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Efficacy and safety of wet-wrap dressings in children with severe atopic dermatitis: influence of corticosteroid dilution

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Summary

Background The wet-wrap treatment involves emollients or corticosteroid dilutions under occlusive wet dressings, and has been reported to be highly effective in severe refractory atopic dermatitis (AD).

Objectives To investigate the influence of different corticosteroid dilutions on the efficacy and hypothalamic–pituitary–adrenal (HPA) axis suppression in children with severe refractory AD having wet-wrap dressings.

Methods Eighteen children were treated with a 50% dilution of fluticasone propionate (FP) 0·05% cream for 2 weeks. In another five children a side-to-side comparison was conducted with 10%, 25% and 50% dilutions of FP cream under wet wrap. A third group of eight children was treated with 0% (= emollient), 5%, 10% or 25% dilutions of FP cream applied on the whole body under wet wrap.

Results After 1 week, a major improvement averaging 74% was observed, without apparent differences between 5%, 10% or 25% dilutions of FP cream under wet wrap, with less improvement in the second week of treatment. The first and second group of children showed HPA axis suppression in only three of 23 children using measurements of 09·00 h serum cortisol after 2 weeks. The third group of children showed HPA axis suppression, as indicated by 06·00 h serum cortisol levels, which was related to the absolute amount of FP applied.

Conclusions This suggests that weaker corticosteroid dilutions had comparable high efficacy, but lower risk of HPA axis suppression.

Key words: atopic dermatitis, hypothalamic–pituitary–adrenal axis, topical corticosteroids, wet-wrap dressings

Severe atopic dermatitis (AD) remains difficult to treat. Although guidelines provide a good framework for managing AD,[1,2] some patients do not improve with conventional therapy and pose a major therapeutic problem. Cyclosporin, the most extensively studied treatment for refractory AD, has been reported to be effective in children with severe AD.[3–5] However, cyclosporin may have potentially severe side-effects, and should not be given for longer than 3 months. In children, therapies such as ultraviolet (UV) A-1,[6] psoralen + UVA,[7] recombinant interferon-γ[8] and systemic corticosteroids are generally not indicated. Thus, there is still a need for an effective treatment in children with severe AD.

In 1991, Goodyear *et al.* described a highly effective method of treatment with dressings in children with severe erythrodermic AD.[9] Their method involved a wet-wrap technique involving the use of open-weave cotton tubular dressings (Tubifast) impregnated with a 10% dilution of betamethasone valerate 0·01% cream applied twice daily according to a standard protocol.[9–11] They observed that 09·00 h cortisol levels at the time of the wet-wrap application were suppressed after 2–5 days, but returned to normal 2 weeks post-therapy.

We have developed a modified protocol using fluticasone propionate (FP) 0·05% cream-emollient

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dilutions (50% on the body and 10% on the face) once daily under wet-wrap dressings.[12] FP is a potent corticosteroid that seems to have an improved benefit/risk ratio.[13,14] In the first part of the present study, 18 children were treated according to this protocol and the systemic side-effects were assessed by 09·00 h serum cortisol. However, 09·00 h serum cortisol is not a sensitive marker of the systemic bioactivity of topical corticosteroids, and other investigators have used weaker corticosteroid dilutions. Therefore, in the second part of the study, different dilutions of corticosteroids were compared and systemic bioactivity was measured by 06·00 h serum cortisol and timed morning urinary cortisol excretion.

The application of corticosteroids under occlusion has previously been associated with a high rate of side-effects, but the widely used technique of wet wrap has not been satisfactorily evaluated. The purpose of this study was to investigate the efficacy and the safety of once-daily wet-wrap dressings with different dilutions of FP and durations of therapy in children with severe AD.

Patients and methods

Patients and design

Thirty-one children (15 boys and 16 girls) with AD according to the criteria of Sampson[15] and Williams *et al.*[16] aged 5 months to 13 years, were included. Disease severity was 'severe' in 29 of the children according to an objective SCORAD >40.[17] The wet-wrap protocol we used was described previously.[12] Briefly, the patients were admitted to hospital and took a bath for 5–10 min once daily, followed by application of the diluted FP 0·05% cream on the whole body. On top of this we applied first a wet and then a dry layer of tubular bandage made of cotton (Tubifast®, Seton Scholl, Oldham, U.K.). This bandage was rewetted every 2 h with water using a spray bottle.

The first group consisted of 18 children who were treated with a 50% dilution of FP cream under wet-wrap dressings for 2 weeks. The objective SCORAD and 09·00 h serum cortisol were measured at the beginning and after 2 weeks of treatment.

The second group of five children had symmetrically localized AD and was treated with different dilutions (10%, 25% and 50%) of FP cream on the left and the right side of the body under wet-wrap dressings. After 1 week, the severity of AD was scored by objective SCORAD on both sides, and treatment was continued with a 10% dilution of FP cream. The levels of 09·00 h serum cortisol were measured at the beginning and after 2 weeks of treatment.

The third group consisted of eight children who were treated with different dilutions of FP cream: two each with 0% (= emollient), 5%, 10% and 25%, under wet-wrap dressings. Objective SCORAD and 06·00 h serum cortisol were measured daily during the first week, and after 2 weeks of treatment. Treatment with topical corticosteroids was stopped 3 days before the baseline cortisol value was assessed, and the total amount of FP cream that was applied was recorded.

Clinical scoring system

The severity of AD was scored using the objective SCORAD,[17,18] which includes the assessment of two items in a standardized manner: (i) extent (applying the rule of nines), and (ii) intensity (erythema, oedema/papulation, oozing/crust, excoriation, lichenification and dryness on a scale of 0–3). This scoring system reflects the modified consensus of the European Task Force on AD. Unlike the initial version called SCORAD index,[19] subjective symptoms are not included in the scoring of AD in the objective SCORAD.[17,18]

Safety analysis

To determine the systemic load of the topical medication we assessed the hypothalamic–pituitary–adrenal (HPA) axis suppression. In the first two groups of 18 and five children, respectively, 09·00 h serum cortisol levels were measured at the beginning and after 2 weeks of treatment. In the third group of eight children, 06·00 h serum cortisol and urinary timed morning cortisol/creatinine ratio were measured daily during the first week of treatment. Local side-effects were assessed visually.

Statistical analysis

Statistical analysis was performed with SPSS 7·5 using Wilcoxon's signed rank test in the first group of children to analyse the improvement of AD and the change in 09·00 h serum cortisol levels. The exact McNemar's test was used in the first group of children to assess the improvement of AD as categorized into mild, moderate and severe. Spearman's rank correlation was used in the third group of children to test relationships between improvement of AD, absolute amount of FP in $\mu g\ m^{-2}$ body surface daily, mean

06·00 h serum cortisol on treatment and mean timed morning cortisol/creatinine ratio on treatment. Statistical significance was defined as $P < 0{\cdot}05$.

Results

In the first uncontrolled group of 18 children, a significant decrease in the objective SCORAD (Wilcoxon's test, $P < 0{\cdot}0001$) after 2 weeks of treatment was observed in 17 children (Fig. 1a). One child was lost to follow-up after 4 days of treatment due to personal reasons. The severity of AD classified into mild, moderate and severe according to the objective SCORAD decreased in all 17 children (Table 1). For the evaluation of safety we assessed the levels of 09·00 h serum cortisol at the beginning of the treatment and after 2 weeks (Fig. 1b). There was no significant decrease in the levels of serum cortisol after 2 weeks of treatment (Wilcoxon's test, $P = 0{\cdot}24$). However, serum cortisol levels were temporarily below the normal range (0·2–0·8 μmol L^{-1}) in three of the 18 children after 2 weeks, indicating a suppression of the HPA axis.

To investigate the efficacy of different dilutions of FP cream under wet wrap, a side-to-side comparison was performed in five children with different dilutions (10%, 25% and 50%) of FP cream on the left and the right side. After 1 week of treatment, the objective SCORAD had decreased markedly in all five children, with no difference between the left and the right side in objective SCORAD or affected body surface (Table 2). We cannot exclude that this lack of difference is due to a systemic effect. However, HPA axis suppression was not evident in any of the five children as assessed by 09·00 h serum cortisol (mean ± SD serum cortisol day 0, 0·42 ± 0·16 μmol L^{-1}; day 14, 0·45 ± 0·17 μmol L^{-1}). Furthermore, we observed substantial improvement in AD after 1 week, with only minor additional improvement in the second week of treatment.

In the third group, three different dilutions of FP cream (5%, $n = 2$; 10%, $n = 2$; 25%, $n = 2$) were applied on the whole body in six children and emollient only in two children, under wet wrap. After 1 week, the two children using only emollient under wet wrap showed minor improvement, whereas the six children in whom 5%, 10% or 25% dilutions of FP cream were applied under wet wrap showed a major improvement in AD (Fig. 2). There was no major difference in efficacy between 5%, 10% and 25% dilutions of FP cream (Fig. 2). A dose–response relationship was seen with the absolute amount of FP in μg m^{-2} daily adjusted for dilution (Spearman's correlation $r = 0{\cdot}97$, $P < 0{\cdot}0005$; Fig. 3). An 80% improvement was achieved with FP 800 μg m^{-2} daily (equivalent to 1·6 g FP 0·05% cream). Absolute amounts of FP > 957 μg m^{-2} daily did not increase efficacy (Fig. 3). Children using FP ≤ 800 μg m^{-2} daily had no suppression of the HPA axis. Again, we observed

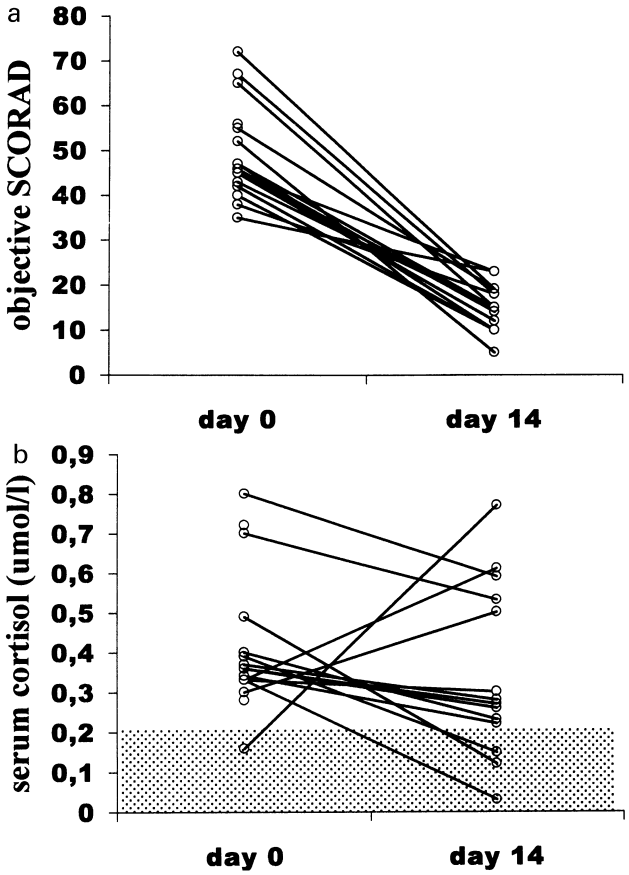

Figure 1. Graphs showing symptom score and systemic load of wet-wrap dressings using a 50% dilution of fluticasone propionate 0·05% cream in 18 children. (a) Objective SCORAD before and after 2 weeks of treatment; (b) 09·00 h serum cortisol levels before and after 2 weeks of treatment. The shaded area indicates hypothalamic–pituitary–adrenal axis suppression.

Table 1. Numbers of children with mild, moderate and severe atopic dermatitis (AD) before and after treatment

	Before treatment $n = 18$	After treatment $n = 17$
Mild AD	0	11
Moderate AD	2	6
Severe AD	16	0

There was one drop-out due to personal reasons. After 2 weeks of treatment, AD improved substantially (exact McNemar's test, $P < 0{\cdot}0001$).

Patient, treatment	Left beginning → after 1 week	Right beginning → after 1 week
A, 10% vs. 50%	44 (65%)[a] → 9 (10%)	44 (65%) → 9 (10%)
B, 25% vs. 50%	50 (55%) → 16 (26%)	50 (55%) → 16 (26%)
C, 10% vs. 25%	55 (50%) → 13 (10%)	59 (30%) → 13 (10%)
D, 10% vs. 25%	43 (60%) → 14 (10%)	43 (66%) → 14 (10%)
E, 10% vs. 50%	40 (35%) → 12 (20%)	40 (35%) → 12 (20%)

[a]The values in the table indicate objective SCORAD and the affected body surface in percentage. An objective SCORAD ≤ 15 indicates mild AD, 15–40 indicates moderate AD and > 40 indicates severe AD.

Table 2. Objective SCORAD and extent of atopic dermatitis (AD) in five patients before and after 1 week of wet wrap with different dilutions of fluticasone propionate on the left and the right side

substantial improvement after 1 week, with little further improvement in the second week of treatment.

Adverse events, other than HPA axis suppression, in the first group ($n = 18$), were upper respiratory tract infection ($n = 6$), folliculitis ($n = 6$), herpes simplex infection ($n = 1$), diarrhoea ($n = 1$) and itching ($n = 1$). In the second group ($n = 5$), we observed upper respiratory tract infection ($n = 2$), folliculitis ($n = 2$), abdominal pain ($n = 1$) and itching ($n = 1$). In the third group ($n = 8$), we observed folliculitis ($n = 5$), balanitis ($n = 1$) and furunculosis ($n = 1$). A generalized folliculitis was observed in both of the children treated with only emollient during the first week.

For a detailed analysis of HPA axis suppression, 06·00 h serum cortisol levels and timed morning urinary cortisol/creatinine ratio were measured daily in the third group of eight children (Table 3). A relationship was found between the daily absolute amount of FP applied (μg m^{-2} body surface daily) and the mean of the daily measurements of 06·00 h serum cortisol levels on treatment over a 7-day period (Spearman's test $r = -0{\cdot}73$, $P < 0{\cdot}05$, $n = 8$). However, there was no relationship between the daily absolute amount of FP applied and the mean of daily measurements of timed morning urinary cortisol/creatinine ratio on treatment over a 7-day period (Spearman's test $r = -0{\cdot}38$, $P = 0{\cdot}5$, $n = 6$).

Discussion

The results of the present study show a dramatic improvement in AD irrespective of the dilution of FP (5%, 10%, 25% and 50%) applied under wet wrap. This is demonstrated both in a left-to-right side comparison in five children and by application of different dilutions in eight children. The improvement of AD was related to the absolute amount of applied corticosteroid in μg m^{-2} body surface. However, absolute amounts of FP

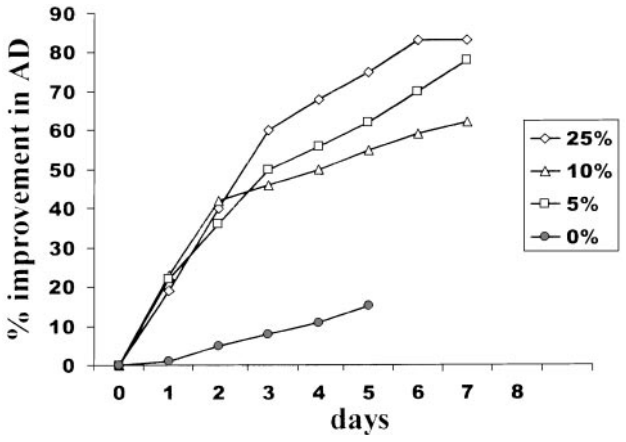

Figure 2. Graph of the relative improvement of atopic dermatitis (AD) in group 3 comprising eight children treated with different dilutions [two each with 0% (= emollient), 5%, 10% and 25%] of fluticasone propionate 0·05% cream. The improvement of AD was measured by objective SCORAD. Lines represent the means of two patients.

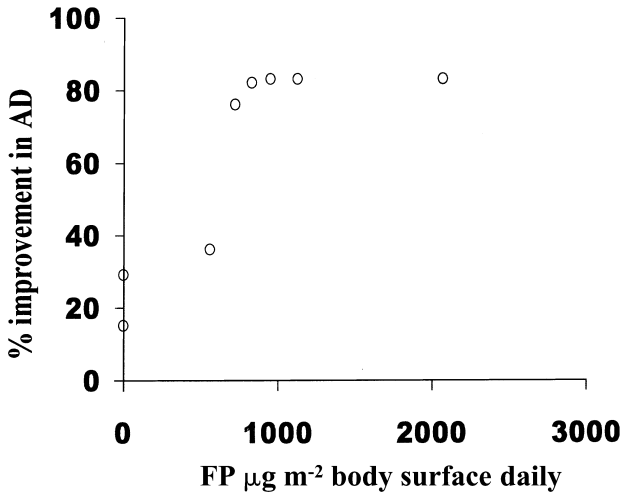

Figure 3. Graph showing the relative improvement of atopic dermatitis (AD) at 7 days against the absolute amount of fluticasone propionate (FP) in μg m^{-2} body surface daily in children treated with different dilutions [two each with 0% (= emollient) 5%, 10% and 25%] of FP 0·05% cream.

Table 3. Amount of fluticasone propionate (FP) in $\mu g\ m^{-2}$ body surface daily, improvement in SCORAD and hypothalamic–pituitary–adrenal axis suppression measured in serum and urine

Patient	FP ($\mu g\ m^{-2}$ daily)	SCORAD improvement	06·00 h serum cortisol[a]	Urinary ratio cortisol/creatinine[a]
1	0	29%	0·28	58·5
2	0	9%	0·46	153·6
3	564	36%	0·55	212·9
4	728	76%	0·39	[b]
5	835	82%	0·36	[b]
6	957	83%	0·09	18·4
7	1129	83%	0·03	6·3
8	2071	83%	0·33	79

[a]Mean values of daily measurement under treatment; [b]urine could not be obtained. The absolute amount of applied corticosteroid (FP $\mu g\ m^{-2}$ daily) was related to the mean of daily measurements of 06·00 h serum cortisol (Spearman's test, $r = -0{\cdot}73$, $P < 0{\cdot}05$) but not to the mean of daily measurements of urinary cortisol/creatinine ratio (Spearman's test, $r = -0{\cdot}38$, $P = 0{\cdot}5$).

$> 800\ \mu g\ m^{-2}$ daily hardly increased efficacy. Taken together, these results indicate that weaker dilutions of FP cream under wet wrap may have efficacy similar to that of stronger dilutions. The improvement in AD occurred mainly during the first week of treatment. During the second week of treatment minor additional improvement was observed, indicating that 1 week of treatment with wet wrap is sufficient.

Most of the side-effects during the first 2 weeks of treatment were probably not related to the treatment. Mild to moderate folliculitis, mainly on the legs, was observed in a large proportion of the children and appears to be related to the treatment. Interestingly, both children treated with only emollient under wet wrap had generalized but mild folliculitis after 4 days. Thus, folliculitis under wet-wrap therapy may be related to occlusion, but in some cases corticosteroids under wet wraps may aggravate the condition.

HPA axis suppression was measured by morning serum cortisol levels. In the first and the second group of children, 09·00 h serum cortisol levels were below the normal range ($0{\cdot}2–0{\cdot}8\ \mu mol\ L^{-1}$) in three of 18 in the first group and none of five in the second group of children. However, 09·00 h serum cortisol has been reported to have large intra- and inter-individual variability, which makes it a rather insensitive screening method for the systemic bioactivity of topical corticosteroids.[20] Therefore, in the third group of eight children, we determined daily 06·00 h serum cortisol levels. The collection time is crucial as a three-fold difference in the levels of serum cortisol between 08·00 h and 10·00 h has been documented.[21]

Additionally, urinary timed morning cortisol/creatinine ratio was assessed, as this measure is reported to have excellent sensitivity.[22,23] Using 06·00 h serum cortisol levels we observed evidence of HPA axis suppression related to the absolute amount of applied corticosteroid. This suggests that decreasing the amount of applied corticosteroid would improve the systemic safety without affecting the efficacy.

FP is a corticosteroid combining potent local efficacy with relatively limited suppression of the HPA axis.[13,14,24] This improved topical/systemic activity ratio[25] is of particular benefit in children, who have a high ratio of body surface to body weight.[26] In an earlier report, Goodyear *et al.*[9] reported that 09·00 h cortisol levels were uniformly low in all of 30 children after 2–5 days of wet-wrap treatment with dilutions of betamethasone valerate 0·01% cream. The difference may be explained partly by their use of twice daily application and also due to the use of a different corticosteroid. A recent review on the efficacy of once daily vs. twice daily applications of corticosteroids reported no evidence to support an advantage of multiple daily applications.[27]

No data are yet available on the efficacy and safety of long-term treatment with wet wrap. We are currently investigating the wet wrap for the long-term treatment of AD. Goodyear *et al.*[9] reported that long-term treatment with wet wraps in five patients at home was unsuccessful because of time-consuming application, decreasing effectiveness, infection and HPA axis suppression. The mode of action of the wet-wrap method is probably a combination of protection of the skin from scratching, cooling of the skin (thereby reducing itching and inflammation), and enhanced penetration of emollients and corticosteroids. Therefore, it is important to establish protocols that are safe and to be aware of the possibility of HPA axis suppression.

The present study is limited by the small sample size and differing measures of HPA axis suppression, and cannot claim to have proved FP under wet wraps to be

safe, because susceptibility for HPA axis suppression is highly variable. However, this treatment was highly effective in severe and refractory AD. Furthermore, these preliminary data suggest that a 5% dilution of the corticosteroid seems to have comparable efficacy, but lower systemic bioactivity, than 10% or 25% dilutions under wet wrap, and that 1 week of treatment is sufficient to achieve major improvement. Further study in a larger number of children will be necessary to establish the efficacy and the safety of weaker corticosteroid dilutions under wet-wrap dressings for long-term treatment, as the practicality and benefits of such long-term treatment are questionable.

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