Emollient efficacy and acceptability in the treatment of eczematous dry skin: A double-blind, randomised comparison of two UK-marketed products

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Abstract

Objective: The aim of this study was to compare the moisturising efficacy and acceptability of physical characteristics of two commonly prescribed emollients licenced in the UK, Doublebase Dayleve gel (DELP) and Diprobase cream (DIPC). Methods: The study was a double-blind, concurrent bi-lateral comparison in female eczema subjects with dry skin. Results: In Part 1, comparing the area under the curve (AUC) change from baseline corneometer readings over 24 h following single applications of the emollients to the volar forearms of 34 subjects, the AUC for DELP was more than three times that seen for DIPC (p < 0.0001). In Part 2, comparing the same outcome measured over 5 days of twice daily applications to the lower legs in 36 subjects, the AUC for DELP was approximately five times that for DIPC (p < 0.0001). 69% of subjects “Like Slightly” or “Like Strongly” DELP compared to 33% for DIPC (p = 0.025). 72% indicated they would use DELP again compared to 33% for DIPC (p = 0.033). 75% of subjects preferred DELP. 17% preferred DIPC and 8% expressed no preference (p = 0.0004).

Introduction

Emollient therapy is the mainstay for treating dry skin conditions including atopic eczema (AE), psoriasis and elderly pruritus (1–3). Emollients work chiefly by maintaining increased skin water content, particularly in the outermost stratum corneum layer.

Prescribers recommend emollient products based primarily on patient preference because treatment concordance depends on patient satisfaction with the product’s physical characteristics. The comparative effectiveness of different emollient products tends to be overlooked because there are few published studies performed under conditions mimicking normal clinical use, and even fewer comparative studies (1,3–6). National Institute for Health and Clinical Excellence has called for more research in this area.

The aim of this study was to compare two commonly UK prescribed licenced emollients, Doublebase Dayleve gel (DELP) and Diprobase cream (DIPC). Their skin moisturising effects are compared using corneometry, a well-established, non-invasive method for accurate determination of skin hydration by measuring changes in electrical capacitance of the stratum corneum (7–10). Physical acceptability is compared by patients’ subjective assessments.

Materials and methods

The study design was a double-blind, randomised, bilateral, concurrent comparisons of DELP gel (Dermal Laboratories Ltd, Hitchin, UK) and DIPC cream (Merck Sharp & Dohme, Hoddesdon, UK) applied to areas of dry skin (without significant flare) on the forearms (Part 1) and the lower legs (Part 2) of eczema sufferers, all between 18 and 65 years of age. Dry skin was defined, for study purposes, as having baseline corneometer readings of less than 45 units, and to be eligible for participation differed by no more than 6 units between the left and right arms/legs. Because excessive hair interferes with corneometry measurements, participation was restricted to females only. Eligible subjects also committed to following a sedentary lifestyle for the duration of their involvement (in order to avoid more frequent washing/bathing than permitted). The two parts of the study were performed approximately a week apart using essentially the same panel of subjects. The study was conducted with full ethics (Reading Independent Ethics Committee, Reading, UK) and regulatory approvals, in compliance with the principles of the Declaration of Helsinki and in accordance with Good Clinical Practice. Written informed consents were obtained from all subjects.

Exclusion criteria were: significant concurrent illness or skin disease currently involving the test sites; history of allergy relevant to the test products or their ingredients; use of any topical or systemic treatment likely to affect skin response; use of oral and topical steroids for any condition within the previous 4 weeks; visible skin abnormality or excessive hair growth likely to interfere with instrumental measurements; irritation, tattoos, scars or birthmarks at the test measurement sites; participation in any other study presently or within the past 3 months; breastfeeding.
and pregnancy. Also, removal of leg hair was not allowed within 48 h prior to, or during participation in Part 2. Employees of either Dermal Laboratories or RSSL Pharma, or their immediate family members, were not allowed to participate.

Commencing 1 week prior to participation, and continuing for the duration of the study, eligible subjects were asked to use only the supplied Simple® soap for washing and were asked not to apply moisturising products to their arms or legs, or to use depilatory products or shave these areas.

### Part 1 – skin hydration following single application

This part of the study compared skin hydration over a 24-h period following single applications of DELP and DIPC emollients. Thirty-four subjects took part in two cohorts.

Two test sites, each measuring 20 cm², were demarcated on both volar (inside) aspects of subjects’ forearms, adjacent to the wrist and flexure, and baseline measurements of skin hydration were performed in triplicate at about 9 am using the Multiprobe Adapter MPA5 with Corneometer CM825 probe (Hydration) (Courage-Khazaka electronic, Germany).

The two test products are white semi-solids, essentially indistinguishable from one another in appearance and texture, and in this part of the study were presented, for blinding purposes, in pre-filled 1 ml syringes. Directly from the syringe, 0.05 ml of each (resulting in 2.5 µl of product being applied per cm²) were performed adjusting for the AUC of the untreated controls, but for Part 2. 

Sensitivity analysis for the primary efficacy variable was undertaken.

Results

Forty-six women were screened. 5 failed screening and 3 were unable to attend the required visits, so 38 were randomised to take part and commenced washout. Two of these failed baseline screening in Part 1, leaving 36 to take part. 34 of these participated in both Parts 1 and 2, and two participated in Part 2 only.

Fourteen subjects used concomitant medication such as contraceptive hormone treatments, anti-depressants, pain relief tablets and asthma inhalers, none of which were considered to interfere with the study outcome. One patient used Aqueous cream on skin other than the study areas.
Three adverse events in three subjects were considered as being possibly related to treatment. They involved minor local skin warmth, rash or tingling reactions to both treatments.

**Part 1 – skin hydration following single applications**

Significant differences were observed between the two cohorts (comprising 19 and 15 subjects), probably owing to differing environmental conditions over their respective treatment days.

For Part 1, the primary efficacy parameter was the AUC change from baseline corneometer readings over 24 h. Following single applications, cumulative increases were statistically significantly greater for patients’ arms treated with DELP compared to arms treated with DIPC (Table 1). This was true for both cohorts. Overall the estimated treatment difference, DELP minus DIPC, was an increased AUC of 306 units (95% CI: 273–338, \( p \approx 0.0001 \)), which represents an increase in skin hydration with DELP of at least three times that seen for DIPC. There was no significant difference between the skin hydration of the untreated area of the DELP arms and the untreated area of the DIPC arms (\( p = 0.75 \)).

Since the AUC was measured over a 24-h period, dividing the treatment difference AUC by 24 gives a value which approximates to a “mean corneometer reading”, and corresponds to an estimated treatment difference for DELP over DIPC of more than 12 units (12.2 for the first cohort and 13.7 for the second cohort).

The difference in mean corneometer readings between the DELP and DIPC arms were shown versus time for the treated and untreated sites (Figure 1), indicating the long-lasting nature of the moisturisation benefit of DELP over DIPC.

The cumulative increase in change from baseline corneometry readings with DIPC were very modest by comparison, and were statistically significant from zero for the second cohort only (Table 1).

**Part 2 – assessment of cumulative skin hydration and product acceptability**

No significant differences were observed between the two cohorts (comprising 21 and 15 subjects). Adherence with the twice daily treatment regimen (as recorded in subjects’ treatment diaries) was good, with only two reported missed applications. There were no significant differences between the amounts of products used on left versus right legs or between products. Subjects typically used between 11 and 22 g of each product (corresponding to 1.2 or 2.5 g per application). Approximately three quarters of the subjects recorded that they bathed their lower legs or showered on both permitted occasions during the evenings of days 2 and 4.

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**Table 1. Part 1 – 24 h AUC change from baseline corneometer reading.**

|                | DELP (n = 34 for both cohorts) | DIPC (n = 34 for both cohorts) | Treatment difference DELP minus DIPC |
|----------------|--------------------------------|--------------------------------|-----------------------------------|
| Adjusted mean  | 382.1                          | 76.4                           | 305.7                             |
| For 1st cohort (n = 19) | 329.2                          | 37.1                           | 292.1                             |
| For 2nd cohort (n = 15) | 442.0                          | 112.4                          | 329.5                             |
| 95% confidence interval (CI) for adjusted mean | 350 to 414                     | 44 to 109                      | 273 to 338                        |
| For 1st cohort (n = 19) | 280 to 379                     | 12 to 87                       | 243 to 341                        |
| For 2nd cohort (n = 15) | 396 to 488                     | 67 to 158                      | 285 to 375                        |
| \( p \) Values for testing whether effect = 0 | <0.0001                        | <0.0001                        | <0.0001                           |
| For 1st cohort (n = 19) | <0.0001                        | 0.13                           | <0.0001                           |
| For 2nd cohort (n = 15) | <0.0001                        | <0.0001                        | <0.0001                           |
| \( p \) Values for effect of cohort | N/A                            | N/A                            | 0.0026                            |
| \( p \) Values for effect of arm (R/L) | N/A                            | N/A                            | 0.0075                            |
| \( p \) Values for effect of allocation | N/A                            | N/A                            | 0.078                            |

**Figure 1. Part 1 – mean corneometer readings for the treatment difference (DELP arm minus DIPC arm) vs. untreated arm by cohort.**

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For Part 2 the primary efficacy parameter was the AUC change from baseline corneometer readings over the 5-day treatment period (104 h from 09.00 on day 1 to 17.00 on day 5). There were only two missed follow-up appointments (involving different subjects). These missing values were linearly interpolated. Both products significantly improved skin hydration from baseline (Table 2). However, DELP performed statistically significantly better than DIPC such that the cumulative increase in skin hydration over the 5 days was estimated to be an increased AUC of 1399 units which represents an increase in skin hydration of approximately five times that seen for DIPC (95% CI: 1180–1618, \( p < 0.0001 \)). This conclusion is from an intention to treat analysis of all 36 subjects randomised in Part 2.

The improved skin hydration of DELP over DIPC was seen at every time point over the 5-day period. The mean corneometer readings are shown in Figure 2. The long-lasting and cumulative benefit of DELP over DIPC is particularly illustrated by the morning readings each day (which were typically 12 h after the latest application of the products the day before) which were significantly greater than the baseline reading (day 1, 9 am) and increased step-wise from day 2 to day 5 – even following the washing/bathing permitted during the evenings of days 2 and 4.

### Willingness to use the products again

One-third of the subjects answered that they would use DIPC again compared to 72% for DELP (Table 4). This difference was statistically significant (Prescott’s test \( p = 0.033 \)).

### Product preference

Three quarters (75%) of subjects preferred DELP, whilst 17% preferred DIPC and the remaining 8% of subjects had no preference (Table 5). This difference was highly statistically significant (Prescott’s test \( p = 0.0004 \)).

### Ten product attributes

Subjects were asked to indicate their level of agreement (from five categories: ‘‘Disagree Strongly’’, ‘‘Disagree Slightly’’, ‘‘Neither agree nor disagree’’, ‘‘Agree Slightly’’ or ‘‘Agree Strongly’’) with each of the 10 statements relating to product attributes, for each leg (Table 6). The percentage of subjects ticking one of the top two categories (‘‘Agree Slightly’’ and ‘‘Agree Strongly’’) was higher for DELP than for DIPC for all of the 10 attributes studied.

### Discussion

AE is a chronic, inflammatory disease affecting children and adults and is associated with abnormalities in skin barrier function (11). Prevailing expert medical advice is that AE patients should apply their emollients generously and frequently in order to maintain the hydration of the stratum corneum, thereby keeping the corneocytes ‘‘plumped up’’, closing cracks and restoring the natural barrier function of the skin (12). Although patients are normally recommended to re-apply their emollient several times...
Table 3. Acceptability of DELP and DIPC.

| Overall product acceptability of… | No. of subjects\(^a\) selecting Like Slightly or Like Strongly | % of subjects\(^a\) selecting Like Slightly or Like Strongly |
|----------------------------------|---------------------------------------------------------------|----------------------------------------------------------|
| DELP                             | 25                                                            | 69%                                                      |
| DIPC                             | 12                                                            | 33%                                                      |
| \(p\) Values for DELP vs. DIPC\(^b\) | \(p = 0.025\)                                                |                                                          |

\(^a\)From total of 36 subjects who were randomised.  
\(^b\)Using Prescott’s test taking into account effect of leg.

Table 4. Willingness to use DELP and DIPC again.

| Willingness to use the product again… | No. of subjects\(^a\) selecting | % of subjects\(^a\) selecting |
|--------------------------------------|----------------------------------|-------------------------------|
| DELP                                 | Yes                              | 26                            | 72%                           |
| DIPC                                 | 12                               | 33%                           |
| \(p\) Values for DELP vs. DIPC\(^b\) | \(p = 0.033\)                    |                               |

\(^a\)From total of 36 subjects who were randomised.  
\(^b\)Using Prescott’s test to take into account effect of leg.

Table 5. Preferred treatment option.

| Preferred leg with… | No. of subjects\(^a\) | % of subjects\(^a\) |
|---------------------|------------------------|---------------------|
| DELP                | 27                     | 75%                 |
| DIPC                | 6                      | 17%                 |
| No preference\(^b\) | 3                      | 8%                  |
| \(p\) Values for DELP vs. DIPC\(^c\) | \(p = 0.0004\)        |                     |

\(^a\)From total of 36 subjects who were randomised.  
\(^b\)Includes one subject who did not answer despite answering the rest of the questionnaire.  
\(^c\)Using Prescott’s test of preference.

Table 6. Percentage of subjects ticking “Agree Slightly” or “Agree Strongly” for 10 product attributes.

| Product attribute | Number and % of subjects\(^a\) ticking “Agree Slightly” or “Agree Strongly” |
|-------------------|---------------------------------------------------------------|
| The test product… | DELP | DIPC |
| … made my skin feel softer | 34 | 25 | 69% |
| … made my skin feel smoother | 34 | 23 | 64% |
| … made my skin feel moisturised | 33 | 24 | 67% |
| … was easy to apply | 32 | 12 | 33% |
| … was easily absorbed into the skin | 30 | 7 | 19% |
| … was acceptable cosmetically | 28 | 15 | 42% |
| … had a pleasant consistency | 27 | 11 | 31% |
| … had an acceptable smell | 26 | 15 | 42% |
| … was soothing | 24 | 20 | 56% |
| … reduced the itching on my leg (if applicable) | 16 | 11 | 37% |

\(^a\)\(n\) and % = number and percentage of subjects who ticked this response, from total of 36 subjects randomised.  
\(^b\)For this attribute, denominator for percentages exclude subjects who ticked “not applicable”.

daily in order to achieve the best therapeutic effect, this is not always possible while they are going about their daily routine, and in practice many, particularly patients who attend school or go to work, only manage to apply one or two applications per day – once in the morning before dressing, and again in the evening before retiring to bed. The dosage regimen used in Part 2 of study was therefore chosen to enable comparison of the two products when used under conditions more relevant to real life situations. The treatment period of 5 days was considered long enough to establish any differences between the two products in cumulative skin hydration whilst maintaining patients’ cooperation.

In this study, DELP gel exhibited statistically significantly greater and longer-lasting cumulative skin hydration in subjects with dry skin than the comparator DIPC cream. Although a single application of each product was shown to significantly improve skin hydration over a 24-h period (for one cohort only, in the case of DIPC), the statistically significant increase in skin hydration for DELP was more than three times that seen for DIPC. When applied twice daily over a period of 5 days, the statistically significant cumulative increase in skin hydration for DELP was approximately five times that seen for DIPC.

These significant performance differences are unlikely to be solely attributed to the slightly higher oil content of DELP compared to DIPC, 30% vs. 21% (Table 7). Other ingredients and the manner in which the products are formulated are also likely contributing factors. For example, an earlier study has indicated that an emollient gel achieved better skin moisturisation than an emollient cream (13). This may be partly explained by their differing substantivities on the skin. In the case of cream formulations, such as DIPC tested in this study, the high oil content is achievable by emulsifying the lipids into the aqueous phase by the addition of standard surfactants. This produces a stable emulsion which can be easily spread to deposit the oils over the skin surface. However, with the subsequent addition of water (e.g. during washing) the residual surfactant serves to effectively remove the oils from the skin. For the emollient gels such as DELP, on the other hand, the oils are emulsified by the incorporation of a polymer carbopol (14,15). The emulsifying properties of this polymer system are destroyed by electrolytes (16), and so the salts present on the surface of the skin cause irreversible separation of the oil and water phases of the gel during application. The oils are then left to form an occlusive barrier over the skin which subsequently is much less readily re-emulsified and dispersed from the skin during washing. Another point of difference is that emollient gels also tend to contain high levels of glycerol, which is a humectant and has the ability to bind and retain water within the entire thickness of the stratum corneum (17–19). In the case of the particular emollient gel tested here, DELP, the formulation also contains a film-former, povi-

Table 7. Doublebase Dayleve gel and Diprobase cream composition.

| Doublebase Dayleve gel (% w/w) | Diprobase cream (% w/w) |
|--------------------------------|-------------------------|
| Isopropyl myristate 15% | White soft paraffin 15% |
| Liquid paraffin 15% | Liquid paraffin 6% |
| Glycerol | Macrogol cetostearyl ether |
| Povidone | Chlorocresol |
| Carborner | Cetostearyl alcohol |
| Sorbitan laureate | Phosphoric acid |
| Triethanolamine | Sodium dihydrogen phosphate |
| Phenoxyethanol | Sodium hydroxide |
| Purified water | Purified water |

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The cosmetic acceptability of emollients is very important because patients are unlikely to use formulations with poor cosmetic appeal, resulting in no clinical benefit (11). In this blinded study, the physical characteristics of DELP were rated statistically significantly more favourably than DIPC for all three parameters analysed (likeability, willingness to use again and preference), and were generally superior for the 10 additional attributes listed. These results are consistent with an earlier study showing a strong preference for an emollient gel in comparison with emollient creams and ointments (22).

Although corneometry is an exceedingly well-established measure of skin hydration, a possible limitation of this study is that the measurements may be regarded as a surrogate clinical end point. It may therefore be helpful if future studies compared the effectiveness of different emollients using therapeutic end points. Although the study population was entirely adult females, the results may be reliably extrapolated to all age groups and both sexes because the products work by physical action only.

Conclusion

Although emollients are widely prescribed in the UK, it is not always possible to apply them frequently, and many patients only manage twice daily applications. In this study comparing two commonly prescribed licenced emollients, we have measured highly statistically significant differences in the degree and duration of skin hydration, and patients have reported substantial differences between their physical acceptability. These results confirm that not all emollients are the same (19) and this is something that healthcare professionals should be aware of when prescribing these products.

Declaration of interest

This study was sponsored by Dermal Laboratories Ltd, Hitchin, UK and carried out by RSSL, Reading, UK.

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