British Journal of Dermatology (1985) **113**, 103–106.

Pharmacology and Treatment

A dimethoxynaphthalene derivative (RS-43179 gel) compared with 0·025% fluocinolone acetonide gel in the treatment of psoriasis

A.LASSUS AND S.FORSSTROM*

Department of Dermatology, University Central Hospital, Helsinki, Finland and *Medical Department (Sweden), Astra-Syntex Scandinavia AB, Sodertalje, Sweden

Accepted for publication 20 November 1984

SUMMARY

Thirty patients were entered into a double-blind trial comparing a dimethoxynaphthalene derivative (RS-43179 gel) and fluocinolone acetonide (Synalar® gel) in the treatment of psoriasis. The two preparations were applied three times daily for 4 weeks, and the patients were assessed at weeks 1, 2, 3, 4, 7 and 9. No significant differences between the two preparations could be detected. By the end of the 4-week treatment period, the number of patients showing a 'Good, Excellent or Clear' therapeutic response was 25 out of 28 after RS-43179 treatment and 26 out of 28 after Synalar® treatment.

Four patients experienced irritation on the side treated with RS-43179. In two of these patients the reaction was severe and the treatment was discontinued, but in the other two patients, the local irritation was only moderate. No other adverse reactions were seen.

Topical steroids are the most popular treatment for psoriasis because of their rapid effect and their superior cosmetic properties. However, the prolonged use of corticosteroids causes frequent and sometimes irreversible side-effects, especially in the form of pronounced skin thinning and striae. For this reason we need to find a suitable alternative which is equally effective, cosmetically acceptable and free from side-effects.

RS-43179 (6-chloro-2,3-dimethoxynaphthalene-1,4-dio-diacetate) is a new, non-steroid compound synthesized by Syntex Corporation which is being evaluated for topical treatment of psoriasis. RS-43179 belongs to a class of compounds called naphthalenes, consisting of mono- and bicyclic oxy- and oxo-compounds, known initially for their antiviral activity. The first compound of this class was developed by Russian workers and subjected to clinical trials in various dermatoses of viral and supposedly viral aetiology. RS-43179 has been tested in psoriasis bioassay screens and has been shown to possess considerable antipsoriatic properties. The mechanism of action of RS-43179 remains obscure, but it was concluded in studies using mice (Syntax Research files, unpublished data) that the compound did not affect cell proliferation or keratinization of normal epidermis.

Correspondence: Ass. Prof. Allan Lassus, Department of Dermatology, University Central Hospital, Helsinki, Finland.

We have conducted a double-blind parallel contralateral comparison of the local effect of RS-43179 1% gel and fluocinolone acetonide 0·025% gel in the treatment of stable chronic psoriasis plaques.

METHODS

Thirty patients (nine male and 21 female, aged 29–73 years, mean age 51) from the Finnish Psoriasis Association volunteered to participate in the study. All patients had a diagnosis of psoriasis vulgaris and had stable symmetrical lesions of similar severity and duration. Two patients had lesions on the lower legs, 10 on the knees and 18 on the elbows. In 21 patients the lesions were severe, and in nine they were moderately severe. Pregnant patients were not permitted to enter the study. The treated lesions at the start had been present in all cases for more than 3 months, and in 13 cases (43%) more than 6 months. The lesions had in all cases been stable and untreated for at least 1 month. Three patients received concomitant medication for cardiovascular disease which was continued throughout the study.

A 1% gel preparation of RS–43179 containing 96% propylene glycol was compared with a 0·025% fluocinolone acetonide gel. The study was double-blind, randomized and the two agents were applied unoccluded three times daily to symmetrical psoriasis plaques for 4 weeks. The patients were scheduled to return for visits at weeks 1, 2, 3, 4, 7 and 9. A 6-point scale ranging from 'Worse' to 'Clear' was used to rate therapeutic effect, based on the assessment of desquamation, erythema, induration and pruritus. Laboratory examinations comprising complete biochemistry, haematology and urinalysis were carried out before and after treatment (at week 0 and 4).

Statistical analysis was performed by the Institute of Research Data Management, Syntex Research, using the sign test, the Wilcoxon Signed-Rank test, and the binomial test (reported in this paper). All tests were two-tailed and P values less than or equal to 0·05 were considered statistically significant. The null hypothesis tested was that there was no difference between the two treatments.

RESULTS

Of the 30 patients entered into the study, 27 were available for analysis at week 1 and 28 were available at weeks 2, 3, and 4 (Table 1). During the treatment period there were no significant differences between the two treatments. Of the 17 patients who did show a difference between treatments, 10 responded better to RS-43179 after the first week of treatment. For subsequent treatment weeks 2, 3 and 4, the proportions of patients responding better to RS-43179 were 11/15, 11/17 and 11/17, respectively.

Generally, a trend toward improved response was evident with both treatments. At the end of the first week of treatment, 9/27 and 13/27 patients, respectively, showed at least a 'Good' response to the fluocinolone and RS-43179 gels. By treatment week 4, 26/28 patients showed at

TABLE 1. Difference in therapeutic response; weeks 1–4

	Week 1	Week 2	Week 3	Week 4
RS-43179 better	10	11	11	11
Synalar better	7	4	6	6
No difference	10	13	11	11
Total	27	28	28	28
Binomial test P value	0·56	0·13	0·26	0·26

TABLE 2. Therapeutic response (number of patients in each grade)

	Worse	Poor	Fair	Good	Excellent	Clear	Total
At week 4 (end of treatment)							
RS-43179	0	0	3	12	6	7	28
Synalar®	0	0	2	17	9	0	28
At week 9 (5 weeks of therapy)							
RS-43179	0	1*	1	5	12	9	28
Synalar®	0	1*	1	4	16	6	28

* Same patient, psoriasis relapsed both sides.
Two patients were withdrawn at visit 2.

least a 'Good' response to fluocinolone while 25/28 showed a 'Good, Excellent or Clear' response to RS-43179 (Table 2).

The number of patients showing no discernible difference between treatments increased remarkably during the post-treatment period. At the end of the study (5 weeks post-treatment) 26/28 patients demonstrated a 'Good, Excellent or Clear' response to both drugs (Table 2).

Power analysis

This is a relatively small clinical trial which has shown no significant difference between two treatments. It may be that a larger trial would have shown some difference and this can be shown by studying the 'power' of this study. With a conservative approach, handling the results from each treatment as independent measurements, the study power may be estimated in the following manner.

Taking 'Excellent', 'Clear', and 'Good' to represent therapeutic success and 'Worse', 'Poor', or 'Fair' to be therapeutic failure, it is apparent from Table 3 that the proportion for a successful outcome is 25/28 or 0·893 with RS-43179, and 26/28 or 0·929 with fluocinolone. Then with 28 measurements per group, using a two-sided test with a 5% level of significance for type 1 error, the probability of type 2 error may then be calculated for varying differences between the treatments.

TABLE 3. Power analysis

Power (%)	Difference in proportions
80	0·21
90	0·24
95	0·275
99	0·33

Thus if the true response rate to fluocinolone is 90%, there is a greater than 95% probability that the true response rate to RS-43179 is 60% or more (Donner, 1984).

DISCUSSION

At the present time no topical non-steroidal antipsoriatic agent is available which is both highly active in clearing psoriasis and cosmetically pleasing. After only 2 weeks of therapy, more than

75% of the patients showed a good–excellent response to the RS-43179 treatment. This rapid response is similar to what is observed after treatment with a potent topical corticosteroid (Wright & MacDuff, 1972).

The follow-up results after 5 weeks of treatment were remarkably good, but were influenced by the fact that the follow-up period occurred during the early summer.

No systemic adverse effects were observed during the study. No laboratory changes attributable to the treatment could be detected. Two patients experienced a severe local irritation which caused discontinuation of the treatment after 1 week. Two other patients reporting side-effects had a similar irritation which was only moderate and occurred later during the treatment. One of them was able to continue the treatment according to the protocol while the other had to decrease the number of daily applications of RS-43179. The latter patient was completely cleared of psoriasis on the treated side and showed no signs of irritation 1 week after the end of treatment. The irritation was of short duration in all patients and did not require any topical or systemic treatment.

The local reactions may have been due to one or more of at least three different factors. The gel formulation contained 96% of propylene glycol, which is an irritant (Hannuksela, Kousa & Pirilä, 1976), and the compound itself is a potential irritant (Syntex Research, unpublished data). Furthermore, RS-43179 has not been demonstrated to possess anti-inflammatory properties strong enough to mask an eventual inflammatory reaction. In addition, at least two foreign related substances with strong irritative properties have been identified in the compound.

In an earlier study with a related compound, also demonstrated to be highly effective as an antipsoriatic agent, one-third of the patients experienced a severe local reaction causing discontinuation of the treatment (Lassus, Forsstrom, unpublished data). On the other hand, one of the patients who discontinued treatment in the present study because of the irritation has been included in a subsequent study and treated with RS-43179 in an ointment formulation and has shown no sign of local irritation. The present study revealed that RS-43179 1% gel is a highly effective drug for the treatment of psoriasis vulgaris but may produce primary irritant contact dermatitis in a few patients.

Considering the results of the power analysis, the response rate to RS-43179 is very acceptable, especially since the side-effect profile appears advantageous. Moreover, if the usual placebo response rate of 30% is assumed to have occurred in this study, the calculation gives further confidence for the efficacy of RS-43179. This suggestion needs confirmation, however, by appropriate controlled trials.

REFERENCES

DONNER, A. (1984) Approaches to sample size estimation in the design of clinical trials—a review. *Statistics in Medicine*, **3**, 199–214.

HANNUKSELA, M., KOUSA, M. & PIRILÄ, V. (1976) Allergy to ingredients of vehicles. *Contact Dermatitis*, **2**, 105.

WRIGHT, E.T. & MACDUFF, M.A. (1972) Comparative clinical study of topical steroid and non-steroid therapy in psoriasis. *Cutis*, **9**, 77.