

DIPHENCYPRONE IN THE TREATMENT OF ALOPECIA AREATA

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Abstract. 27 patients suffering from either extensive alopecia areata ($n=5$) or alopecia totalis ($n=22$) were treated topically with diphenyprone, a new potent contact allergen. The duration of treatment ranged from 4 to 17 months. Unilateral induction of hair growth after unilateral treatment was observed in 23 patients. A continuous response after continuous treatment has been observed so far in 18 of these patients. Thus, diphenyprone was found to be as effective as DNCB or squaric acid dibutylester in the treatment of alopecia areata. Unlike DNCB, diphenyprone is not mutagenic in the Ames test. Compared with squaric acid dibutylester, diphenyprone is more stable and thus more suitable for storage when dissolved in acetone. Further investigative evaluation of diphenyprone may show whether this drug is suitable for a more general use in the treatment of severe forms of alopecia areata.

Key words: Alopecia areata; Therapy; Contact allergy; Diphenyprone

Controlled studies have shown that the application of potent contact allergens induces regrowth of hair in all forms of alopecia areata, including alopecia totalis (6). Extensive trials have been performed so far only with two sensitizers, dinitrochlorobenzene (2, 5) and squaric acid dibutylester (7). In order to improve the applicability of this method, we decided to use diphenyprone, a new potent contact sensitizer. The results obtained with this compound are reported here.

Description of diphenyprone

Diphenyprone is a term that we propose as a short form for 2,3-diphenylcyclopropenone-1. The structure is given in Fig. 1. Its molecular formula is $C_{15}H_{10}O$; the melting point is 119-120°C. Stute et al. (11) provided evidence that diphenyprone is a potent contact allergen in both man and animals. In guinea pigs, one single application of 3% diphenyprone in acetone (0.05 ml/animal) was sufficient to sensitize all animals. The sensitizing capacity was found to be as high as that of dinitrochlorobenzene or squaric acid dibutylester.

Thus, diphenyprone should not be used for industrial purposes. Cross sensitizations to other chemicals have so far not been observed. In the bacterial plate incorpora-

tion assay (Ames test) diphenyprone was found not to be mutagenic at concentrations of 50 and 100 $\mu\text{g/ml}$, in both the presence and absence of mammalian microsomes (11). We therefore considered diphenyprone suitable for a therapeutic trial in alopecia areata.

PATIENTS AND METHODS

Initially, the trial comprised 30 patients with alopecia areata. Three patients dropped out of the study after some weeks because they could no longer keep the weekly appointments. Five of the remaining 27 patients suffered from extensive hair loss (>25% bald area), and 22 patients had alopecia totalis. There were 11 men and 16 women. Their ages varied from 15 to 57 years. All patients were informed about the investigative nature of the proposed treatment and signed an information consent form. At present, the duration of treatment ranges from 4 to 17 months.

Using acetone as solvent, we prepared eight different concentrations of diphenyprone (2.0, 1.0, 0.5, 0.1, 0.05, 0.01, 0.001 and 0.0001%). The treatment consisted of regular applications of 1-2 ml of one of these preparations. The solution was painted on with a swab stick on one-half of the scalp. The other side served as a control region. Sensitization was obtained with a 2% solution applied once to one-half of the scalp. Fourteen days later, eczema was already present in 9 cases, indicating that the amount of diphenyprone still present in the skin was sufficient to elicit the allergic reaction without a second application. If no reaction was observed, a 0.1% solution was applied on the 14th and 21st day of treatment, and on further weekly applications, the concentration was adjusted to the patient's reactivity against the allergen, the aim being to maintain a mild eczema without blistering or oozing.

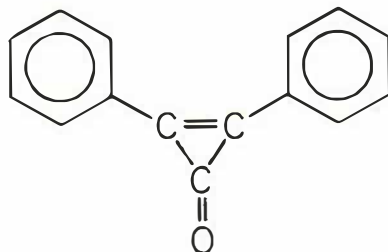


Fig. 1. Structure of diphenyprone (2,3-diphenylcyclopropenone-1).

Table I. Results of unilateral treatment of alopecia areata with diphencyprone

Number of patients	27
Unilateral response	23
No response	4

RESULTS

The results are summarized in Tables I and II. No therapeutic effect has been noted so far in 4 cases after a period of treatment ranging from 4 to 8 months. 23 patients showed a significant difference in hair growth between the treated and untreated sides. Hair regrew either exclusively on the treated side (Fig. 2a, b), or the regrowth was faster and denser on this side. The unilateral response was observed in most cases within 3 months. One patient responded after only 3 weeks, whereas in another patient unilateral hair growth started after 10 months of treatment. When the difference between the two sides became evident, both sides were treated (Fig. 2c, d). In 5 patients who had shown an initial response, subsequent treatment failed to maintain a continuous response in spite of the fact that an eczematous reaction was still present. In 4 of these cases, however, unilateral hair growth started again after continuing the treatment with lower concentrations of diphencyprone.

Side effects

The side effects were essentially the same as those observed after application of dinitrochlorobenzene or squaric acid dibutylester. In 11 patients, the initial application of the 2% solution resulted in a mild irritation of the skin with some itching for two or three days. In the eliciting phase, occasionally the eczematous reaction was so severe that the treatment had to be discontinued for a week, and subsequently a lower concentration of the allergen had to be chosen. No patient, however, abandoned the trial by reason of an undesired severe reaction.

Laboratory tests

The following laboratory tests were performed before treatment and every 3 months during treatment: red blood cell count, white blood cell count, thrombocytes, methemoglobin, examination for reticulocytes, toxic granules and Heinz bodies,

blood levels of creatinine, uric acid, urea, bilirubin, transaminases, γ -GT and alkaline phosphatase. No abnormalities were noted.

DISCUSSION

Our results indicate that for the treatment of severe forms of alopecia areata, diphencyprone is as effective as dinitrochlorobenzene and squaric acid dibutylester. Unlike dinitrochlorobenzene, diphencyprone is not mutagenic in the bacterial plate incorporation assay. Moreover, diphencyprone is more stable than squaric acid dibutylester and thus more suitable for storage when dissolved in acetone.

In some patients, an increase in the concentration of diphencyprone failed to maintain the response, whereas a decrease in the dosage was followed again by regrowth of hair. This indicates that, in any individual case, the appropriate dosage is decisive for the therapeutic effect.

Some authors are still doubtful about the concept that contact allergy is the essential mechanism of this mode of treatment. In the past, it has repeatedly been claimed that non-antigenic irritants may be effective in stimulating the regrowth of hair in alopecia areata (3), and various irritants such as phenol (8) and anthralin (9) have been recommended until very recently. In controlled studies, however, non-antigenic irritants did not show any therapeutic effect. This applies to croton oil (10, 12), sodium lauryl sulphate (1) and anthralin which has been tested by us in 30 patients (unpublished data).

In conclusion, the results obtained with diphencyprone lend further support to the view that contact allergy, and not merely an irritation of the skin, is essential for the therapeutic effect observed in alopecia areata (4). Further testing of diphencyprone for safety and applicability may reveal whether the drug can be recommended for general use in the treatment of extensive forms of this hair disease.

Table II. Results of continuous treatment with diphencyprone in those patients who showed a unilateral response

Number of patients	23
Continuous response	18
Discontinuous response	4
Failure to maintain the response	1

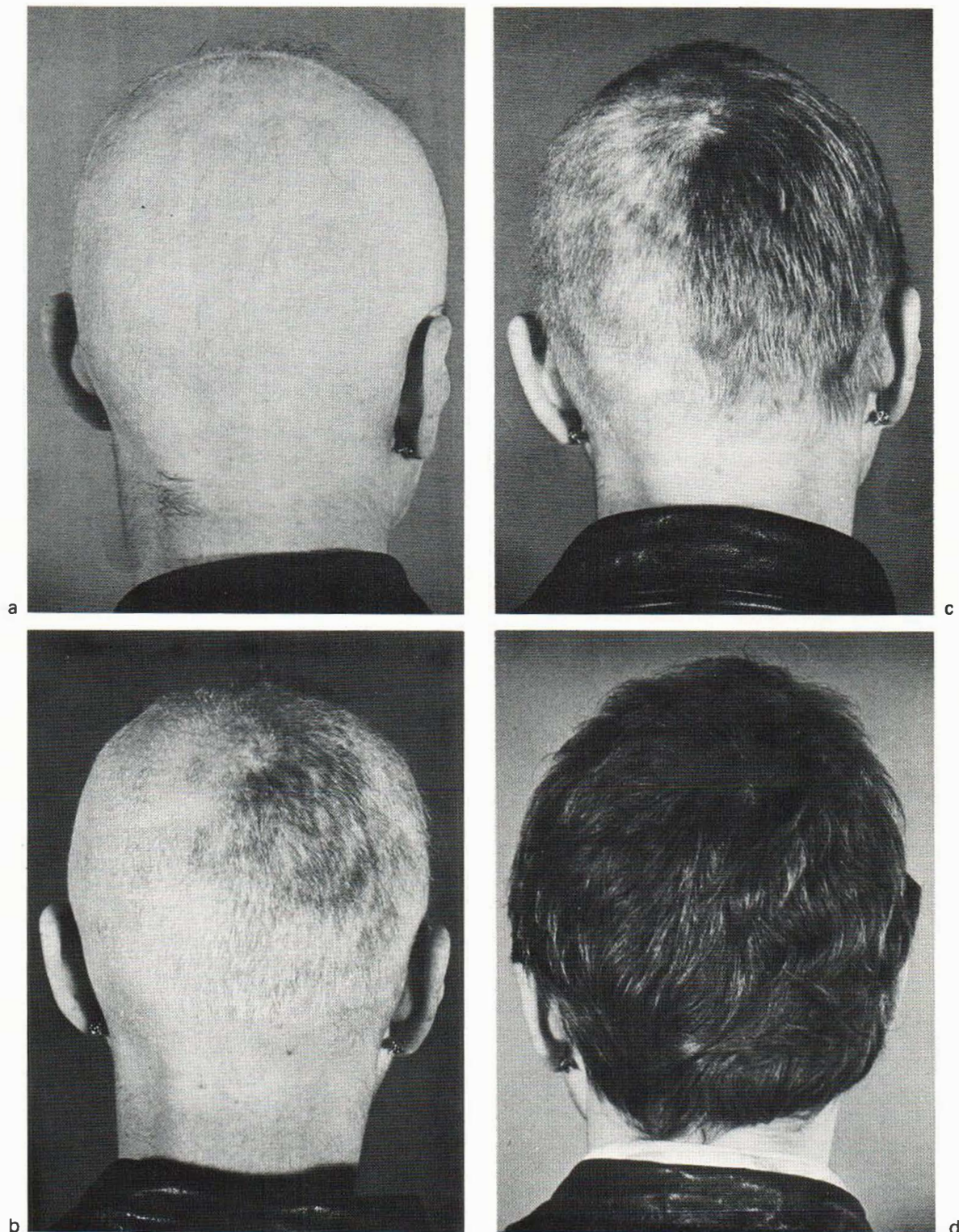


Fig. 2. Treatment of alopecia areata with diphencyprone. (a) Before treatment. (b) 15-week treatment of right side.

(c) Subsequent 6-week treatment of both sides. (d) 19-week treatment of both sides.

REFERENCES

1. Büchner, U., Echternacht-Happle, K. & Happle, R.: Irritant versus allergic contact dermatitis for the treatment of alopecia areata. *Arch Dermatol Res* 264: 123, 1979.
2. Daman, L. A., Rosenberg, E. W. & Drake, L.: Treatment of alopecia areata with dinitrochlorobenzene. *Arch Dermatol* 114: 1036, 1978.
3. Galewsky, E.: Erkrankungen der Haare und des Haarbodens. *In* Handbuch der Haut- und Geschlechtskrankheiten, vol. XIII/1 (ed. J. Jadassohn), p. 129. Springer, Berlin, 1932.
4. Happle, R.: Antigenic competition as a therapeutic concept for alopecia areata. *Arch Dermatol Res* 267: 109, 1980.
5. Happle, R., Cebulla, K. & Echternacht-Happle, K.: Dinitrochlorobenzene therapy for alopecia areata. *Arch Dermatol* 114: 1629, 1978.
6. Happle, R. & Echternacht, K.: Induction of hair growth in alopecia areata with D.N.C.B. *Lancet* ii: 1002, 1977.
7. Happle, R., Kalveram, K. J., Büchner, U., Echternacht-Happle, K., Göggelmann, W. & Summer, K.-H.: Contact allergy as a therapeutic tool for alopecia areata: application of squaric acid dibutylester. *Dermatologica* 161: 289, 1980.
8. Hoede, M.: Treatment of alopecia areata with phenolum liquefactum caustic process and simultaneous belladonna dose. *In* Hair Research, Status and Future Aspects (ed. C. E. Orfanos, W. Montagna & G. Stüttgen), pp. 341-342. Springer, Berlin, 1981.
9. Schmoeckel, C., Weissmann, I., Plewig, G. & Braun-Falco, O.: Treatment of alopecia areata by anthralin-induced dermatitis. *Arch Dermatol* 115: 1254, 1979.
10. Stüttgen, G. & Kentsch, V.: Comparison of DNCB and croton oil in the therapy of alopecia areata. *In* Hair Research, Status and Future Aspects (ed. C. E. Orfanos, W. Montagna & G. Stüttgen), p. 343. Springer, Berlin, 1981.
11. Stute, J., Hausen, B. M. & Schulz, K. H.: Diphenylcyclopropenon—ein stark wirksames Kontaktallergen. *Dermatosen* 29: 12, 1981.
12. Swanson, N. A., Mitchell, A. J., Leahy, M. S., Headington, J. T. & Diaz, L. A.: Topical treatment of alopecia areata. Contact allergen vs primary irritant therapy. *Arch Dermatol* 117: 384, 1981.

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