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# Activity of Terbinafine in Experimental Fungal Infections of Laboratory Animals

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**The allylamine derivative terbinafine is the first antifungal agent with primary fungicidal properties against dermatophytes which acts systemically after oral application as well as locally after topical application. Comparative oral studies carried out with griseofulvin and ketoconazole in model infections such as guinea pig trichophytosis and microsporosis revealed terbinafine to be superior to the reference compounds both clinically and mycologically. An excellent antimycotic activity of terbinafine was also demonstrable after topical treatment of guinea pig dermatophytoses caused by *Trichophyton mentagrophytes* or *Microsporum canis*. Results of comparative chemotherapeutic studies carried out with econazole and tolnaftate demonstrated superior efficacy of terbinafine in the treatment of both trichophytosis and microsporosis. Skin infections of guinea pigs caused by *Candida albicans* and vaginal candidiasis in rats proved to be responsive to a topical application of terbinafine also. However, the reference compounds, clotrimazole and miconazole, exhibited activity superior to that of terbinafine in both models.**

The antifungal activity of the allylamine derivative terbinafine [SF 86-327; (E)-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-*N*-methyl-1-naphthalenemethanamine hydrochloride] against a broad spectrum of medically important fungi in vitro has been described in previous papers (1, 3, 5, 6, 8). It is highly active against *Trichophyton*, *Epidermophyton*, and *Microsporum* species in vitro, with MICs ranging from 0.001 to 0.01 μg/ml. The compound shows good activity against *Aspergillus* species (MIC range, 0.05 to 1.56 μg/ml), *Scopulariopsis brevicaulis* (MIC, 0.8 μg/ml), and *Sporothrix schenckii* (MIC range, 0.1 to 0.4 μg/ml) and also has activity against yeasts, with MICs ranging from 0.1 to >100 μg/ml. Nondermatophytic fungi isolated from nails and the skin as well as from subcutaneous infections also proved to be susceptible to terbinafine to various degrees.

The compound is primarily fungicidal against dermatophytes, molds, and dimorphic fungi, whereas the type of action against yeasts is species dependent and either primarily fungicidal (*Candida parapsilosis*) or fungistatic (*Candida albicans*) (5).

The present paper describes the efficacy of topically or orally administered terbinafine in experimental fungal infections caused by *Trichophyton mentagrophytes*, *Microsporum canis*, and *Candida albicans* in laboratory animals.

(These data were presented in part at the 13th International Congress of Chemotherapy, 28 August–2 September 1983, Vienna, Austria [5].

## MATERIALS AND METHODS

**Laboratory animals.** Female Pirbright white guinea pigs, obtained from Savo-Ivanovas (Kisslegg, Federal Republic of Germany), were used for skin infections. The animals were housed individually in Makrolon cages (type IV) in basic laboratory animal facilities under standard environmental conditions (22 ± 1°C room temperature, 55 ± 5% humidity, 8 to 12 air changes per h, 12-h day–12-h night cycle). The animals had free access to pelleted food and water. They were used for experiments at about 6 weeks of age and 300 to 350 g of body weight after a 7-day period of adaption.

Crl:CD (SD) BR rats were used for vaginal studies. The animals were obtained from Charles River Wiga, Sulzfeld, Federal Republic of Germany, at weaning age and weighing 50 to 60 g and used for experimentation after an adaption period of 1 week. They were housed in groups in Makrolon cages (type IV) under the conditions described above. The animals were conditioned for intravaginal infection with *C. albicans* by a single subcutaneous injection of estradiolbenzoate (4 mg/kg, dissolved in sesame oil) 3 days before infection.

**Antimicrobial agents.** Terbinafine (SF 86-327, lot no. 80 901) was synthesized at Sandoz Forschungsinstitut, Vienna (10). The following reference compounds were kindly made available by the manufacturing companies: tolnaftate (H. Lundbeck u. Co., Copenhagen, lot no. EL-75), clotrimazole (Bayer AG, Wuppertal Elberfeld, lot no. Pt 0782 A), econazole (Cilag-Chemie, Schaffhausen, lot no. 780766), miconazole (Janssen Pharmaceutica, Beerse, lot no. E 25/1), ketoconazole (Janssen Pharmaceutica, lot no. C 4701), and griseofulvin (Biochemie, Kundl, lot no. 15819/9).

**In vitro testing.** For the serial dilution test, the MIC for dermatophytes was determined in Sabouraud dextrose (2%) broth (E. Merck; initial pH, 6.5). Malt extract broth (E. Merck; initial pH, 6.5) was used for yeasts.

Glass tubes (16 by 160 mm) were filled with 0.1 ml of drug solution, 1.8 ml of broth medium, and 0.1 ml of fungal suspension, yielding a final concentration of $10^3$ CFU/ml. Control tubes contained 0.1 ml of drug vehicle instead of the test compound.

Test tubes were incubated for 2 (yeasts) or 7 (dermatophytes) days at 30 or 37°C (yeasts) before reading. The MIC was defined as that concentration at which, compared with the growth control, no macroscopic signs of fungal growth were detectable.

**Test organisms, chemotherapeutic models.** *Trichophyton mentagrophytes* Δ158 and *Microsporum canis* Δ846 were cultivated on Kimmig agar (E. Merck, Darmstadt, Federal Republic of Germany) at 30°C for 7 days. The inoculum was prepared and stored as previously described (2). When

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TABLE 1. Topical efficacy of terbinafine, econazole, and tolnaftate in the guinea pig trichophytosis (*T. mentagrophytes* Δ158) model[a]

| Compound (MIC for *T. mentagrophytes* Δ158) | Concn (%) | % Efficacy | | No. of animals mycologically cured/8 animals infected |
|---|---|---|---|---|
| | | Clinical | Mycological | |
| Terbinafine (0.006 μg/ml)[b] | 0.001 | 35 | 10 | 0 |
| | 0.002 | 49 | 16 | 0 |
| | 0.004 | 57 | 25 | 0 |
| | 0.008 | 58 | 41 | 0 |
| | 0.015 | 68 | 57 | 1 |
| | 0.03 | 74 | 94 | 7 |
| | 0.06 | 83 | 100 | 8 |
| Econazole (0.8 μg/ml) | 0.125 | 10 | 0 | 0 |
| | 0.25 | 21 | 0 | 0 |
| | 0.5 | 25 | 0 | 0 |
| | 1.0 | 38 | 7 | 0 |
| | 2.0 | 43 | 13 | 0 |
| Tolnaftate (0.1 μg/ml) | 0.125 | 38 | 25 | 0 |
| | 0.25 | 47 | 29 | 1 |
| | 0.5 | 57 | 60 | 1 |
| | 1.0 | 58 | 82 | 4 |
| | 2.0 | 69 | 82 | 4 |
| Placebo (PEG 400–ethanol) | 0 | 0 | 0 | 0 |
| Controls | 0 | 0 | 0 | 0 |

[a] Treatment once daily on 7 consecutive days starting 48 h after inoculation.
[b] $ED_{50}$, ca. 0.02%.

required, the inoculum was thawed, diluted, and used directly to infect the guinea pigs.

Before inoculation the hair was shorn from the backs of albino guinea pigs with electric clippers. An open glass cylinder (2 cm high and 3.5 cm in diameter) was laid on the widest part of the back (lumbar region), and 0.1 ml of the inoculum ($10^6$ infective particles) was abraded into the portion of skin encircled by the cylinder with a roughened glass pestle. The animals were then divided into test groups of 8 or 10 marked with ear tags.

Each guinea pig was treated topically with 0.4 ml of test compounds spread on the infected skin area of the animal with a Drigalski spatula. For this purpose the drugs were dissolved in a mixture of polyethylene glycol 400-ethanol (75:25, vol/vol). The treatment was applied once daily on 7 consecutive days beginning 48 or 72 h after inoculation.

For oral treatment the compounds were suspended in 2% methyl cellulose with 0.5% Tween 80, and 0.5 ml of the various doses was administered by stomach tube. The treatment was given once daily on 9 consecutive days, commencing on the day of inoculation. Groups of animals were maintained alongside the treated animal groups to serve as controls, receiving either drug vehicle only or no treatment.

Mycological status was assessed 3 days after the last treatment for the topical treatment and 24 h after the last treatment for the oral treatment.

The mycotic focus of each animal was divided into quadrants and four hair samples (approximately 10 hairs per sample) from each quadrant were put onto dermatophyte test medium plates (Merck). These plates were incubated at 30°C for 7 days and then examined for fungal growth with a binocular microscope. Hair samples taken from untreated control animals were consistently positive. The effectiveness of a compound in reducing the number of positive hair samples per treated group was expressed as a percentage of the corresponding untreated control group of animals. In the clinical assessment of local changes of the infected skin area, scores from 0 to 4 were used (0, no findings; 1, few slightly erythematous places on the skin; 2, well-defined redness, swelling with bristling hairs; 3, large areas of marked redness, incrustation, scaling, bald patches, ulcerated in places; 4, same as the control, mycotic foci well developed with ulceration in some cases). The percent efficacy was calculated by the formula $100 - T \times (100/K)$, where $T$ and $K$ are the mean numbers of mycologically positive hair samples (or the mean clinical score) for the test group and control group, respectively (4).

Topical activity of terbinafine was compared with the activities of econazole and tolnaftate. For comparison of systemic activities, griseofulvin and ketoconazole were used as reference compounds.

**Skin infections with *C. albicans*.** Skin infections were performed with *C. albicans* Δ9. The inoculum was prepared from a 2-day-old shaken culture, grown in Sabouraud dextrose (2%) broth (Merck) at 30°C.

Prior to infection, an area (ca. 8 by 8 cm) of the dorsal trunk was razor-shaved and swabbed with 70% isopropyl alcohol. A 0.1-ml amount of the yeast suspension, containing $3 \times 10^7$ yeast cells, was applied and distributed on a circular area about 4 cm in diameter with a rough pestle and light pressure. The inoculation site was dressed with Parafilm M and gauze reinforced with cloth adhesive tape. The dressings were removed after 3 days.

For topical dermal applications, gels of 2.0, 1.0, and 0.5% terbinafine, prepared with Tween 80, Aqualose L75 (Golden Dawn; Westbrook Lanoline Co., Bradford, England), and distilled water (1:3:6) were used. A 0.5-ml amount of this preparation was administered twice daily on 5 successive days. Treatment was started on day 4 after inoculation.

The activity of terbinafine against skin infections with *C. albicans* was evaluated on days 5, 7, and 10 by reisolation of yeasts from scales, transferred to Sabouraud dextrose (2%) agar plates containing streptomycin sulfate. Animals were

TABLE 2. Topical efficacy of terbinafine, econazole, and tolnaftate in the guinea pig microsporosis (*M. canis* Δ846) model[a]

| Compound (MIC for *M. canis* Δ846) | Concn (%) | % Efficacy | | No. of animals mycologically cured/8 animals infected |
|---|---|---|---|---|
| | | Clinical | Mycological | |
| Terbinafine (0.006 μg/ml)[b] | 0.015 | 52 | 0 | 0 |
| | 0.03 | 63 | 25 | 0 |
| | 0.06 | 63 | 35 | 0 |
| | 0.125 | 66 | 69 | 1 |
| | 0.25 | 68 | 94 | 6 |
| | 0.5 | 69 | 100 | 8 |
| | 1.0 | 75 | 100 | 8 |
| Econazole (0.02 μg/ml) | 0.125 | 38 | 0 | 0 |
| | 0.25 | 52 | 0 | 0 |
| | 0.5 | 55 | 0 | 0 |
| | 1.0 | 57 | 44 | 1 |
| | 2.0 | 58 | 54 | 2 |
| Tolnaftate (0.02 μg/ml) | 0.125 | 8 | 0 | 0 |
| | 0.25 | 36 | 0 | 0 |
| | 0.5 | 40 | 0 | 0 |
| | 1.0 | 52 | 0 | 0 |
| | 2.0 | 60 | 0 | 0 |
| Placebo (PEG 400–ethanol) | 0 | 0 | 0 | 0 |
| Controls | 0 | 0 | 0 | 0 |

[a] Treatment once daily on 7 consecutive days starting 72 h after inoculation.
[b] $ED_{50}$, ca. 0.2%.

TABLE 3. Systemic efficacy of terbinafine, griseofulvin, and ketoconazole in the guinea pig trichophytosis (*T. mentagrophytes* Δ158) model[a]

| Compound (MIC for *T. mentagrophytes* Δ158) | Dose (mg/kg of body wt) | % Efficacy | | No. of animals protected/no. infected[b] | $ED_{50}$ (mg/kg) |
|---|---|---|---|---|---|
| | | Clinical | Mycological | | |
| Terbinafine (0.006 μg/ml) | 2 | 68 | 68 | 4/10 | ~3 |
| | 4 | 85 | 73 | 4/10 | |
| | 6 | 98 | 100 | 10/10 | |
| | 8 | 100 | 100 | 10/10 | |
| Griseofulvin (12.5 μg/ml) | 20 | 53 | 25 | 0/9* | ~38 |
| | 40 | 75 | 88 | 7/10 | |
| | 60 | 100 | 100 | 9/9* | |
| | 80 | 100 | 100 | 10/10 | |
| Ketoconazole (25 μg/ml) | 20 | 5 | 3 | 0/10 | ~51 |
| | 40 | 33 | 37 | 1/9* | |
| | 60 | 89 | 93 | 8/10 | |
| | 80 | 84 | 100 | 10/10 | |
| Placebo (2% Tylose–Tween 80) | | 0 | 0 | 0/10 | |
| Controls | | 0 | 0 | 0/10 | |

[a] Oral treatment once daily on 9 consecutive days starting on the day of inoculation.
[b] *, One animal died during the course of treatment.

considered to be cured when attempts to reisolate *C. albicans* failed. The activity of terbinafine was assessed in comparison with a reference group treated with a gel containing 0.5% clotrimazole and with a control group treated with the vehicle only. For confirmation of data, two separate identically designed studies were performed, with 10 animals per group in each study.

**Vaginal infections with *C. albicans*.** Strains Δ9, Δ88, and Δ124 were used for intravaginal infections. The yeast cells were cultured as described above.

For infection, 50-μl suspensions, containing ca. $3.5 \times 10^4$ or $3.5 \times 10^6$ yeast cells, were instilled into the vagina.

Gel preparations of 4, 2, 1, 0.5, and 0.1% terbinafine were used for vaginal treatment. The compound was dissolved in dimethyl sulfoxide and mixed with polyethylene glycol 400 and Aerosil (APOKA, Austria, ÖAB 9) in a proportion of 4:5:1. Eight doses of 0.1-ml gels were administered intravaginally (4 h after the infections, in the morning and evening of days 1, 2, and 3, and finally in the morning of day 4 after infection).

TABLE 4. Systemic efficacy of terbinafine and griseofulvin in the guinea pig microsporosis (*M. canis* Δ846) model[a]

| Compound (MIC for *M. canis* Δ846) | Dose (mg/kg of body wt) | % Efficacy | | No. of animals protected/no. infected[b] | $ED_{50}$ (mg/kg) |
|---|---|---|---|---|---|
| | | Clinical | Mycological | | |
| Terbinafine (0.006 μg/ml) | 2.5 | 23 | 0 | 0/10 | ~19 |
| | 5 | 41 | 6 | 0/9* | |
| | 10 | 42 | 14 | 1/9* | |
| | 20 | 90 | 73 | 4/10 | |
| | 40 | 100 | 100 | 10/10 | |
| | 80 | 100 | 100 | 10/10 | |
| Griseofulvin (0.8 μg/ml) | 5 | 43 | 15 | 1/10 | ~14 |
| | 10 | 64 | 75 | 2/9* | |
| | 20 | 87 | 87 | 6/9* | |
| | 40 | 100 | 100 | 10/10 | |
| | 80 | 100 | 100 | 7/7* | |
| Placebo (2% Tylose–Tween 80) | | 0 | 0 | 0/10 | |
| Controls | | 0 | 0 | 0/10 | |

[a] Oral treatment once daily on 9 consecutive days starting on the day of inoculation.
[b] *, 1 or 3 animals died during the course of treatment.

TABLE 5. Topical efficacy of terbinafine and clotrimazole in experimental cutaneous candidiasis (*C. albicans* Δ9) in guinea pigs[a]

| Compound (MIC for *C. albicans* Δ9) | Concn (%) | Cure rate (% of animals) at day postinfection: | | |
|---|---|---|---|---|
| | | 5 | 7 | 10 |
| Terbinafine (12.5 μg/ml) | 0.5 | 0 | 30 | 60 |
| | 1.0 | 30 | 70 | 84 |
| | 2.0 | 85 | 90 | 100 |
| Clotrimazole (3.13 μg/ml) | 0.5 | 60 | 100 | 100 |
| Drug vehicle | | 0 | 0 | 20 |

[a] Treatment twice daily on 5 consecutive days starting 4 days after inoculation (0.5 ml per treatment).

The efficacy of topical treatment with terbinafine was determined by reisolation of *C. albicans* from vaginal smears. Four days after the last treatment, a cotton swab wetted with saline was inserted into the vagina, rotated, and plated on Sabouraud dextrose agar containing streptomycin sulfate. The plates were incubated at 30°C and examined for colonies after 48 h. Treatment was considered successful if the agar plates were negative.

Cure rate after terbinafine treatment was compared with that in controls receiving drug vehicle only or gels containing clotrimazole and miconazole. Either 10 or 20 animals were used per group.

## RESULTS AND DISCUSSION

The outstanding efficacy of terbinafine as a topical antifungal agent can be shown in the trichophytosis model by applying a 0.03 to 0.06% solution of the drug to the skin for 7 days. The efficacy of terbinafine was concentration dependent and, assessed either clinically or mycologically, significantly superior to that of the standards, econazole and tolnaftate (Table 1). A probit analysis of the appropriate curative antimycotic effect revealed 0.02% terbinafine as the effective dose at the 50% level ($ED_{50}$) in infected animals. Since 100% cure was not obtained with econazole or tolnaftate, $ED_{50}$ concentrations could not be assessed for these compounds. Similar results were obtained for guinea pigs infected with *M. canis* (Table 2). In this investigation, treatment once daily on 7 consecutive days was started 72 h after inoculation of the skin area. All animals treated with terbinafine were cleared of the *M. canis* infection following

TABLE 6. Topical activity of terbinafine in experimental vaginal candidiasis in rats[a]

| Compound (MICs for strains in inoculum) | Concn (%) | Cure rate (% of animals) on day 4 after last treatment | | |
|---|---|---|---|---|
| | | Δ9 | Δ88 | Δ124 |
| Terbinafine (12.5, 25, 25 μg/ml) | 1 | 95 | 90 | 50 |
| | 2 | 90 | 65 | 70 |
| | 4 | 100 | 75 | 70 |
| Clotrimazole (3.13, 3.13, 12.5 μg/ml) | 0.5 | —[b] | — | 78 |
| Drug vehicle | | 15 | 20 | 7 |

[a] Treatment: one dose on day 0 (4 h after inoculation) and day 4, two doses on days 1, 2, and 3 (0.1 ml per treatment). The inoculum was $3.5 \times 10^4$ mixed *C. albicans* Δ9, Δ88, and Δ124 cells.
[b] —, Not done.

TABLE 7. Topical efficacy of terbinafine in experimental vaginal candidiasis in rats[a]

| Compound (MIC for *C. albicans* Δ124) | Strain Δ124 inoculum | Concn (%) | Cure rate (% of animals) on day 4 after last treatment |
|---|---|---|---|
| Terbinafine (25 μg/ml) | $3.5 \times 10^4$ | 0.1 | 20 |
| | | 0.5 | 50 |
| | | 1.0 | 40 |
| | | 2.0 | 70 |
| | $3.5 \times 10^6$ | 0.1 | 10 |
| | | 0.5 | 0 |
| | | 1.0 | 10 |
| | | 2.0 | 0 |
| Miconazole (12.5 μg/ml) | $3.5 \times 10^4$ | 0.1 | 90 |
| | $3.5 \times 10^6$ | 0.1 | 30 |
| Drug vehicle | $3.5 \times 10^4$ | | 0 |
| | $3.5 \times 10^6$ | | 0 |

[a] Treatment: single doses on day zero (4 h after inoculation) and day 4, two doses on days 1, 2, and 3 (0.1 ml per treatment).

the application of 0.5 or 1% of active ingredient. With an $ED_{50}$ of approximately 0.2% terbinafine was significantly superior to the standards, econazole and tolnaftate. Only two of eight animals treated with econazole were cured at the highest dose level of 2%. No animal was mycologically cleared with tolnaftate at concentrations up to 2%. These results show that topical treatment with a concentration between 0.06 and 0.5% of terbinafine gives a high mycological cure rate. Such a result in this infection model (4) indicates an excellent ability of the compound to penetrate into the depth of the hair follicles and kill the fungi during a short treatment period.

In view of the self-limiting nature of the guinea pig dermatophytosis model, requiring that chemotherapeutic trials be completed during the proliferation phase of the infection, the time for treatment and mycological diagnosis was limited (4). Treatment with orally administered antifungal agents was therefore started on the day of inoculation. The potential of the compounds to protect hair roots against an invasion by fungi was used as a parameter of systemic activity.

Under these conditions, excellent activity against trichophytosis was achieved with a dose of 4 to 6 mg/kg given orally daily for 9 days, starting on the day of infection (Table 3). Compared by the calculated $ED_{50}$, terbinafine was significantly more effective than the reference compounds, griseofulvin and ketoconazole, with $ED_{50}$s of ca. 3, 38, and 51 mg/kg, respectively.

In the guinea pig microsporosis model with the same oral treatment scheme (once daily on 9 consecutive days, with a calculated $ED_{50}$ of ca. 19 mg/kg of body weight, based on the mycological parameters), the efficacy of terbinafine was comparable to that of griseofulvin (Table 4). It is of course possible that the efficacy of the orally administered drugs may be influenced by such factors as the degree of absorption and elimination time.

The topical activity of terbinafine in cutaneous candidiasis is shown in Table 5. Since the results of both studies agreed very well, mean values are given. In comparison with vehicle-treated animals, terbinafine gel caused a dose-dependent eradication of *C. albicans* from infected skin. At the dose level of 0.5%, the activity of terbinafine was inferior to that of clotrimazole.

Topical application of terbinafine caused elimination of yeast cells from the rat vagina. The activity was dependent on the inoculum and on the in vitro susceptibility of the strains used (Tables 6 and 7). The reference compounds, clotrimazole and miconazole, exhibited activity superior to that of terbinafine in this model.

Toxicological investigations carried out in vitro and in vivo revealed a very low toxic potential of terbinafine. The compound was neither mutagenic nor teratogenic and was well tolerated in mice, rats, and dogs (7).

In view of the excellent antimycotic activity obtained after oral or topical administration of terbinafine in various model infections for superficial mycoses, the compound was selected to be tested under clinical conditions in the treatment of human mycoses. Preliminary clinical studies in a variety of indications have confirmed the very promising results of these animal studies (9).

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