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Combination Dermatological Products: a Comparison of Betamethasone Dipropionate/ Clotrimazole/Gentamicin Sulphate and Flumethasone Pivalate/Clioquinol Creams

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The combination creams, betamethasone dipropionate/clotrimazole/gentamicin sulphate and flumethasone pivalate/clioquinol, were compared in patients with corticosteroid responsive dermatoses and/or cutaneous fungal and/or bacterial infections. Medication was applied to affected areas twice daily for 28 days. Of 67 patients enrolled, 31 treated with betamethasone/clotrimazole/gentamicin and 33 given flumethasone pivalate/clioquinol were evaluated for efficacy and safety each week during therapy and once 14 days post-therapy. Disease signs and symptoms were less severe in the group given betamethasone/clotrimazole/gentamicin than in the comparative group at days 7 ($P = 0.04$), 21 ($P = 0.02$), 28 ($P = 0.09$), and 42 ($P = 0.09$) and at patients' last valid visit ($P = 0.06$). By the last valid visit, signs/symptoms had improved by 82% for patients treated with betamethasone/clotrimazole/gentamicin versus 68% for those treated with flumethasone pivalate/clioquinol. Patients given betamethasone/clotrimazole/gentamicin had statistically significantly better therapeutic responses than those given flumethasone pivalate/clioquinol at day 7 and, by the last valid visit, 19/31 (61%) patients given betamethasone/clotrimazole/gentamicin compared to 15/33 (45%) given flumethasone pivalate/clioquinol had a complete cure or an excellent therapeutic response. Median time of onset of relief of erythema and pruritus was approximately 2 days, regardless of treatment. No adverse reactions were reported.

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INTRODUCTION

The accurate diagnosis of skin disorders is a challenge to the medical practitioner since dermatoses often are of mixed aetiology. In particular, patients with inflammatory dermatoses may develop secondary fungal and/or bacterial infections, or cutaneous fungal or bacterial infections may be complicated by severe inflammation. Thus, microscopic and microbiological testing may be required to facilitate accurate identification of the specific cause(s) of various skin disorders. When such tests cannot be done, it is difficult for the practitioner to diagnose accurately and, hence, prescribe appropriate treatment.

Skin diseases may be extremely uncomfortable for affected patients, so treatment with a fast-acting medication frequently is desired. A combination anti-inflammatory/anti-fungal/anti-bacterial preparation may be an ideal therapeutic choice when the practitioner cannot diagnose skin disease of mixed aetiology, but feels that prompt treatment is required. Sch 411 cream* is such a combination product and contains three agents: 0.05% betamethasone dipropionate, 1.0% clotrimazole and gentamicin sulphate (equivalent of 0.1% gentamicin). Betamethasone dipropionate is a corticosteroid with anti-inflammatory, anti-pruritic and vasoconstrictive properties and is clinically effective in patients with psoriasis and other corticosteroid responsive dermatoses.[1–3] With a rapid onset of action, betamethasone dipropionate provides fast relief of swelling, itching and redness.[4] The anti-fungal component, clotrimazole, has a broad spectrum of activity.[5,6] Susceptible fungi include *Epidermophyton, Microsporum* and *Trichophyton* spp, *Coccidioides immitis, Histoplasma capsulatum,* and *Aspergillus* and *Candida* spp.[6] The antibiotic component, gentamicin sulphate, is a broad spectrum agent active against many Gram-negative bacteria of clinical significance, including *Enterobacter, Escherichia, Klebsiella* and *Serratia* spp, and *Pseudomonas aeruginosa,* as well as certain Gram-positive organisms, such as *Staphylococcus aureus*.[6,7]

The aim of this clinical study was to compare the efficacy and safety of betamethasone/clotrimazole/gentamicin cream and another combination preparation with anti-inflammatory, anti-fungal and anti-bacterial properties in patients with corticosteroid responsive dermatoses and possible cutaneous fungal and/or bacterial infections. The comparative product used was a 0.02% flumethasone pivalate/3.0% clioquinol combination (Locorten-Vioformo®).

PATIENTS AND METHODS

Patient selection

This was a randomized, open, parallel-group study. Informed consent and parental or guardian consent were obtained, as appropriate. Patients were enrolled for study if they had non-infectious inflammatory dermatoses and/or cutaneous fungal and/or bacterial infections and were at least 12 years of age.

Excluded from the study were patients with diabetes or auto-immune, hepatic, renal, metabolic or severe systemic disease. Likewise, patients with a history of abnormal renal function or drug-induced ototoxicity, and those with evidence of systemic fungal or bacterial involvement, e.g. temperature above

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38°C, were not enrolled. In addition, pregnant or lactating women and those not practising contraception were excluded. Patients who were hypersensitive to components of the study medications or in whom treatment with corticosteroids, anti-fungal agents or aminoglycosides was contra-indicated were not accepted. Lastly, enrollment was precluded if patients were using other investigational agents, had used topical or systemic steroids within 1 and 2 weeks prior to initiation of treatment, respectively, or had used topical or systemic anti-fungal or anti-bacterial agents within 1 week prior to initiation of treatment.

Before therapy, at day 0, a medical history was taken and a physical examination performed on each patient. The total area affected by skin disease was recorded on a dermogram. A single test site was selected within this area, and was scraped and swabbed to obtain specimens for potassium hydroxide mount, Gram's stain, and fungal and bacterial cultures. The investigator scored the severity of erythema, exudation, maceration, papules, pruritus, pustules, scaling and vesicles at the test site on a four-point scale (0, absent or none; 1, mild; 2, moderate; or 3, severe). In order to be enrolled, a patient was to have sign/symptom severity scores that totalled at least 6 and erythema that was at least mild in severity.

Dosage and administration

At day 0, patients were randomly assigned to one of the two treatment groups and were told to apply a thin layer of medication to the affected area including the test site, once in the morning and evening for 28 days. The creams were dispensed in identical 30 g tubes labelled only by patient number. A 1 week supply of the study medication was given to patients on days 0, 7, 14 and 21 (visits 1–4, respectively). Patients discontinued treatment on the morning of day 28 (visit 5) and were asked not to apply any medication to the test site between this visit and day 42 (visit 6).

Bathing of the involved area with soap and water and concomitant therapy with agents that would not affect the course of the primary diagnosis were permitted during the study. Patients were asked not to use systemic or topical anti-inflammatory, anti-fungal, anti-bacterial or antiseptic agents, and no medication other than the study creams was to be applied to the test site.

Criteria for efficacy evaluation

Severity of the aforementioned signs and symptoms was rated on the four-point scale on days 0, 7, 14, 21, 28 and 42 (±2 days) corresponding to visits 1–6, respectively. The investigator also graded patients' overall disease condition on this scale on days 7, 14, 21, 28 and 42, and described patients' clinical therapeutic response compared to the baseline findings as 'complete cure', 100% improvement; 'excellent', approximately 75% to < 100% improvement; 'good', approximately 50% to < 75% improvement; 'fair', approximately 25% to < 50% improvement; 'poor', some, but < 25% improvement; and 'treatment failure', worsening of signs and symptoms after 3 days of therapy or no apparent response after 1 week.

In addition, patients recorded when onset of relief of erythema and pruritus occurred on a diary card given at day 0. Relief was described as 'none', 'a little', 'some' or 'a lot'. Patients began their diary entries on the evening of day 0, before the first application of test medication. Subsequent diary entries were made twice daily prior to application of medication through the morning of day 7. Date and time of the initial

application of medication and of each entry were also noted. On day 7, the investigator reviewed the diary card with each patient to establish the date and time of onset of action of study medication, i.e. when erythema and pruritus had been relieved.

Criteria for evaluation of safety

Throughout the study, adverse reactions, whether described by the patient or noted by the investigator, were to be recorded by type, date of onset, duration, severity and relationship to study medication.

Statistical analyses

The sex distribution of treatment groups and the number of patients in each group who reported relief of erythema and pruritus were compared by the χ^2-test (or Fisher's exact test if the expected cell frequency was <5); median times of onset of relief were compared by Wilcoxon's rank sum test. Other efficacy data (mean totals of sign/symptom severity scores, mean scores for patients' overall disease condition and clinical therapeutic response) and other patient characteristics (age, total duration of primary diagnosis and duration of current exacerbation of skin disease pre-therapy) were analysed by Student's *t*-test.

RESULTS

Of 67 patients enrolled for study, 33 were assigned to the group treated with betamethasone/clotrimazole/gentamicin and 34 to the group treated with flumethasone pivalate/clioquinol. Three patients did not return after the initial visit, so a total of 64 patients, 31 in the group given betamethasone/clotrimazole/gentamicin and 33 in the comparative group, were evaluated for efficacy and safety.

Table 1
Characteristics of the patient population studied by treatment group

	Betamethasone/clotrimazole/gentamicin ($n = 31$)	Flumethasone pivalate/clioquinol ($n = 33$)
Sex (no. of patients)		
Male	13	13
Female	18	20
Age (years)		
Mean	28.6	38.2
Median	24.0	30.0
Range	13–66	14–75
Duration of current exacerbation of skin disease pre-treatment (months)		
Mean	2.0	1.5
Median	1.0	1.0
Total duration of primary diagnosis (months)		
Mean	48.9	15.1
Median	3.0	2.0

Among the 31 patients treated with betamethasone/clotrimazole/gentamicin who were evaluated for efficacy, the primary diagnosis was dermatitis for 22 (71%), eczema for seven (23%), and candidiasis and tinea for one (3%) patient each. Of the 33 patients treated with flumethasone pivalate/clioquinol who were included in the efficacy evaluation, 21 (64%) had dermatitis and 12 (36%) had eczema. Specimens for fungal cultures were taken at day 0 for 5/31 patients given betamethasone/clotrimazole/gentamicin and for 6/33 given flumethasone pivalate/clioquinol; 10 of these cultures were positive. In addition, specimens for bacterial cultures were obtained for 27/31 patients given betamethasone/clotrimazole/gentamicin and for 30/33 in the comparative group; bacterial pathogens were isolated for 14 patients on betamethasone/clotrimazole/gentamicin and for 15 patients in the comparative group. Additional patient characteristics are shown by treatment group in Table 1. Both groups were statistically comparable in terms of patients' sex, weight, height, total duration of primary diagnosis and duration of current exacerbation of skin disease pre-treatment, although patients given betamethasone/clotrimazole/gentamicin were significantly ($P=0.04$) younger than those given flumethasone pivalate/clioquinol; mean ages were 28.6 and 38.2 years, respectively. This difference was not considered to be clinically significant.

Previous therapy was reported by two patients treated with betamethasone/clotrimazole/gentamicin, one of whom had used an anti-histamine and cold cream for approximately 1 month, and the other an anti-fungal agent for 2 months. One patient given flumethasone pivalate/clioquinol had been treated previously with a topical corticosteroid for 2 months. Only one patient was treated concomitantly during the study; a patient in the comparative group used medication for insomnia.

Efficacy of study medications

Evaluation of signs and symptoms. Before therapy, at day 0, the mean total of severity scores for signs and symptoms of erythema, exudation, maceration, papules, pruritus, pustules, scaling and vesicles was 12.5 in the group given betamethasone/clotrimazole/gentamicin and 12.4 in the comparative group. Accordingly, severity of disease initially was comparable in both groups. At days 7 and 21, however, the mean totals were significantly less in the group given betamethasone/clotrimazole/gentamicin than in the comparative group ($P = 0.04$ and 0.02, respectively). Differences in the mean totals between treatment groups were marginally significant at days 28 and 42, and at patients' last valid visit* ($P = 0.09$, 0.09 and 0.06, respectively); these differences continued to favour the betamethasone/clotrimazole/gentamicin cream over the flumethasone pivalate/clioquinol preparation. At patients' last valid visit, the mean total of the severity scores was 2.2 in the group given betamethasone/clotrimazole/gentamicin versus 4.0 in the group given flumethasone pivalate/clioquinol.

At all visits, the percentage improvement† was greater in the group

*The last valid visit was the last visit at which each patient was evaluated for efficacy.

† Percentage improvement is the difference between the mean totals of the severity scores at day 0 (baseline) and at each of days 7, 14, 21, 28 and 42 or at the last valid visit, divided by the mean total at day 0 and multiplied by 100.

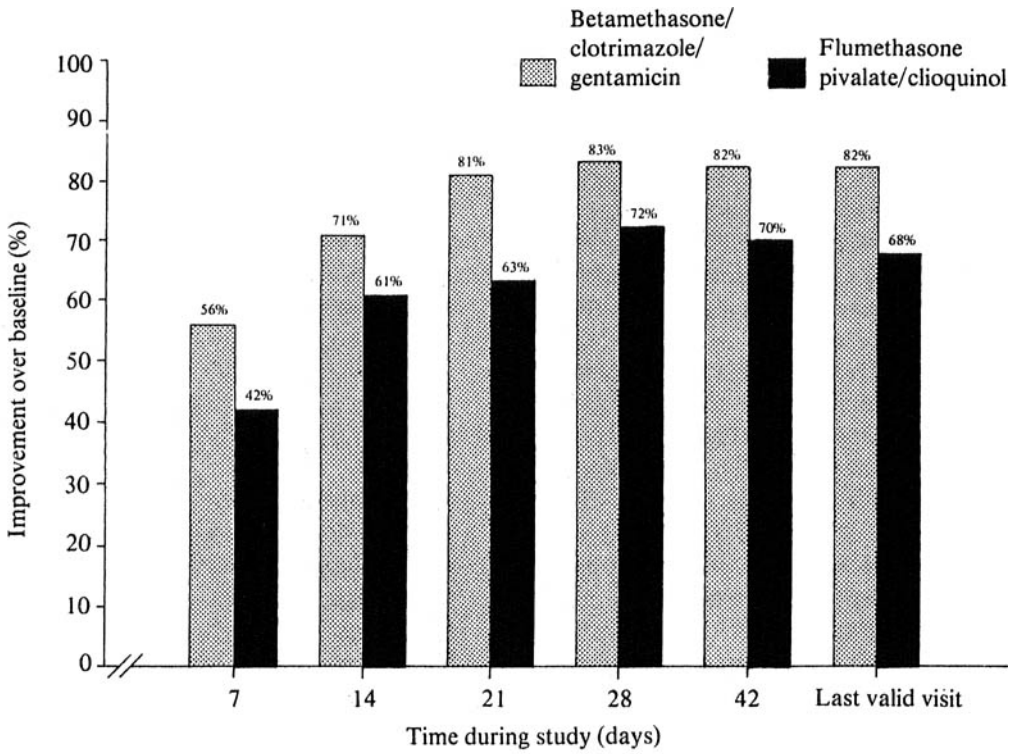

Fig. 1. The percentage improvement in skin disease signs and symptoms in patients treated with either betamethasone/clotrimazole/gentamicin cream or flumethasone pivalate/clioquinol cream. (Percentage improvement is the difference between the mean totals of the sign/symptom severity scores at day 0 (baseline), and at each of days 7, 14, 21, 28 and 42 or the last valid visit, divided by the mean total at day 0 and multiplied by 100.)

given betamethasone/clotrimazole/gentamicin than in the comparative group. Figure 1 illustrates that the signs and symptoms improved by 56% for patients given betamethasone/clotrimazole/gentamicin and by 42% for those given flumethasone pivalate/clioquinol within 1 week of initiating therapy. At patients' last valid visit, the former group had an 82% improvement and the comparative group, a 68% improvement.

Evaluation at day 0 demonstrated that the three most frequently reported and most severe signs and symptoms among patients of both treatment groups were pruritus, erythema and scaling. The mean severity scores are shown in Table 2. It is noteworthy that mean severity scores at the last valid visit for pruritus, erythema and scaling were markedly less for patients given betamethasone/clotrimazole/gentamicin than for those given flumethasone pivalate/clioquinol. Futhermore, throughout the study, patients treated with betamethasone/clotrimazole/gentamicin showed a greater improvement in these signs/symptoms compared to patients treated with flumethasone pivalate/clioquinol. For example, by day 7, pruritus,

Table 2
Mean severity scores and percentage improvement in pruritus, erythema and scaling for the two treatment groups

Sign/ symptom	Betamethasone/clotrimazole/gentamicin			Flumethasone pivalate/clioquinol		
	Mean severity score		Improvement (%)	Mean severity score		Improvement (%)
	Day 0	Last valid visit		Day 0	Last valid visit	
Pruritus	2.9	0.7	77	3.0	1.2	60
Erythema	2.8	0.7	77	2.7	1.0	62
Scaling	2.3	0.4	85	2.2	0.7	69

Table 3
The effect of treatment on the number of patients (%) showing absence of disease and a complete clinical therapeutic cure at days 21, 28 and 42 and at last valid visit

	Betamethasone/clotrimazole/gentamicin				Flumethasone pivalate/clioquinol			
	Day 21	Day 28	Day 42	Last valid visit	Day 21	Day 28	Day 42	Last valid visit
Disease absent	10/31 (32)	13/31 (42)	15/31 (48)	15/31* (48)	5/33 (15)	7/32‡ (22)	10/32‡ (31)	10/33 (30)
Complete clinical therapeutic cure	10/31 (32)	13/31 (42)	14/31 (45)	14/31† (45)	5/33 (15)	7/32‡ (22)	9/32‡ (28)	9/33 (27)

* $P = 0.08$ versus the group given flumethasone pivalate/clioquinol.
† $P = 0.09$ versus the group given flumethasone pivalate/clioquinol.
‡ Sample size reduced by one patient who was a treatment failure.

scaling and erythema had improved by 61%, 57% and 41%, respectively, in patients given betamethasone/clotrimazole/gentamicin as opposed to 41%, 40% and 34%, respectively, for patients given the comparative treatment. The percentages of improvement in pruritus, scaling and erythema at the last valid visit are shown in Table 2.

Evaluation of overall disease condition. In general patients from both groups had mild or moderate skin disease on days 7 and 14. Thereafter, skin disease was absent in more patients given betamethasone/clotrimazole/gentamicin than in the comparative group (Table 3).

Evaluation of clinical therapeutic response. Patients given betamethasone/clotrimazole/gentamicin had significantly ($P = 0.05$) better responses than those given flumethasone pivalate/clioquinol at day 7 and marginally better responses ($P = 0.09$) at the last valid visit. At other visits, clinical responses for the treatment groups were statistically comparable.

Differences between treatment groups in the number of patients who were completely cured favoured the group given

betamethasone/clotrimazole/gentamicin from day 21 through the end of the study (Table 3).

Evaluation of onset of action. By day 7, 27/30* (90%) patients treated with betamethasone/clotrimazole/gentamicin and 30/33 (91%) given flumethasone pivalate/clioquinol reported relief of erythema and 29/30* (97%) and 29/33 (88%) patients, respectively, experienced relief of pruritus. Treatment groups were similar with regard to times of onset of relief of erythema and pruritus. Specifically, the median time of onset of relief of erythema was 2.0 days, regardless of treatment group, and for pruritus, this was 2.3 days in the group given betamethasone/clotrimazole/gentamicin and 2.0 days in the group given flumethasone pivalate/clioquinol.

Safety of study medications

No adverse reactions were experienced by any of the 64 patients included in the safety analysis.

DISCUSSION

The present trial indicated that betamethasone/clotrimazole/gentamicin cream was efficacious and well tolerated in patients with corticosteroid responsive dermatoses and/or cutaneous fungal and/or bacterial infections. The cream's multiple pharmacological effects produced favourable clinical results, i.e. patients had a 56% improvement in signs and symptoms at day 7. In contrast, patients treated with flumethasone pivalate/clioquinol had a 42% improvement by day 7. Moreover, at the same time, clinical therapeutic responses were statistically significantly better in patients given betamethasone/clotrimazole/gentamicin than in the comparative group. By patients' last valid visit, a complete cure or an excellent clinical response was evident in 19/31 (61%) patients treated with betamethasone/clotrimazole/gentamicin and 15/33 (45%) patients treated with flumethasone pivalate/clioquinol.

Three recent trials[8–10] also verify the efficacy of twice daily treatment for 4 weeks with betamethasone/clotrimazole/gentamicin cream in patients with corticosteroid responsive dermatoses and/or cutaneous fungal and/or bacterial infections. In the study by Dominguez,[8] the superior efficacy of betamethasone/clotrimazole/gentamicin cream over flumethasone pivalate/clioquinol was demonstrated. After 1 and 2 weeks of therapy, patients treated with betamethasone/clotrimazole/gentamicin had significantly ($P = 0.02$) better clinical responses than patients treated with flumethasone pivalate/clioquinol. By patients' last valid visit, skin disease was absent and a complete cure was achieved in 17/30 (57%) patients given betamethasone/clotrimazole/gentamicin versus 11/31 (35%) given flumethasone pivalate/clioquinol. The former preparation was also superior to the combination triamcinolone acetonide/neomycin/gramicidin/nystatin (Kenacomb®) in two other independent studies.[9, 10] The trial by Meth[9] demonstrated that mean totals of sign/symptom severity scores were statistically comparable between treatment groups at the initial pre-therapy visit, but significantly less ($P < 0.01$) at all subsequent visits in the group given betamethasone/clotrimazole/gentamicin than in the group given the triamcinolone acetonide

*Sample size was reduced by one patient who reported relief prior to initiating therapy.

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combination cream. Furthermore, at these visits, patients' overall disease condition and clinical response to therapy were significantly ($P<0.01$) better for patients treated with betamethasone/clotrimazole/gentamicin than with the triamcinolone acetonide combination cream. In the study by Gutierrez-Aldana,[10] 25/28 (89%) patients given betamethasone/clotrimazole/gentamicin as compared to 19/28 (68%) given the triamcinolone acetonide combination cream, were either completely cured or had an excellent clinical response 2 weeks post-therapy ($P<0.01$). Moreover, betamethasone/clotrimazole/gentamicin cream provided a significantly faster ($P<0.01$) onset of relief of erythema and pruritus, two signs/symptoms which may be especially uncomfortable for the patient, than either of the other comparative preparations.[8,9]

In conclusion, this clinical study showed that the combination cream, betamethasone/clotrimazole/gentamicin, applied twice daily for 28 days, was efficacious in patients with corticosteroid responsive dermatoses and/or cutaneous fungal and/or bacterial infections. Moreover, these findings suggest that it was more favourable than the comparative combination cream, flumethasone pivalate/clioquinol. Both study medications were safe and well tolerated; no adverse experiences were reported.

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