was mainly in arm movement, which has been shown to be due to itch-provoked scratch; but there was some increase in leg movement which is associated with restlessness (1). Thus PUVA mostly caused itch and some restlessness, whereas dithranol caused little of either. It appears that the 'irritation' or 'burn' which is a common complication of dithranol treatment leads to restlessness and not itch. The mechanism of the itch provoked by PUVA is not clear, particularly as it tended to occur after several treatments and appeared to decrease despite continued treatment. Whether PUVA-induced itch is due to production of pruritogen or a lowering of itch threshold is not known. An observation of practical importance is that patients in whom scratching was provoked by treatment are those who had the highest pre-treatment levels. It may therefore be that patients with considerable pruritus before treatment should be treated simultaneously with a drug such as nitrazipam (4) and a corticosteroid concomitantly with the first few exposures to UVA.

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Clinical Trial of a Potent Non-halogenated Topical Steroid, BUDESONIDE

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Abstract. In a double-blind, randomized multi-centre study, 116 patients with psoriasis have been treated for 1–3 weeks with budesonide ointment (Preferid®, Draco/Tika; a subsidiary of AB ASTRA), a new non-halogenated topical steroid. In a series of 11 patients a 0.025% budesonide ointment was significantly superior to placebo. In a second series, of 54 patients, a 0.025% budesonide ointment was significantly superior to 0.025% fluocinolone acetonide ointment (Synalar®, ICI). In a third series, of 51 patients, a 0.010% budesonide ointment was compared with 0.025% fluocinolone acetonide ointment. No statistically significant difference between these two preparations was found to exist. No adverse reactions were observed.

Key words: Budesonide; Fluocinolone acetonice; Placebo; Clinical trial; Psoriasis; Topical steroid.

New topical steroids with ever-increasing potency continue to be produced. Unfortunately, both the number and severity of local as well as systemic side effects have increased in proportion to the potency, thus limiting the usefulness of the most potent preparations (1, 4, 5).

Halogenation of the steroid molecule has been considered necessary in order to attain the topical anti-inflammatory effect of potent corticosteroids.

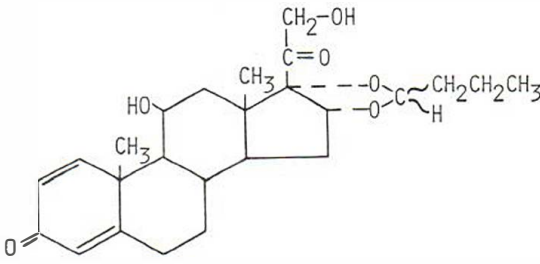

Fig. 1. 16α,17α-Butylidenedioxy-11β,21-dihydroxypregn-1,4-diene-3,20-dione (budesonide, INN).

Table I. *Results of objective and subjective evaluation of the effect of treatment with 0.025 % and 0.010 % budesonide ointment compared with placebo and 0.025 % fluocinolone acetonide ointment*

	Preference for budesonide	Preference for ref. preparation	No diff.	*p*-value[a]
Budesonide 0.025 % – placebo (N=11)				
Doctor's opinion	10	1	0	0.012
Patients' opinion	11	0	0	0.001
Budesonide 0.025 % – fluocinolone acetonide 0.025 % (N=54)				
Week one (N=54)				
Doctor's opinion	25	4	25	0.0002
Patients' opinion	26	5	23	0.0002
Week two (N=50)				
Doctor's opinion	20	4	26	0.002
Patients' opinion	27	5	18	0.0002
Budesonide 0.010 %—fluocinolone acetonide 0.025 % (N=51)				
Week one				
Doctor's opinion	14	14	23	1.0
Patients' opinion	11	18	22	0.26
Week two				
Doctor's opinion	13	15	23	0.85
Patients' opinion	8	18	25	0.08

[a] The *p*-values were calculated according to the two-sided sign test.

(3). However, halogenation also increases the risk of side effects (9).

In animal models it was found that acetalization of the 16α, 17α-hydroxy groups with *n*-butyraldehyde in non-halogenated corticoids markedly improved the local anti-inflammatory potency, without a corresponding rise in systemic activity. In cotton-pellet tests, the selected compound budesonide (Fig. 1) had the same high local anti-inflammatory potency as halogenated potent corticoids (9). Similar results were obtained regarding skin-blanching according to the Stoughton-McKenzie test (6).

The aim of the present clinical trials was to study the topical potency of budesonide ointment. Psoriasis was chosen as the trial disease (1).

PATIENTS AND METHODS

The trial was performed in three parts.

	No. of pats.
1. Budesonide 0.025% ointment versus base only (=placebo)	11
2. Budesonide 0.025% ointment versus fluocinolone acetonide 0.025% ointment	54
3. Budesonide 0.010% ointment versus fluocinolone acetonide 0.025% ointment	51

Patients suffering from psoriasis vulgaris with at least two stable symmetrical lesions of the same morphology, suitable for paired comparisons, were selected for the studies. Children and pregnant women were excluded. No steroid preparations had been used for at least 2 weeks prior to the test period, and no other anti-psoriatic treatment was used during the trial.

Budesonide 0.025% and 0.010% was supplied in an ointment base with the following composition: budesonide 25 mg, propylene glycol, cera alba, paraffin. liquid., vaseline. alb. q.s. ad 100 g. The fluocinolone acetonide was used in its commercial formulation (Synalar®): fluocinolone acetonide 25 mg, acid. citr., propylene glycol, adeps lan., et vaselin. alb. q.s. ad 100 g. The budesonide ointment base was used as a placebo. The ointments were supplied in a randomized fashion in identical-looking tubes marked 'right' and 'left'. The patients were instructed to apply the ointments twice daily to the selected areas.

In the placebo trial the effect of the treament was evaluated once, after 1–3 weeks, when a difference in morphology between the two compared sites was noticed. In the comparisons with fluocinolone acetonide the evaluations were made after 1 and 2 weeks. Both the doctor's and the patient's opinions as to which side (right or left), if any, improved most were also recorded. Sequential analysis was used as an aid in determining the extent of each part of the trial (2). However, patients who had already started at the time when no new admissions were accepted, were permitted to continue, and are also included in the analysis.

RESULTS

The detailed results are shown in Table I.

In the comparison between budesonide 0.025 %

and placebo, the active preparation was found to produce a statistically significant improvement after only 11 patients.

In the comparison between budesonide 0.025% and fluocinolone acetonide 0.025%, the former preparation was significantly superior to the latter after 1 and 2 weeks.

In the comparison between budesonide 0.010% and fluocinolone acetonide 0.025%, no statistically significant differences in effect between the two ointments were demonstrated after 1 and 2 weeks.

DISCUSSION

The first part of the study demonstrated that 0.025% budesonide ointment had a marked clinical effect on psoriasis after 1–3 weeks of treatment, giving a statistically significant better effect than placebo in a series of only 11 patients, evaluated with sequential analysis.

The second part of the investigation showed that 0.025% budesonide ointment was more potent than the reference substance, fluocinolone acetonide 0.025% in its commercial composition (Synalar®). This is well known to be a very effective topical steroid preparation (1). When the concentration of budesonide was lowered to 0.010%, its effect was still at the same level as the 0.025% fluocinolone acetonide ointment.

The results suggest that budesonide is the first very potent non-halogenated steroid for topical use. The halogen substitution in the steroid nucleus is thus not mandatory for high topical activity if an optimal substitution is introduced in the 16α, 17α-position.

The introduction of halogen reduces the rate of oxidative biotransformation (7). *In vitro* experiments on rat liver have shown that budesonide is biotransformed more rapidly than the halogenated 16α, 17α-acetal triamcinolone acetonide (8). This could explain the fact that budesonide in animal models has caused relatively less systemic corticoid activity than has halogenated 16α, 17α-acetal steroids (9).

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Metronidazole and *Demodex folliculorum*

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Abstract. In vitro survival of *Demodex folliculorum* was tested in the presence of various concentrations of metronidazole (Flagyl). Demodex was found to survive in

Table I. *In vitro survival of Demodex folliculorum in presence of various concentrations of metronidazole*

Metronidazole (μg/ml)	Survival *Demodex folliculorum* Control	Treated
2	1	105	95
2	2.5	195	195
2	10	60	95
2	1000	0	225