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In Vivo Antimycotic Activity of Naftifine

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Naftifine, a new antifungal agent belonging chemically to the allylamines, was tested for its in vivo activity after topical application against guinea pig skin infections caused by *Trichophyton mentagrophytes*, *T. mentagrophytes* var. *quinckeanum*, or *Microsporum racemosum*. Compared with standard compounds, naftifine proved to be highly effective mycologically and clinically after topical application in the above models.

Naftifine (*E*)-*N*-methyl-N-(1-naphthylmethyl) -3-phenyl-2-propen-1-amine-hydrochloride, an allylamine derivative, is highly active against *Trichophyton*, *Epidermophyton*, and *Microsporum* species in vitro (minimal inhibitory concentration [MIC] range, 0.1 to 0.2 μg/ml). It also shows good activity against *Aspergillus* species (MIC range, 0.8 to 12.5 μg/ml) and *Sporothrix schenckii* (MIC range, 0.8 to 1.5 μg/ml). However, *Candida* species are somewhat less susceptible, with an MIC range of 1.5 to >100 μg/ml. It has a primarily fungicidal action against both dermatophytes and yeasts, and its in vitro efficacy is pH dependent, increasing at values above pH 4 (2; A. Georgopoulos, D. Berney, G. Petranyi, J. Drews, and H. Mieth, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 19th and 11th Int. Cong. Chemother., abstr. no. 153, 1979). This in vitro profile was considered to be interesting enough to justify an investigation of the compound in vivo. The results of these studies using model infections are reported here.

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MATERIALS AND METHODS

Laboratory animals. Male albino guinea pigs with a body weight of 300 to 400 g were kept in fully air-conditioned animal rooms at 20 to 22°C, and eight animals were randomly assigned to each test group.

Infection material. *Trichophyton mentagrophytes* var. *quinckeanum* (Δ158), *T. mentagrophytes* (Δ56066), and *Microsporum racemosum* (Δ101) were cultivated on Kimmig agar (E. Merck, Darmstadt) at 30°C for 7 days. The inoculum was prepared and stored as previously described (1, 2). When required, the inoculum was thawed, diluted, and used directly to infect the guinea pigs.

Infection of animals. The back of each animal was shorn and then depilated with a freshly prepared 12.5% aqueous sodium sulfide solution. Subsequently, the inoculum, containing 10^6 infective particles in 0.1 ml, was abraded into a 3.5-cm-diameter area of skin using a roughened glass pestle. This regularly produced a 100% infection.

Therapy. Each guinea pig was treated with 0.4 ml of a solution of the test compound. For this purpose, naftifine (batch 77901), miconazole (batch E 25/1), and econazole (batch 780766) were prepared in polyethylene glycol 400/ethanol (75:25, vol/vol). Tolnaftate (batch EL-75) was dissolved in polyethylene glycol 400/acetone (75:25, vol/vol). Unless otherwise stated the treatment was given once daily on 7 consecutive days beginning 48 h after infection.

All compounds were made available by the courtesy of the manufacturing companies. The econazole cream used was that available from the market.

Evaluation. The extent of any local clinical changes was recorded for each animal on day 3 and 11 postinfection. Scores from 0 to 4 were used, where 4 implies no difference from the untreated control group. The mycological effectiveness of a compound was assessed on day 11 postinfection using the "hair follicle test" (G. Petranyi and H. Mieth, 15. Wiss. Tagung der Deutschsprachigen Mykolog. Ges. 1980; G. Petranyi and H. Mieth, submitted for publication). In this test the incidence of infection in the skin foci of the individual animals was assessed and expressed as a percentage cure. Three days after the last treatment (11 days after infection), a hair sample (comprising approximately 10 individual hairs) was taken from each quadrant of the infected skin area. The four hair samples from each animal were placed in the four quadrants of a Mycosel agar plate (BBL Microbiology Systems), incubated at 30°C and 60% relative humidity for 7 days, and then examined for fungal growth under a binocular microscope. Hair samples taken from the untreated control groups (4 samples per animal giving a total of 32 per group) 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 untreated control group of animals (percentage efficacy = $100 - (T \times 100)/K$ where T is the mean number of positive hair samples [or mean clinical score] in the test group and K is the same for the control group).

RESULTS AND DISCUSSION

The topical efficacy of naftifine in the dermatophytosis model with *T. mentagrophytes*

TABLE 1. *Efficacy of naftifine, tolnaftate, and miconazole in the guinea pig dermatophytosis model (T. mentagrophytes var. quinckeanum Δ158) after topical application once daily for 7 consecutive days*

Compound	Percentage efficacy										Animals showing mycological cure/total animals				
	Clinical					Mycological									
	2.0[a]	1.0	0.5	0.25	0.125	2.0	1.0	0.5	0.25	0.125	2.0	1.0	0.5	0.25	0.125
Naftifine	94	72	71	58	50	100	100	91	75	40	8/8	8/8	6/8	3/8	1/8
Tolnaftate	79	63	61	55	50	84	79	40	38	25	4/8	4/8	1/8	1/8	0/8
Miconazole	47	33	19	16	5	5	0	0	0	0	0/8	0/8	0/8	0/8	0/8
Placebo I, PEG 400/ethanol[b]			0					0					0/8		
Placebo II, PEG 400/acetone			0					0					0/8		
Infection control			0					0					0/16		

[a] Concentration in percent.
[b] PEG, Polyethylene glycol.

TABLE 2. *Efficacy of naftifine and econazole in the guinea pig dermatophytosis model (T. mentagrophytes Δ56066) after topical application once daily on 7 consecutive days, beginning 48 h postinfection*

Compound	Concn (%)	Percentage efficacy		Animals showing mycological cure/total animals
		Clinical	Mycological	
Naftifine	0.125	63	72	3/8
	0.25	58	97	7/8
	0.5	69	100	8/8
	1.0	74	100	8/8
Econazole	0.125	52	22	0/8
	0.25	57	47	0/8
	0.5	60	66	2/8
	1.0	58	91	5/8
Controls		0	0	0/8

var. *quinckeanum* was compared with that of tolnaftate and miconazole (Table 1). Under the test conditions, only the primarily fungicidal naftifine and tolnaftate were mycologically effective. However, the 100% mycological cure achieved with 2 and 1% naftifine did not lead to a complete clinical cure although the regression of the clinical symptoms was dose dependent. No significant antifungal activity could be demonstrated for miconazole, probably due to the primarily fungistatic action of this and other imidazoles which may thus require a longer administration period to produce a mycological cure. However, in another experiment using *T. mentagrophytes* Δ56066, both antifungal and clinical activity could be demonstrated for econazole, another imidazole derivative (Table 2). Naftifine was again highly active with concentrations as low as 0.25 to 0.5% producing a 97 to

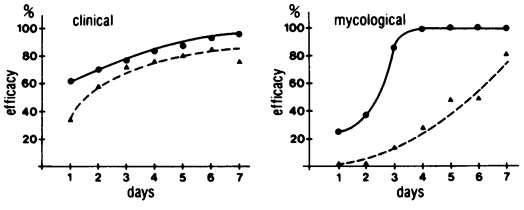

FIG. 1. *Antimycotic efficacy of 1% naftifine (●) or econazole (▲) cream in the guinea pig trichophytosis model (T. mentagrophytes var. quinckeanum Δ158) after topical application once daily on 7 consecutive days.*

100% mycological cure, whereas even 1% econazole gave only a 91% cure.

Using naftifine as a 1% formulated cream, 100% mycological cure was achieved after the fourth treatment (Fig. 1). In comparison, the

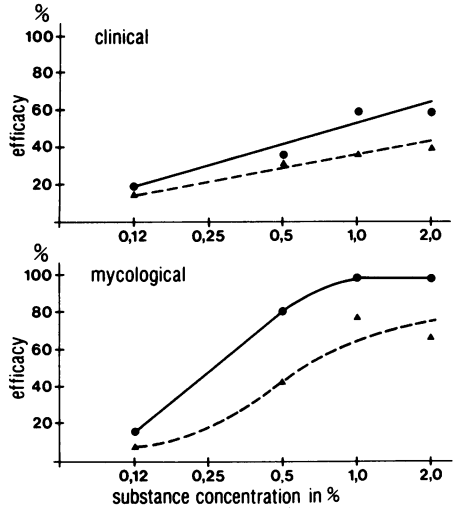

FIG. 2. *Antimycotic efficacy of naftifine (●) and tolnaftate (▲) in the guinea pig microsporosis model (M. racemosum Δ101) after topical application for 7 consecutive days beginning on day 4 postinfection.*

effectiveness of the fungistatic econazole (Pevaryl cream 1%) increased more slowly but continuously over the treatment period.

The efficacy of naftifine and tolnaftate against microsporosis caused by *M. racemosum* is summarized in Fig. 2. Both compounds showed a similar activity to that demonstrated against trichophytosis (Table 1). The somewhat reduced clinical efficacy probably stemmed from delaying the onset of therapy to day 4 after infection when the symptoms were already more severe.

In view of these experimental results and the fact that epidermal drug concentrations in humans after two topical applications of a 1% naftifine cream per day are many times as high as the MICs of both dermatophytes and yeasts (unpublished data), naftifine is being tested clinically for its efficacy against dermatomycoses.

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