$ spores/ml by counting with a hemocytometer.

**(iii) Production of tinea unguium and tinea pedis.** Guinea pigs were infected by a slight modification of the method described previously (25, 26). In brief, two paper disks (4 by 8 mm; AA disk; Whatman Japan KK) were immersed in the fungal suspension, applied between the toes of the hind paw (between the second and third toes and between the third and fourth toes) with a foam pad (Reston self-adhering foam pads [catalog no. 1560]; 3M Co.), and fixed with an adhesive elastic tape (Elastopore; Nichiban, Tokyo, Japan) (day 0 postinfection). The disks were removed on day 21 postinfection.

**(iv) Histological examination of nail tissue.** Nails were taken from infected animals on day 60 postinfection. The nails were fixed in 10% (vol/vol) buffered neutral formalin solution, decalcified in 10% (vol/vol) buffered formic acid for 1 month, fixed again in the formalin solution, and embedded in paraffin. Thin paraffin sections of the nails were examined by light microscopy after staining with periodic acid-Schiff stain.

**(v) Drugs and treatment.** KP-103, amorolfine, or terbinafine was dissolved in a mixture of polyethylene glycol 400-ethanol (75:25, vol/vol) (1, 17, 24–26) at 1% for topical application. Terbinafine hydrochloride tablets (Lamisil) were purchased from Novartis Pharma KK and suspended in coconut oil with a mortar, and the suspension was dispensed into capsules for oral administration. A 1% solution (0.1 ml) of KP-103, amorolfine, or terbinafine was topically applied to the nails and whole sole of the foot of guinea pigs once daily, or a capsule of terbinafine was orally administered to guinea pigs at a once-daily dose of 40 mg/kg of body weight. Each treatment was started on day 60 postinfection and continued for 30 consecutive days. The control group of animals was infected and received vehicle therapy.

**(vi) Evaluation of therapeutic efficacy.** The therapeutic efficacy for tinea unguium was evaluated by the method reported previously (26) with a slight modification. Two days after the last treatment, all animals were sacrificed and nails were taken from the treated feet, which were wiped with a cotton swab containing 70% ethanol. The length of each nail was measured with a vernier caliper. The nail sample was minced with scissors, homogenized in phosphate-buffered saline (PBS) (pH 7.4) containing 2% trypsin, and digested at 37°C for 1 h. After centrifugation, the precipitate was washed with 10 ml of PBS three times by centrifugation at 3,000 × *g* for 10 min to remove trypsin and the remaining drug and was suspended in 4 ml of sterilized water. The suspension was dialyzed with a cellulose membrane tube in distilled water at 4°C for 14 days to eliminate completely the drugs in the nails. The suspension was centrifuged at 3,000 × *g* for 10 min, and the precipitate was suspended in 1 ml of PBS. One hundred microliters of the sample and serial 10-fold dilutions thereof were spread onto an SDA plate containing 1 g of cycloheximide, 100 mg of gentamicin, 50 mg of chloramphenicol, and 50 mg of flucytosine, per liter, to select the fungi. The plates were incubated for 10 days at 30°C, and fungal colonies were counted. The CFU were enumerated, and the $\log_{10}$ of CFU in the nails per foot was calculated (assay limit, 10 CFU per foot). Nail specimens yielding more than one fungal colony were regarded as fungus positive. The therapeutic efficacy against plantar tinea pedis was evaluated by the same method reported previously (26), on the basis of fungus-positive feet (percentage) and the $\log_{10}$ of CFU in the treated plantar skin per foot (assay limit, 20 CFU per foot).

**(vii) Statistical analysis.** Nail and skin samples with negative culture results were considered to contain 10 and 20 CFU, respectively, for numerical and statistical purposes. The frequency of fungus-positive nails or plantar skin per foot was analyzed by Fisher's exact probability test. The $\log_{10}$ of CFU in nails and plantar skin and the length of the nails were analyzed by the Kruskal-Wallis test (Tukey-type comparison test). *P* values of less than 0.05 were regarded as significant.

## RESULTS

**In vitro antidermatophyte activity in the presence of keratin powder.** It is known that many antifungal agents are inactivated when bound to keratin (21, 24, 25). To predict the potency of antifungal activity of KP-103 in infected nails, we investigated the influence of keratin on its in vitro antidermatophyte activity. Table 1 shows the MICs of KP-l03, amorolfine, and terbinafine for *T. mentagrophytes* SM-110 in SDB with and without 5% keratin powder. Amorolfine and terbinafine were 8- and

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TABLE 1. Influences of keratin powder on the antifungal activities of KP-103 and reference antifungal drugs against *T. mentagrophytes* SM-110[a]

| Compound | MIC (μg/ml) for *T. mentagrophytes* SM-110 | | Reduction in activity (B/A ratio) |
|---|---|---|---|
| | SDB alone (A) | SDB with 5% keratin (B) | |
| KP-103 | 0.2 | 0.2 | 1 |
| Amorolfine | 0.025 | 0.2 | 8 |
| Terbinafine | 0.006 | 0.2 | 32 |

[a] Inoculum size, $10^4$ microconidia/ml. The MIC was read after incubation at 30°C for 7 days in each assay medium.

32-fold, respectively, less active against the dermatophytes in SDB containing 5% keratin than in SDB alone. However, the antifungal activity of KP-l03 was not affected by keratin. Thus, KP-103 was as active as amorolfine and terbinafine in the presence of 5% keratin, although it was less active than the reference drugs in SDB alone.

**Affinity to keratin powder.** To clarify the high antifungal activity of KP-103 in the presence of keratin, we examined its affinity to keratin powder in comparison with those of amorolfine and terbinafine. Amorolfine and terbinafine showed extremely high rates of binding to keratin of 91.8 and 96.0%, respectively. On the other hand, the rate of binding of KP-103 to keratin was at the lower level of 62.8% compared to the reference drugs. Figure 1 shows the rates of release of KP-103, amorolfine, and terbinafine from each drug-preloaded keratin powder. Even though KP-103 was bound to keratin in saline containing 5% keratin, it was readily released from keratin by the washings with saline. The 10-times washings of KP-103-preloaded keratin yielded the cumulative rate of release of KP-103 from keratin of 66.8%. On the other hand, under the same experimental conditions, the cumulative rates of release of amorolfine and terbinafine from keratin were 39.1 and 21.6%, respectively, and the reference drugs showed a lower level of release from keratin than KP-103.

**Therapeutic efficacy against experimental tinea unguium in guinea pigs.** *T. mentagrophytes* SM-110 invaded the nails of guinea pigs at day 60 postinfection (Fig. 2). Once-daily topical treatment with 1% solutions (0.1 ml) of KP-103, amorolfine, and terbinafine or oral treatment with a capsule of terbinafine at a daily dose of 40 mg/kg was started on day 60 postinfection and continued for 30 consecutive days. Table 2 shows the length and fungal burden of infected nails that were taken 2 days after the last treatment. In the vehicle-treated control animals, the nails collapsed and the average length of the nails was shorter than that of intact nails (11.82 ± 1.24 mm). Similarly, in the topical amorolfine-, topical or oral terbinafine-treated animal, nails collapsed and the length of nails did not significantly differ from those of the vehicle-treated animals. On the other hand, topically applied KP-103 was highly effective in inhibiting the development of nail collapse, and the length of KP-103-treated nails did not differ from that of intact nails and was significantly longer than that of nails of oral terbinafine-treated animals. The viable dermatophytes were recovered from all nails of the vehicle-treated control animals. All drugs tested failed to sterilize all of the 10 infected nails. Topical amorolfine and topical or oral terbinafine were ineffective even in terms of reducing the fungal burden. By contrast, topically applied KP-103 significantly reduced fungal burden in the infected nails compared with the burdens found in vehicle- and oral-terbinafine-treated groups.

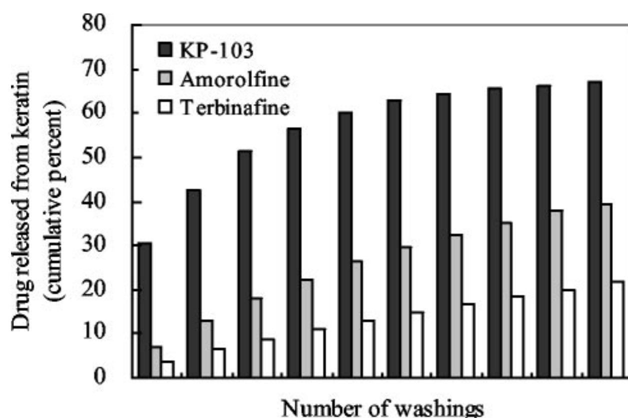


FIG. 1. Release of KP-103 or two reference antifungal drugs from the drug-preloaded keratin powder. The drug-bound keratin was washed in saline at 37°C for 10 min with shaking (75 rpm), and this procedure was repeated 10 times.

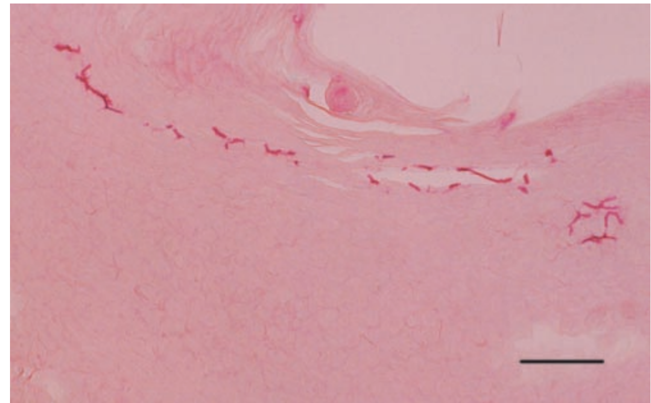

FIG. 2. Histological examination of the nails of guinea pig hind paws, 60 days after *T. mentagrophytes* SM-110 inoculation. The fungi invaded the nail plate. Bar = 40 μm.

**Therapeutic efficacy against experimental plantar tinea pedis in guinea pigs.** Table 3 shows the therapeutic effect of KP-103, amorolfine, and terbinafine on the fungal burden of the plantar skin in the same animals that were used for evaluation of their therapeutic effect on tinea unguium. Topical KP-103 and topical or oral terbinafine achieved mycological eradication for all of the 10 infected plantar skin sites. Topical amorolfine significantly reduced fungal counts in the infected plantar sites and sterilized 4 of the 10 infected plantar skin sites.

## DISCUSSION

Antifungal drugs such as lanoconazole, butenafine, terbinafine, and amorolfine developed in recent years have potent in vitro antidermatophyte activity (11, 14, 18, 28) and accumulate

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TABLE 2. Therapeutic efficacies of KP-103 and reference drugs in a guinea pig model of tinea unguium[a]

| Treatment | No. of feet with culture-positive nails/total no. of feet (%) | Log CFU in nails/foot (mean ± SD) | Length (mm) of nails (mean ± SD) |
|---|---|---|---|
| Topical vehicle | 10/10 (100) | 3.70 ± 0.44 | 9.47 ± 1.02 |
| 1.0% KP-103 solution | 10/10 (100) | 2.20 ± 0.56[b] | 11.64 ± 1.29[c,d] |
| 1.0% amorolfine solution | 10/10 (100) | 3.26 ± 0.54 | 9.66 ± 1.65 |
| 1.0% terbinafine solution | 10/10 (100) | 3.21 ± 0.47 | 10.33 ± 1.49 |
| Oral vehicle | 10/10 (100) | 3.76 ± 0.67 | 9.41 ± 1.78 |
| Terbinafine (40 mg/kg/day, p.o[e]) | 10/10 (100) | 3.80 ± 0.44 | 9.46 ± 1.69 |

[a] Treatment was started on day 60 postinfection and continued for 30 days.
[b] $P < 0.01$ versus the topical-vehicle-, oral-vehicle-, and oral-terbinafine-treated groups.
[c] $P < 0.01$ versus the topical-vehicle-, oral-vehicle-, topical-amorolfine, and oral-terbinafine-treated groups.
[d] $P < 0.05$ versus the topical-terbinafine-treated group.
[e] p.o., orally.

in the horny layer and nails at high levels when topically applied (1, 15, 19, 29). In our previous study with a guinea pig tinea pedis model (26), we demonstrated that the therapeutic efficacy of lanoconazole was not correctly assessed by the conventional culture method because of a carryover of the drug remaining in the treated skin tissues to the culture media for detecting fungi. Similarly, even when lanoconazole, butenafine, terbinafine, and amorolfine were administered topically to guinea pigs with tinea unguium once a day for 20 days and culture studies were performed on day 2 posttreatment, these drugs yielded all negative cultures for all nail specimens from the guinea pigs because of their carryover effects to culture medium (data not shown). We, therefore, found that the persisting drug should be eliminated from the treated nails before the culture study to evaluate correctly their therapeutic effects. To our knowledge, there has been no study of the therapeutic effects of antifungal agents against animal models of tinea unguium. This is probably because the sterility of the treated nails determined by the conventional method does not correlate with the finding that the existing antifungal drugs are almost entirely ineffective for human tinea unguium by topical application (13, 23). The present study is the first to report on the therapeutic efficacies of antifungal agents in an animal model of tinea unguium.

In the present study, we successfully eliminated drugs from all treated nails using the new technique with trypsin treatment and the dialysis procedure of treated tissues that we reported previously (26), with resultant detection of infecting fungi in all

TABLE 3. Therapeutic efficacies of KP-103 and reference drugs in a guinea pig model of tinea pedis[a]

| Treatment | No. of feet with culture-positive skin/total no. of feet (%) | Log CFU in skin/foot (mean ± SD) |
|---|---|---|
| Topical vehicle | 10/10 (100) | 4.37 ± 0.33 |
| 1.0% KP-103 solution | 0/10 (0)[b] | <1.3[b] |
| 1.0% amorolfine solution | 6/10 (60) | 1.74 ± 0.45[c] |
| 1.0% terbinafine solution | 0/10 (0)[b] | <1.3[b] |
| Oral vehicle | 10/10 (100) | 3.85 ± 0.68 |
| Terbinafine (40 mg/kg/day, p.o.[d]) | 0/10 (0)[b] | <1.3[b] |

[a] Treatment was started on day 60 postinfection and continued for 30 days.
[b] $P < 0.01$ versus the topical-vehicle- and oral-vehicle-treated groups.
[c] $P < 0.05$ versus the topical-vehicle-treated group.
[d] p.o., orally.

treated nails. The dialysis period of 14 days was necessary for removing all drugs tested from the treated nails, which was longer than the 3 days used for plantar skin tissues previously (26). This is presumably because antifungal agents have a high binding affinity to keratin (24, 28) and more accumulated in the nails than in the skin tissues. It is suggested that the method is useful for evaluating the therapeutic efficacy of antifungal agents against the tinea unguium model of animals because it permits the complete recovery of viable fungi from all drug-treated nails, whereas the conventional method does not recover fungi because of the drug carryover effects. Moreover, the results obtained by the new method in the present study correlated well with clinical knowledge that tinea unguium responds more poorly to antifungal chemotherapy than does tinea pedis (13, 23).

Since dermatophytes parasitize the keratinized tissues of the horny layer of the epidermis, hair, and nails, the therapeutic efficacy of applied antifungal agents depends on not only their in vitro antifungal activities but also their pharmacokinetic properties in the keratinized tissues (27). KP-103 was 8- and 32-fold, respectively, less active than amorolfine or terbinafine against *T. mentagrophytes* SM-110 in SDB medium. However, KP-103 was more effective than the reference drugs for inhibiting nail collapse or reducing the fungal burden of the nails. These results suggest that KP-103 shows a better pharmacokinetics in the nails than the reference drugs.

To predict the pharmacokinetics of KP-103 in the nails, we examined the influence of keratin on its antifungal activity and its affinity to keratin compared with those of amorolfine and terbinafine. Terbinafine and amorolfine showed a greatly decreased antifungal activity in the presence of 5% keratin. This was because the reference drugs have extremely high rates of binding to keratin of more than 90%. Uchida et al. (29) also reported that terbinafine showed a high rate of keratin binding, 88.4%, when incubated in a buffer with 10% keratin. These results suggest that these reference drugs will be further inactivated in the nails, because about 90% of the constituent of nails is keratin. In contrast, the antifungal activity of KP-103 was not affected by keratin because of its lower affinity to keratin, suggesting that KP-103 largely exists in the nails as an active form that is not bound to keratin. Antifungal agents bound to keratin need to be released readily from it to effectively diffuse into the deeper nail plate and sterilize infected nails. Even though KP-103 was bound to keratin suspended in saline, it was readily released from keratin by washing with

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saline. Its release from keratin was higher than those of amorolfine and terbinafine. It is likely that KP-103 diffuses in the nails without being trapped by keratin.

Topical amorolfine and topical or oral terbinafine were not effective in reducing the fungal burden of the nails, although the reference drugs reduced or eradicated the fungal burden in plantar skin tissues. These results suggest that the two reference drugs were possibly inactivated by keratin in the nails, although they were absorbed into the nails as in plantar skins. On the other hand, topical KP-103 was effective for both reducing the fungal burden of nails and eradicating infection in plantar skins. The effectiveness of KP-103 for tinea unguium is presumably due to its high activity and good penetration into the nails, which are achieved by its lower keratin affinity.

It was reported that orally administered terbinafine is effective for the treatment of human tinea unguium (3, 4, 12, 30, 31). However, in the present study, oral terbinafine was not effective for the tinea unguium in the guinea pig model. This discrepancy is possibly due to the fact that the treatment period of 30 days for guinea pigs was shorter than that necessary to show therapeutic effect against human tinea unguium, which is at least 3 months (4, 30, 31). It was reported that a concentration of terbinafine (0.1 to 1.53 μg/ml) higher than its MIC (0.001 to 0.02 μg/ml) for dermatophytes was achieved in the nails when it was orally administered to patients with tinea unguium at a daily dose of 250 mg for 28 days (2). In the present study, since guinea pigs were orally treated with terbinafine for 30 days at a daily dose of 40 mg/kg, which is about 10-fold higher than that used in humans, a high concentration of terbinafine would be achieved in the nails. However, terbinafine failed to reduce the fungal burden in the affected nails. This finding also suggests that terbinafine would be inactivated by its strong binding to keratin in the nails.

In conclusion, KP-103 is a very promising antifungal candidate in the treatment of human tinea unguium because topically applied KP-103 exhibits a better therapeutic effect than oral terbinafine and possibly allows shorter periods of treatment, which improves patient compliance and yields no risk of systemic adverse effects and drug interactions, unlike oral antifungal drugs.

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