A CLINICAL EVALUATION OF THE FUNGICIDAL PROPERTIES OF 5-CHLORO-2(*p*-DIETHYLAMINOETHOXYPHENYL) BENZTHIAZOLE

NAPIER THORNE, M.D., M.R.C.P.

Physician in Charge, Skin Department, Prince of Wales's General Hospital, Tottenham

K. M. HARVEY, M.B., CH.B.

Late Registrar, Skin Department, The London Hospital

The chemistry, antibacterial and antifungal activity of various benzthiazole derivatives have been studied by Ross *et al.* (1959) and Payne *et al.* (1959). Stephens, working in the research laboratories of The Crookes Laboratories Ltd., has synthesized a compound derived from 2-phenylbenzthiazole which has the following molecular structure:

Payne found that this base, 5-chloro-2(*p*-diethylaminoethoxyphenyl) benzthiazole ('Episol'), had marked antifungal and antibacterial properties.

TABLE I.—IN VITRO ACTIVITY OF EPISOL AGAINST COMMON ORGANISMS (Payne *et al.*, 1959)

Organism	Minimum inhibitory concentration $\mu\text{g/ml}$.
<i>C. albicans</i>	25
<i>E. floccosum</i>	30
<i>M. audouinii</i>	25
<i>M. canis</i>	35
<i>T. rubrum</i>	25
<i>T. rubrum</i> 2nd strain	25
<i>T. mentagrophytes</i>	20
<i>T. mentagrophytes</i> 2nd strain	25
<i>T. sulphureum</i>	10
<i>T. verrucosum</i>	10
<i>Staph. aureus</i>	4
<i>Staph. aureus</i> (penicillin resistant strain)	2
<i>Strep. pyogenes</i>	4
<i>B. coli</i>	>800
<i>B. cereus</i>	4
<i>Salmonella typhi</i>	>800
<i>Pseud. aeruginosa</i>	>800
<i>Trichomonas vaginalis</i>	50

In strengths of 0.2 per cent. it would inhibit growth of common pathogenic fungi and was bactericidal to gram-positive bacteria. This activity was enhanced by the presence of serum.

It was further found that this substance had an extremely low toxicity. The LD₅₀ determined subcutaneously in mice was 2,300 mg per kilo.

When applied to the skin of 40 healthy volunteers the preparation caused no irritation or skin sensitization.

When designing this preliminary trial it was decided to assess the effect of 5-chloro-2(*p*-diethylaminoethoxyphenyl) benzthiazole on those types of fungus infections which proved most resistant to other available fungicides. Three preparations were used, a lotion containing 0.5 per cent. 5-chloro-2(*p*-diethylaminoethoxyphenyl) benzthiazole in 70 per cent. alcohol, a cream containing 0.5 per cent. 5-chloro-2(*p*-diethylaminoethoxyphenyl) benzthiazole in a non-greasy base, and a powder containing 0.5 per cent. 5-chloro-2(*p*-diethylaminoethoxyphenyl) benzthiazole in talc. One or more of these three was applied twice daily to the infected area, the individual preparations used depending entirely on the site and the authors' personal preferences. Scrapings were taken before and during the trial for mycological examination and culture, but in view of the uncertainty of growth of some fungi initial diagnosis and assessment of progress was judged on combined clinical and pathological findings.

Of 22 cases of fungus infection treated with 5-chloro-2(*p*-diethylaminoethoxyphenyl) benzthiazole the presence of fungus was confirmed microscopically in 21 cases and the fungus cultured in 13 of them prior to treatment. The sites

TABLE II.—SHOWING EFFECT OF TREATMENT WITH 5-CHLORO-2-(*p*-DIETHYLAMINOETHOXYPHENYL) BENTHIAZOLE

Case	Sex	Age	Sites Infected	Fungus found		Duration of Infection	Past Treatment	Preps. Used	Duration of Treatment	Results
				Microscopy	Culture					
1	F	28	(a) Toe nails. (b) Sole and toe clefts.	Yes Yes	No No	?	None.	Lotion. Powder.	5 months.	Cleared.
2	F	53	(a) Breast. (b) Heel.	Yes Yes	<i>T. mentagrophytes</i> .	6 years.	Pig Magenta co. Mycil. Asterol.	Ointment. Lotion.	6 months.	Considerable initial improvement but not complete clearance.
3	F	24	Feet.	Yes	No	8 months.	Asterol for 3/12 with improvement.	Ointment. Powder.	3 months.	Cleared.
4	M	31	(a) Groins. (b) Buttocks. (c) Feet.	Yes	No	5 years.	Iodine. Asterol. 30% Ac. sal. ointment	Powder. Ointment.	6 months.	Cleared from all but one area in 6/52 and from final area in 6/12.
5	M	32	Toe clefts and beneath toes.	No	No	10 years.	Whitfield's ointment. Asterol.	Ointment. Lotion. Powder.	8 months.	Marked improvement in 10/52. Cleared in 8/12.
6	F	54	(a) Finger and toe nails. (b) Sole of foot.	Yes Yes	No <i>T. mentagrophytes</i> .	2 years.	Whitfield's ointment. X-ray therapy.	Lotion. Ointment.	(a) 1 year. (b) 4 months.	Very slight improvement after 1 year. Cleared in 15/52.
7	M	41	Feet.	Yes	No	6 weeks.	Pig Magenta co.	Lotion. Powder.	8 weeks.	Cleared after 8/52.
8	F	2	(a) Trunk. (b) Scalp. (c) Face.	Yes	<i>M. canis</i> .	2 months.	Whitfield's ointment.	Lotion. Ointment.	8 weeks.	Skin lesions cleared but no effect on hair infection.
9	M	4	Scalp hair.	Yes	<i>M. canis</i> .	2 months.	None.	Lotion.	2 months.	No improvement.
10	M	26	(a) Palms. (b) Soles.	Yes Yes	No No	15 months	Dettol ointment. Zinc paste.	Ointment.	3 months.	Palms unaffected. Soles cleared in 8/52.
11	M	6	Scalp and scalp hair.	Yes	<i>M. audouinii</i> .	3 months.	X-ray epilation was partly successful.	Lotion.	4 months.	Controlled skin infection but hair had to be epilated with forceps.
12	M	10	(a) Scalp. (b) Left arm.	Yes Yes	<i>M. audouinii</i> . "	6 weeks.	None.	Lotion. Ointment.	6 weeks.	No improvement.
13	F	48	(a) Leg. (b) Foot. (c) Buttocks. (d) Nails.	Yes Yes	<i>T. rubrum</i> . "	8 years.	Whitfield's ointment.	Ointment. Powder.	10 weeks (then defaulted).	Skin improving. Nails slight improvement.
14	M	3	(a) Scalp. (b) Face. (c) Arms. (d) Legs.	Yes (Woods light)	No Positive $\equiv$ Microsporion finet.)	?	None.	Lotion.	10 weeks.	Skin cleared. A very few infected hairs present were epilated with forceps.

	M	9	Scalp and scalp hair.	Yes	<i>M. audouini</i> .	?	None.	Lotion.	4 weeks.	Used to prevent spread of infection while X-ray epilation carried out.
15	M	5†	Scalp and scalp hair.	Yes	<i>M. audouini</i> .	5 months.	None.	Lotion.	4 weeks.	Used to prevent spread of infection while X-ray epilation carried out.
16	M	4	Scalp hair.	Yes	<i>M. audouini</i> .	8 weeks.	None.	Lotion.	8 weeks.	No improvement but no spread to new areas.
17	F	28	(a) Trunk. (b) Legs.	Yes	No.	?	None.	Lotion.	6 months.	Cleared.
18	F		(a) Trunk. (b) Legs.	Yes	<i>T. mentagrophytes</i> .	2 years.	None.	Lotion. Powder. Ointment.	Some improvement.	
19	M	36	(a) Nails. (b) Palms.	Yes	<i>T. rubrum</i> .	6 years.	Many and various.	Ointment. Lotion. Powder.	1 year.	Slight but definite nail improvement Skin lesions not completely clear.
20	M	12	(a) Feet. (b) Nails.	Yes Yes	No. No.	2 years.	Asterol. Pulv. ac. salicyl.	Lotion (nails only).	4½ months.	Some improvement.
21	M	41	(a) Nails. (b) Feet.	Yes Yes	No No	4 years.	Whitfield's ointment. Asterol.	Lotion. Ointment (nails only).	6 months.	No striking change.
22	M	30	(a) Groins. (b) Toe clefts.	Yes Yes	<i>T. rubrum</i> . " "	3 weeks.	Iodine ointment. Half strength Whit- field's ointment.	Powder and ointment (toe clefts only).	7 weeks	Some improvement.

of infection were as follows: scalp 8, face 2, hands 2, trunk 3, arms 2, buttocks 2, groins 2, legs 3, feet 12 and nails 6. In a number of the patients two or more sites were involved.

The infection had been present for between 2 and 10 years in nine cases and from 3 weeks to 15 months in ten others. In the remaining three cases the exact duration was unknown.

Of the 42 sites treated, cure was achieved in 15, improvement in 19 and in eight there was no change.

Thirteen cases had been treated previously with other fungicides, including Castellani's paint, Whitfield's ointment, salicylic acid ointment, undecylenic acid ointment, tincture of iodine and well-known proprietary preparations which had failed to achieve a cure. In six of these cases 5-chloro-2-(*p*-diethylaminoethoxyphenyl) benzothiazole appeared to be more effective, in a further six cases as effective, and in the remaining one case less effective than the medicament previously used.

The time interval for clearance was too variable for comparison in so small a series. Those cases which were cured responded in a period of six weeks to six months.

There were no serious side-effects such as kerion formation or flare up of *T. pedis* as occurs when some fungicides are used.

Comments

This trial showed that 'Episol' is effective in clearing *M. audouini* and *M. canis* infection of the glabrous skin and it was found to cure or improve *T. interdigitale* infection and improve *T. rubrum* infection of the skin. Treatment of *M. canis* and *M. audouini* infection of hairs and *T. rubrum* infection of nails was ineffective. The one case of *M. furfur* infection included in this series cleared after six months' treatment. The antifungal properties *in vitro* are at least equal to those of other currently-used fungicides. Our clinical results suggest that this is also the case when used therapeutically.

It was useful to have three alternative preparations (lotion, cream and powder) to allow for freedom of choice according to the site infected and whether dry or moist.

Acknowledgments

We wish to thank The Crookes Laboratories Ltd. for supplying the 'Episol' used in this trial.

BIBLIOGRAPHY

- ROSS, J. W., SHAPERO, M., STEPHENS, F. F., TUNNAH, E. J., WALLIS, E. K. (1959), forthcoming publication.
PAYNE, D. B., SHARPE, C. J., STEPHENS, F. F., TUNNAH, E. J. (1959), forthcoming publication.