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Tolciclate: Further Antimycotic Studies

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In vitro comparison on dermatophytes showed, on a microgram-per-milliliter basis, that tolciclate was more active than clotrimazole and miconazole in inhibiting the growth of dermatophytes in Sabouraud agar with and without 10% horse serum.

Tolciclate [*O*-(1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)-*m*,*N*-dimethylthiocarbanilate] is an antimycotic agent with specific activity on dermatophytes (2). In vitro it is as active as tolnaftate, but shows greater liposolubility, which might be important for in vivo activity. In fact, when applied topically for 10 days to guinea pigs infected acutely with *Trichophyton mentagrophytes* (synonymous with *T. asteroides*) strain Juntendo and *Microsporum canis* ATCC 11621, it is about three times more active than tolnaftate (1).

The present report is concerned with the comparative activities of tolciclate, miconazole, and clotrimazole against various dermatophytes in vitro.

The 22 strains of dermatophytes examined in this comparison are listed and identified with respect to genus and species in Table 1. Ten of these strains (marked with *a*) were recent clinical isolates, and the tests were made after not more than three passages in culture; the other 12 were freshly subcultured, just before the test, from lyophilized preparations obtained from culture collections (ATCC, CBS, etc.). The minimum inhibitory concentrations (MIC) of tolciclate (Carlo Erba, Milano), miconazole, and clotrimazole nitrate (Prodotti Gianni, Milano) were determined by a twofold dilution procedure in Sabouraud agar with 2% glucose as the basal medium. The test drugs, as dry powders, were dissolved in dimethylformamide or in alcohol, in the case of clotrimazole, diluted in water, and incorporated in the melted agar medium, which was then poured into plates. An automatic inoculator (Multipoint Inoculator, Denley) was used to apply 1 μl of fungal suspensions containing 10^6 cells per ml.

The MIC values were read after 5 days of incubation at 26°C.

Assays with plain Sabouraud medium and with medium containing 10% horse serum were run in parallel. Four assessments of the activity of each drug against each strain were carried out, and the geometric mean of the four MIC values was calculated.

Figure 1 sets out the cumulative percentages of strains inhibited in relation to the concentrations of drug in the medium. Tolciclate, with or without serum, was the most active drug. Taking, for example, the findings in plain Sabouraud, the concentration of 0.06 μg/ml inhibits 100% of the strains investigated, whereas at the same level clotrimazole and miconazole inhibit only 27 and 13% of the strains, respectively. To

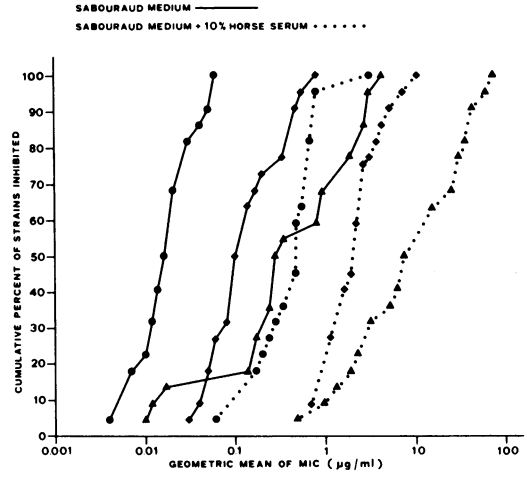

FIG. 1. *In vitro activity of tolciclate (●), miconazole (▲), and clotrimazole (◆) against 22 strains of dermatophytes.*

achieve 100% inhibition, concentrations of 0.8 μg of clotrimazole per ml and 4.4 μg of miconazole per ml were required.

In Sabouraud agar plus 10% serum, 100% inhibition was obtained with a concentration of 3.1 μg of tolciclate per ml, compared with 10.5 μg of clotrimazole per ml and 70.7 μg of miconazole per ml. Tolciclate had already inhibited 95% of the strains at a concentration of 0.8 μg/ml.

Tolciclate thus emerges in vitro as the most

TABLE 1. *Strains used and their origin*

Strain	Source
Trichophyton mentagrophytes	(Robin) Blanchard var. interdigitale (Priestley) Georg CBS 101.68
Trichophyton mentagrophytes	ATCC 9533
Trichophyton mentagrophytes I. de C.[a]	Carlo Erba, Milano
Trichophyton mentagrophytes Juntendo	Fujisawa, Osaka
Trichophyton mentagrophytes Desalle	Farmitalia, Milano
Trichophyton mentagrophytes F. G.[a]	Farmitalia, Milano
Trichophyton tonsurans	Malmsten CBS 375.49, Cochet
Trichophyton tonsurans L.[a]	Clinica Dermatologica Università di Milano
Trichophyton tonsurans 369	Laboratorio Crittogamico Italiano Università di Pavia
Trichophyton schoenleinii	Lebert CBS 174.40, Leontieff
Trichophyton rubrum	(Castell.) CBS 303.60, de Vries
Trichophyton rubrum Negroni[a]	Facultad de Medicina, Buenos Aires
Trichophyton verrucosum Negroni[a]	Facultad de Medicina, Buenos Aires
Trichophyton violaceum L.[a]	Clinica Dermatologica Università di Milano
Microsporum canis	ATCC 11621
Microsporum canis P.[a]	Università di Pavia
Microsporum audouinii	Gruby CBS 312.54, de Vries
Microsporum audouinii L.[a]	Clinica Dermatologica Università di Milano
Microsporum cookei Negroni[a]	Facultad de Medicina, Buenos Aires
Microsporum gypseum	ATCC 14683
Epidermophyton floccosum	ATCC 10227
Epidermophyton floccosum L. 472[a]	Clinica Dermatologica Università di Milano

[a] Clinical isolate.

active of the drugs tested here. In a previous study it also proved very active in experimental guinea pig infection (1); it showed good penetrability into the skin of the guinea pig, low acute toxicity in the mouse, rat, and dog (mean lethal dose >4,000, >6,000, and >5,000 mg/kg, respectively), low chronic toxicity in the rat, and caused no irritation even after repeated local application to the skin of a rabbit and a rat. Tolciclate can therefore be considered promising for specific topical therapy of dermatophyte infection in humans.

LITERATURE CITED

1. de Carneri, I., G. Monti, A. Bianchi, S. Castellino, G. Meinardi, and V. Mandelli. 1976. Tolciclate against dermatophytes. Arzneim. Forsch. 26:769–772.
2. Melloni, P., R. Metelli, V. Vecchietti, W. Logemann, S. Castellino, G. Monti, and I. de Carneri. 1974. New antifungal agents. Eur. J. Med. Chem. 9:26–31.