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Effect of Salicylic Acid on the Activity of Betamethasone-17,21-Dipropionate in the Treatment of Erythematous Squamous Dermatoses

Robert Elie, MD, PhD, *Clinical Pharmacologist, Centre de Recherche, Hôpital Louis H Lafontaine, Montréal, (Québec), Canada*

Louis-Philippe Durocher, MD, FRCP(C), *Dermatologist, Hôpital Maisonneuve-Rosemont, Montréal, (Québec), Canada*

Edward C Kavalec, BSc *Pharmacy, Clinical Research Associate, Schering Canada Inc., Pointe Claire, (Québec), Canada*

Forty adult out-patients with erythematous squamous dermatoses of the scalp were treated in this 21-day double-blind study with an alcohol base lotion containing either 0·05% betamethasone-17,21-dipropionate, 2% salicylic acid, 0·05% betamethasone-17,21-dipropionate + 2% salicylic acid or their respective placebo. The four treatments were assigned randomly to the patients according to a 2 × 2 orthogonal factorial design. Changes in severity of redness, scaling, pruritus and size of lesions were evaluated. Since very few patients presented with excoriation and lichenification, these symptoms could not be ascertained. Results were assessed for significance by covariance analysis where initial status was used as regressor. A potentiation of the betamethasone-17,21-dipropionate activity by salicylic acid was observed for scaling. An additive effect was noted for redness and pruritus. According to the physician's global evaluation, patients treated with the combination drug showed a better evolution than those treated with placebo.

The results suggest that addition of a keratolytic agent enhances the corticosteroid effect in the treatment of erythematous squamous dermatoses.

Introduction

Since the introduction of hydrocortisone in 1952, and its application to the treatment of skin lesions (Sulzberger & Witten 1952), many potent topical preparations have been introduced in dermatology (Kaidbey & Kligman 1974, Stoughton 1975, Stoughton 1977). However, most corticosteroids have been of little efficacy in treating squamous lesions since the penetration into the skin was impaired by hyperkeratosis.

Short-term use of halogenated corticosteroids in treating acute squamous dermatoses has been successful (Viglioglia 1972, Fredriksson & Gip 1974, Leeming & Bor 1974, Pasternak 1977). Long-term use of these molecules in patients with chronic dermatoses has induced serious adverse effects, particularly skin atrophy (Senddon 1969, Senddon 1972, Senddon 1976, Burry

Reprint requests to: Robert Elie, MD, PhD, Centre de Recherche, Hôpital Louis H Lafontaine, Montréal, (Québec), Canada

1973, Pasternak 1977, Stoughton 1977, Jackson 1978).

In an attempt to minimize the incidence of serious side-effects by reducing total daily dose formerly required, different formulations aimed at increasing steroid penetration into the skin have been introduced (Eriksson 1975, Fredriksson 1976a, Fredriksson 1976b, Gip & Hamfelt 1976). Attempts have been made to combine low doses of topical corticosteroids with low doses of salicylic acid, a well known keratolytic agent (Wilkinson 1972, Davies & Marks 1976, Gip & Hamfelt 1976, Roberts, Marshall & Marks 1980). In some preparations, the introduction of salicylic acid inactivated the steroid molecule by converting the salt from its 17C to the 21C position (Ricciati & Lester 1977). In others, combination with salicylic acid resulted in active, pharmacologically stable compounds, as either the steroid used had no radical at 17C (hydrocortisone or flumethasone-21-pivalate) or it had radicals at both 17C and 21C (betamethasone-17,21-dipropionate). Moreover, when the molecule was not so inactivated, salicylic acid increased the efficacy of the corticosteroid (Eriksson 1975, Go & Wuite 1976, Mattelaer 1979, Lindemayr 1981) through a still unknown mechanism.

The purpose of this study was to determine if addition of the keratolytic agent salicylic acid (2%) to betamethasone-17,21-dipropionate (0·05%) would result in potentiation of corticosteroid activity or an addition of their respective effects.

Methods

Sixteen men and twenty-four women, ranging in age from 20 to 64 years (mean 36·5 years), with moderate to severe psoriasis, seborrhoeic dermatitis or neurodermatitis of the scalp were selected and gave their informed consent to the study (Table 1). Disease status was stable in twenty-eight cases and exacerbating in twelve. Most patients (75%) had suffered from their dermatologic disease for 1 or more years. One week prior to admission to the study, current topical corticosteroid medications were discontinued, as well as other medications that could influence the dermatosis. At the end of this 1-week wash-out period, redness, lichenification, excoriation, scaling, pruritus, burning sensation and total area of the lesions

Table 1

Patient characteristics

	No. of patients
Diagnosis:	
– Psoriasis	22
– Seborrhoeic dermatitis	17
– Neurodermatitis	1
Duration of disease:	
< 6 months	6
> 6 months < 12 months	4
> 12 months	30
Disease status:	
– Stable	28
– Exacerbating	12

(cm^2) were clinically evaluated using a 5-point ordinal scale (0 = none to 4 = very severe).

According to a random drug allocation, ten patients were treated with a lotion containing 0·05% betamethasone-17,21-dipropionate*, ten others with the same vehicle plus 2% salicylic acid, ten with the same vehicle plus 0·05% betamethasone-17,21-dipropionate and 2% salicylic acid** and ten with the vehicle only. During the 21-day treatment period, the patients applied the assigned medication twice a day to the dermatologic lesions. In addition, patients were required to clean the scalp every 2 days with a non-medicated shampoo.

At the end of 1, 2 and 3 weeks of treatment, the same clinical signs were assessed by the same evaluator. Compliance to drug application was appraised qualitatively by the clinician after discussion with the patient and assessment of unused medication. At the end of treatment, a clinical global evaluation was made.

The effects of the four treatment groups (betamethasone-17,21-dipropionate effect, salicylic acid effect, and combination effect) were assessed weekly for significance at a critical 5% level using variance and covariance analyses. The Day 0 evaluations were used as regressors.

Comparisons of placebo with each other

*Diprosone® Lotion, Schering Canada Inc.
**Diprosalic® Lotion, Schering Canada Inc.

treatment (salicylic acid, betamethasone-17,21-dipropionate, and their combination) were made through the variance/covariance analysis. However, significance of these contrasts was assessed after transformation of the "F" values into "t", using the Dunnett's "t" distribution (Winer 1971).

Results

No significant differences among the four treatment groups were observed in age, sex, height, weight or in patients' clinical characteristics. Also, no significant differences among the treatment groups were found before drug application in redness, lichenification, excoriation, scaling, pruritus, burning sensation or total area of the lesions.

Patients treated with the drug combination (0·05% betamethasone-17,21-dipropionate plus 2% salicylic acid) evidenced less redness than those treated with placebo after the second week ($t = 3·03$, $p < 0·02$) and third week ($t = 3·41$, $p < 0·01$) of treatment (Table 2). Since the greater effect of the combination cannot be explained by a potentiation of the betamethasone-17,21-dipropionate activity by the salicylic acid ($F^1 = 1·07$ for the first week and $F^1 = 0·22$ for the third week of therapy), the addition of salicylic acid effect to that of betamethasone-17,21-dipropionate cannot be ruled out.

A potentiation of betamethasone-17,21-dipropionate activity by salicylic acid ($F^1 = 2·89$, $p < 0·05$) was observed after 1 week of therapy for scaling (Figure 1). After 2 weeks of treatment the efficacy of the combination was still greater than placebo ($t = 2·58$, $p < 0·05$) but the potentiation was no longer demonstrable ($F^1 = 2·33$, $p > 0·10$).

After 3 weeks of treatment, pruritus decreased significantly with betamethasone-17,21-dipropionate ($t = 3·36$, $p < 0·01$), salicylic acid ($t = 3·66$, $p < 0·01$), and to a greater extent ($t = 4·42$, $p < 0·01$) with the combination of the two drugs.

Lichenification, excoriation and burning sensation were seen rarely in the patients evaluated. Therefore, differences among the treatment groups were assessed using Fisher Exact Probability tests to compare frequency distributions. No heterogeneity of distribution could be found.

Finally, the clinician's global evaluation showed that the patients treated with the 0·05% betamethasone-17,21-dipropionate + 2% salicylic acid combination improved

Table 2

Comparison of 2% salicylic acid, 0·05% betamethasone-17,21-dipropionate, and their combination on some dermatologic variables

Variable	*Day*	*Placebo*	*2% Salicylic acid*	*0·05% Betamethasone-17, 21-dipropionate*	*0·05% Betamethasone-17, 21-dipropionate + 2% salicylic acid*
Redness	14	1·74	1·78	1·30	0·98‡
	21	1·76	1·48	1·09	0·63†
Scaling	14	1·20	1·24	1·03	0·42*
	21	1·19	0·83	0·83	0·50
Pruritus	14	1·01	0·70	0·67	0·32
	21	0·92	0·20†	0·26†	0·02†
Physician's global evaluation	14	3·30	2·70	2·60	1·70‡
	21	3·10	2·20	2·20	1·55‡

(Adjusted mean values except for physician's global evaluation)

*$p < 0·05$, ‡$p < 0·02$ and †$p < 0·01$, by comparison to placebo using Dunnett's "t" distribution.

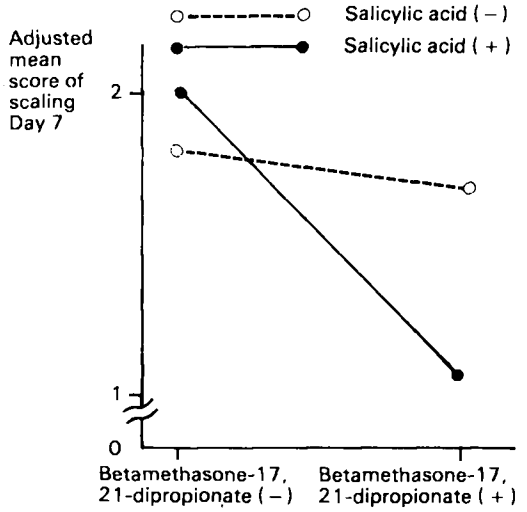

Fig 1 *Potentiation of the anti-scaling effect of betamethasone-17,21-dipropionate by salicylic acid*

significantly by comparison to those treated with placebo after 2 weeks ($t = 4{\cdot}04$, $p < 0{\cdot}01$) and after 3 weeks ($t = 3{\cdot}02$, $p < 0{\cdot}02$) of treatment.

No adverse effects were spontaneously reported and no deleterious effects were observed by the evaluator.

Discussion

Drug combinations in fixed schedules are not generally recommended. Additive effects and interactions could be obtained by adjusting relative dosages of the agents. However, in some situations, where indiscriminate compounding may lead to either inactivated compounds, more toxic preparations or less efficacious drugs, fixed combinations of agents are of clinical interest.

Salicylic acid is a well known keratolytic agent which has been frequently used for treating dermatoses with hyperplastic corneal layer (Goodman & Gilman 1980). Its use in high concentrations for long periods of time on extensive lesions has led to salicylate intoxication (Martindale 1977) and thereby has limited its usefulness. However, since this drug has shown a keratolytic effect at concentrations as low as 1% (Martindale 1977) without significant absorption (Gip & Hamfelt 1976, Landi 1977), its combination with betamethasone-17,21-dipropionate appears to be safe for the short-term treatment of squamous dermatoses.

Whenever treatment is longer than a few weeks, it might be advisable to use the combination until the keratolytic effect is obtained and to continue therapy with the corticosteroid alone thereafter.

In this study, the addition of 2% salicylic acid increased the efficacy of 0·05% betamethasone-17,21-dipropionate in relieving redness, scaling and pruritus. A potentiation of the anti-scaling effect of betamethasone-17,21-dipropionate by salicylic acid was evidenced.

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