Development of new treatment modalities for atopic dermatitis
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Chapter 10

Randomised comparison of the type 4 phosphodiesterase inhibitor cipamfylline cream, cream vehicle and hydrocortisone 17-butyrate cream in atopic dermatitis

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Chapter 10

SUMMARY

Background: Therapeutic options to treat atopic dermatitis are limited. Leukocytes from atopic patients have an abnormally high activity of cyclic AMP phosphodiesterase (PDE), which can be normalised in vitro by PDE inhibitors. Cipamfylline is a new potent and selective inhibitor of PDE 4.

Objectives: To compare the efficacy and safety of up to 14 days topical treatment with cipamfylline (0.15%) cream with vehicle and with hydrocortisone 17-butyrate (0.1%) cream.

Patients/methods: International, multicentre, prospective, randomised double-blind, left-right studies of cipamfylline vs vehicle and cipamfylline vs hydrocortisone 17-butyrate in adult patients with stable symmetrical atopic dermatitis on the arms.

Results: Both cipamfylline and hydrocortisone 17-butyrate reduced the Total Severity Score significantly (p<0.001). The reduction with cipamfylline was significantly greater than that with vehicle (difference vehicle-cipamfylline 1.67 95% CI 1.06, 2.28; p<0.001) and was significantly less than with hydrocortisone 17-butyrate (difference hydrocortisone-cipamfylline -2.10 95% CI -2.93, -1.27; p<0.001). Investigator and patient assessments of the overall treatment response showed a similar picture

Conclusions: Cipamfylline cream, is significantly more effective than vehicle, but significantly less effective than hydrocortisone 17-butyrate cream in the treatment of atopic dermatitis.
INTRODUCTION

Atopic dermatitis is a chronically relapsing, pruritic inflammatory skin disease with a characteristic cutaneous morphology and distribution in genetically predisposed individuals. It is an extremely common disease affecting about 10% of infants (1-3), and represents a considerable health care burden (4). There has been an increase in prevalence of atopic dermatitis in recent years (3, 5), but the reasons for this are unclear.

Therapeutic agents for atopic dermatitis are limited and inadequate. Glucocorticoids are used almost exclusively, but their use in a chronic and relapsing condition is unsatisfactory due to potential toxicity, particularly in small children (6).

The pathogenesis of atopic dermatitis is unknown, but there appears to be a genetic predisposition (7). Recent studies have indicated a fundamental defect in leukocytes from patients with atopic dermatitis (8). Atopic leukocytes have an abnormally high activity of cyclic AMP phosphodiesterase (PDE) activity (9-12). The increased PDE activity and associated abnormal immunological states can be normalised by PDE inhibitors in vitro (10, 13).

Cipamfylline is a novel xanthine, a theophylline analogue and is a potent and selective inhibitor of phosphodiesterase type 4 (PDE 4). It has a similar activity profile and potency to CP 80, 633 which is the only PDE 4 inhibitor known to be clinically effective in atopic dermatitis (14). To facilitate topical, local application cipamfylline has been formulated in a cream. We report a double-blind, randomised 'proof of concept' study in atopic dermatitis assessing the efficacy and safety of cipamfylline cream relative to its cream vehicle and to a control treatment with the moderately potent corticosteroid hydrocortisone 17-butyrate cream (WHO class group II).

MATERIALS AND METHODS

The study was multinational and multicentre and included males and females, aged 18 years and over, with a diagnosis of atopic dermatitis, according to the criteria proposed by Hanifin and Rajka (15). Patients had stable, symmetrical lesions on both arms, with a minimum total severity score of 6 for a selected target lesion. Females of child-bearing potential had a negative urine pregnancy test and used adequate contraception throughout the study.

Exclusion criteria were suspected microbial, fungal or viral superinfection, scarring or hyperpigmentation within the target lesions, treatment with systemic antihistamines, antibacterials or topical therapies other than emollients in the previous week, suspected hypersensitivity to the components of the study
medication, unstable/uncontrollable medical disorders, inability to comply with the study protocol, treatment with an investigational drug in the previous 3 months, current participation in any clinical trial or previous participation in the current study or expected exposure to excessive amounts of sun or ultraviolet light during the study. Pregnancy, breast feeding or desire to become pregnant were also exclusion criteria.

Patients were randomly assigned to one of two treatment groups, cipamfylline/vehicle or cipamfylline/hydrocortisone. Within each treatment group, patients were allocated to double-blind, left-right treatment at random according to computer generated random numbers tables and basis. The randomisation code was available to the investigator to be opened only in an emergency and was also held by the Quality Assurance Manager at Leo Pharmaceutical Products.

Treatment
Cipamfylline cream contained 1.5 mg/g cipamfylline. Hydrocortisone-17-butyrate cream contained 0.1% hydrocortisone-17-butyrate (Locoid; Yamanouchi Pharma) and vehicle cream was the vehicle of cipamfylline cream. The creams, which were indistinguishable by sensory evaluation, were provided in identical tubes and labelled without giving any indication of content. All treatments were applied twice daily with a maximum application of 2 g of each per day, equivalent to 4 finger-tip units (FTUS)(16). The treatment area was defined as from the wrist skin crease to the shoulder.

Patients were instructed to wash their hands thoroughly after applying the first cream before applying the second cream to the other arm for up to 14 days. No other topical treatment was allowed on the arms. Topical treatment for lesions elsewhere on the body comprised hydrocortisone 0.1% (Yamanouchi Pharma) and/or an emollient (Locobase; Yamanouchi Pharma).

Assessments Patients were seen on entry, after a wash-out period of 7 days when treatment commenced and after 3, 7, and 14 days of treatment. Patients who required only an emollient on the arms on completion of randomised treatment were followed up 7 days later.

Demographic data were recorded at the first visit. Symmetrical target lesions, one on each arm, were selected and documented. On commencement of treatment and at all subsequent visits (including follow-up) the following assessments were made by the investigator on the target lesion(s); severity of erythema, oedema/papulation, oozing/crusting, excoriations, lichenification, assessed and graded on a four point scale (0=absent, 1=mild, 2=moderate, 3=severe) from which a Total Severity Score was calculated; overall response to treatment since commencement of treatment on day 3, 7, and 14 and recorded as 'worse', 'no change', 'minimal improvement', 'moderate improvement', 'marked
improvement' or 'completely cleared'. Patients similarly assessed the overall response to treatment for the target lesions and the cosmetic acceptability of treatment recorded as 'unacceptable', 'acceptable', 'good' or 'very good'. Patients assessed the severity of pruritus associated with target lesions during the previous 24 hours, on a 10 cm visual analogue scale, ranging from "no itching" (score 0) to "worst possible itching" (score 10.0).

Patients were questioned regarding compliance with treatment and treatment tubes collected for weighing to determine the amount of medication used. Serum levels of cipamfylline Blood samples were taken on commencing treatment and after 3, 7 and 14 days of treatment for routine haematology (haemoglobin, leukocytes and differential, erythrocytes, platelets) and blood chemistry (bilirubin, alkaline phosphatase, aspartate aminotransferase, creatinine, sodium, potassium), and were analysed at central laboratories, LDS Diagnostic Laboratories, Montreal, Canada and CRL Medinet, The Netherlands. Serum concentrations of cipamfylline were determined in random blood samples taken on commencing treatment and at all subsequent visits, including follow-up, by HPLC assay consisting of solid phase extraction and reverse phase HPLC with UV detection at Leo Pharmaceutical Products, Denmark. The lower limit of quantification was 2 ng/ml.

Adverse events were recorded at each on-treatment visit.

Sample size
The sample size of 40 patients in each left-right treatment group was based on the ability to detect a difference between treatments of 2.5 in the absolute change from baseline to end-of treatment in the Total Severity Score, with a power of 80% using a two-tailed paired t-test and an a of 0.05.

Analyses of efficacy and safety
Criteria for efficacy and safety were specified in the study protocol and the statistical analysis plan finalised after blind review of the actual outcome data, but before the study was unblinded. The Primary Response Criterion was the absolute change in Total Severity Score from baseline to end of treatment (defined as the last on-treatment visit). Changes in individual signs, distribution of the overall response to treatment, changes in the assessment of pruritus, acceptability of treatment and the proportion of patients relapsing (defined as the requirement for treatment of atopic dermatitis on the target lesions) during follow-up were secondary response criteria. All randomised patients who received any trial medication and who contributed any efficacy data comprised the Intention-To-Treat (ITT) population on which all efficacy analyses were performed. A Per Protocol Population was analysed in respect of the Primary
Response Criterion only. The safety population comprised all patients given randomised treatment and who attended at least one further visit.

Statistics
Changes in scores within treatments and between treatments were compared using the paired t-test. Paired assessments of the overall treatment responses were compared using Wilcoxon signed rank sum test. Percentages of patients experiencing treatment specific adverse events, defined as cutaneous adverse events in the randomised treatment area, and relapses during the following period were compared between treatments by McNemar's test, with exact P-values as implemented in StatXact17. All comparisons were two tailed and p<0.05 was considered significant. 95% confidence intervals of differences were determined.

Ethics
The study was approved by National Regulatory Authorities and by the relevant Institutional Review Boards. All patients gave signed informed consent. The study protocol and the conduct of the trial were designed to comply with the guidelines produced by the International Conference in Harmonisation on Good Clinical Practice and published by the European Agency for the Evaluation of Medicinal Products as "Notes for Guidance on GCP" CCPMP/ICH/135/95 approved 17 July 1996.

RESULTS
A total of 108 patients was recruited at 14 centres in Canada, Denmark, The Netherlands and the United Kingdom. The profile of randomised patients in the study is shown in Table 1 and Figure 1. For randomised patients, the two treatment groups were comparable as were the scores for the target lesions and the score for pruritus in respect of treatment allocated. Characteristics of randomised patients were consistent across countries. Two patients failed to attend for further visits and another patient withdrew voluntarily without providing any efficacy data. The safety population, therefore comprised 101 patients (52 in the cipamfylline/vehicle group and 49 in the cipamfylline/hydrocortisone 17-butyrate group). The Intention- To- Treat population comprised 100 patients (52 in the cipamfylline/vehicle group and 48
### Table 1: Demographics of Randomised Patients

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>cipamfylline/vehicle</th>
<th>cipamfylline/hydrocortisone-17-butyrate</th>
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</thead>
<tbody>
<tr>
<td>cipamfylline</td>
<td>vehicle</td>
<td></td>
</tr>
<tr>
<td>Males/Females</td>
<td>25/29</td>
<td>17/32</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>33.1 (18-61)</td>
<td>32.9 (18-64)</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>72.6 (45-110)</td>
<td>75.7 (42-125)</td>
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<table>
<thead>
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<th>Target Lesion Scores (Mean ±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
</tr>
<tr>
<td>2.06 (0.49)</td>
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<tr>
<td>2.06 (0.53)</td>
</tr>
<tr>
<td>2.16 (0.43)</td>
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<tr>
<td>2.02 (0.38)</td>
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<tr>
<td>Oedema/papulation</td>
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<tr>
<td>1.89 (0.46)</td>
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<tr>
<td>1.89 (0.50)</td>
</tr>
<tr>
<td>1.86 (0.53)</td>
</tr>
<tr>
<td>1.90 (0.59)</td>
</tr>
<tr>
<td>Oozing/crusting</td>
</tr>
<tr>
<td>0.63 (0.81)</td>
</tr>
<tr>
<td>0.54 (0.72)</td>
</tr>
<tr>
<td>0.73 (0.73)</td>
</tr>
<tr>
<td>0.71 (0.74)</td>
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<tr>
<td>Excoriation</td>
</tr>
<tr>
<td>1.39 (0.76)</td>
</tr>
<tr>
<td>1.37 (0.81)</td>
</tr>
<tr>
<td>1.29 (0.74)</td>
</tr>
<tr>
<td>1.33 (0.66)</td>
</tr>
<tr>
<td>Lichenification</td>
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<td>1.80 (0.71)</td>
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<tr>
<td>1.70 (0.77)</td>
</tr>
<tr>
<td>1.65 (0.69)</td>
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<tr>
<td>1.67 (0.69)</td>
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<tr>
<td>Pruritus Score</td>
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<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td>5.48 (2.58)</td>
</tr>
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<td>5.21 (2.54)</td>
</tr>
<tr>
<td>5.17 (2.68)</td>
</tr>
<tr>
<td>5.33 (2.74)</td>
</tr>
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</table>
in the cipamfylline/hydrocortisone 17-butyrate group). There were protocol deviations involving 3 patients. These were asymmetrical Total Severity Scores in one patient, recent use of disallowed medication, Evening Primrose oil, in another patient and disallowed topical medication throughout the study in a further patient. These patients were excluded from the Per Protocol Population (comprising 50 patients in the cipamfylline/vehicle group and 47 patients in the cipamfylline/hydrocortisone group). Eighty-four patients, (44 in the cipamfylline/vehicle group and 40 in the cipamfylline/hydrocortisone 17-butyrate group) attended the post-treatment follow-up.

Efficacy data applicable to specific visits, days 7 and 14 for 1 patient who used disallowed topical medication and day 14 data for a further 6 patients who used disallowed systemic medication during randomised treatment, i.e. antihistamines (3), used disallowed topical medication during randomised treatment, i.e. steroids/emollients (2), and where the day 14 visit was performed late two weeks after completing randomised treatment (1) were
Figure 2: Total Severity Score of atopic dermatitis, during two weeks treatment with cipamfylline cream and hydrocortisone 17-butyrate (above) and cipamfylline and vehicle (down).
Figure 3: Overall assessment of response of atopic dermatitis to treatment with cipamfylline cream, cream vehicle and hydrocortisone 17-butyrate by investigators (above) and by patients (down).
excluded from the analyses.

**Response to randomised treatment**

The Total Severity Score during the study is shown in Figure 2. There was a statistically significant reduction in the Total Severity Score from baseline to the end of treatment with all three "treatments" (p<0.002). In the cipamfylline/vehicle group, the difference between treatments was statistically significant and in favour of cipamfylline (difference vehicle-cipamfylline; 1.67, 95% CI 1.06, 2.28; p<0.001). In the cipamfylline/hydrocortisone-17-butyrate group, the difference between treatments was statistically significant and in favour of hydrocortisone 17-butyrate (hydrocortisone-cipamfylline; -2.10, 95% CI -2.93, -1.27; p<0.001). The results based on the Per Protocol Population were very similar to those for the Intention-to-Treat population.

Comparison of the difference between treatments in the change from baseline to end-of-treatment for the individual severity score showed a similar picture to that seen with the Total Severity Score (cipamfylline/vehicle group; statistically significant difference in favour of cipamfylline; erythema p=0.002; excoriation p=0.005; lichenification p=0.001; oedema/papulation p<0.001 and oozing/crusting p<0.001; cipamfylline/hydrocortisone 17-butyrate group; statistically significant difference in favour of hydrocortisone 17-butyrate; erythema p=0.007; oozing/crusting p=0.005; oedema/papulation p<0.001; excoriation p<0.001 and lichenification p=0.001).

Assessments by investigator and patient of the overall treatment response at the end of treatment are shown in Figure 3. The response to cipamfylline was a statistically significantly better in the cipamfylline/vehicle group (investigator p=0.003, patient p=0.008). In cipamfylline/hydrocortisone 17-butyrate group, the response was statistically significantly better with hydrocortisone 17-butyrate (investigator p<0.001, patient p<0.001).

The mean score for pruritus, as assessed by the patient, is shown in Figure 4. At the end of treatment, pruritus was statistically significantly improved in favour of cipamfylline in the cipamfylline/vehicle group (p<0.001) and in favour of hydrocortisone 17-butyrate in the cipamfylline/hydrocortisone 17-butyrate group (p<0.001).

Overall, patients found the treatments to be cosmetically acceptable in 96% of assessments (186/194). There was no statistically significant difference in patients' assessment of the cosmetic acceptability of the cipamfylline and vehicle creams. However, the hydrocortisone 17-butyrate cream was considered statistically significantly more acceptable than the cipamfylline cream by patients (p<0.001).
Figure 4: Pruritus Score for atopic dermatitis, during two weeks treatment with cipamfylline cream and cream vehicle (above) and treatment with cipamfylline cream and hydrocortisone 17-butyrate (down).
Compliance with randomised treatment
Compliance with the treatments was good, 39 out of 52 patients in the cipamfylline/vehicle group and 40 out of 48 patients in cipamfylline/hydrocortisone 17-butyrate group complying fully with the trial medication. The amount of medication used, which was determined for 49 patients in the cipamfylline/vehicle group and for 44 patients in cipamfylline/hydrocortisone 17-butyrate group, was similar between treatment groups and between treatments. On average, the amount of study medication used during a week ranged from 8.2 g for the hydrocortisone 17-butyrate arm in the second week of treatment to 10.4 g for the cipamfylline arm in the first week of treatment in the same group.

Follow-Up after randomised treatment
The incidence of relapse was assessed in 44 patients in the cipamfylline/vehicle group and in 40 patients in the cipamfylline/hydrocortisone 17-butyrate group. In the cipamfylline/vehicle group, relapse was recorded on both treated sides for 21 patients, on the cipamfylline treated side only for 2 patients, and on the vehicle treated side only for 5 patients. No relapse was seen on either side for 16 patients. The difference in relapse rates for the two treatments, is not statistically significant. In the cipamfylline/hydrocortisone 17-butyrate group, relapse was recorded on both treated sides for 8 patients, on the cipamfylline treated side only for 9 patients and on the hydrocortisone 17-butyrate treated side only for 1 patient. No relapse was seen on either side for 22 patients. Relapse was statistically significantly more common on the cipamfylline treated side compared with the hydrocortisone 17-butyrate treated side (p=0.022).

Adverse events and laboratory monitoring
In the cipamfylline/vehicle group, 29 (55.8%) patients reported a total of 63 adverse events. In the cipamfylline/hydrocortisone 17-butyrate group, 20 (40.8%) patients reported a total of 41 adverse. Adverse drug reactions listed by System Organ Class are shown in Table 2. The application site disorders mainly comprised stinging/itching/burning on application. Skin and appendage disorders comprised mainly worsening of eczema in the cipamfylline/vehicle group and pruritus/prickly feeling in the cipamfylline/hydrocortisone group. All central and peripheral nervous system disorders involved headaches.

There was no statistically significant differences between treatments in the incidence of treatment specific adverse events (defined as cutaneous adverse events occurring on the randomised treatment areas considered by the investigator to be possibly or probably treatment related), in either treatment group (p=0.13 for both groups). Two patients ceased treatment due to unacceptable adverse events. One patient in the cipamfylline/vehicle group
stopped treatment after 5 days due to flare up of the eczema on the vehicle treated side and on areas outside the treatment areas. The other patient in the cipamfylline/hydrocortisone 17-butyrate group stopped treatment after 7 days due to flare up of eczema outside the treatment area.

Laboratory analysis indicated no unexpected or untoward effect on the haematology and blood chemistry parameters monitored.

**Serum concentrations of cipamfylline**

In the cipamfylline/vehicle group, 17 (32.7%) out of 52 patients had detectable levels of cipamfylline in serum samples on at least one occasion (11 on one occasion, 5 on 2 occasions and 1 on 3 occasions). After 3 days treatment 7 patients had values between 2.1 and 11.6 mg mL$^{-1}$, after 7 days 7 patients had between 2.1 and 5.7 mg mL$^{-1}$ and at 14 days 9 patients had between 2.3 and 6.3 mg mL$^{-1}$. Seven days after treatment one patient had 2.3 mg mL$^{-1}$ cipamfylline in serum (this patient had 5.7 mg mL$^{-1}$ and 3.5 mg mL$^{-1}$ after 7 and 14 days treatment respectively).

Three patients in the cipamfylline/hydrocortisone 17-butyrate group had measurable serum concentrations of cipamfylline prior to commencing treatment. One patient had measurable levels on only one occasion, another patient had levels at three visits (2.3-7.6 mg mL$^{-1}$) and a final patient had measurable levels at all visits (8.2-40 mg mL$^{-1}$ the highest concentration being detected in the post-treatment follow-up). These results could not be explained by any concomitant medication patients were taking. Among the remaining 46 patients, 15 (32.6%) had detectable levels of cipamfylline on at least one occasion (11 on one occasion, 3 on 2 occasions and 1 on 3 occasions). After 3 days treatment, 6 patients had values between 2.1 and 9.8 mg mL$^{-1}$, after 7 days 8 patients had values between 2.0 and 5.7 mg mL$^{-1}$ and after 14 days, 6 patient had values between 2.4 and 4.0 mg mL$^{-1}$. No cipamfylline was detected in samples taken seven days after treatment was completed.

No correlation between the change in the Total Severity Score from baseline to end of treatment and the maximum recorded serum concentration of cipamfylline was seen in either the cipamfylline/vehicle group ($r=0.03$) or the cipamfylline/hydrocortisone 17-butyrate group ($r=0.01$). No relationship between the cipamfylline serum concentrations and adverse events could be detected.
DISCUSSION

This study has demonstrated that cipamfylline, a new PDE4 inhibitor, is more effective than vehicle in treating atopic dermatitis, but is less effective than a group II steroid, hydrocortisone 17-butyrate.

Our study was a randomised, double-blind, parallel group study involving two arms in which cipamfylline was compared with vehicle and the corticosteroid, hydrocortisone 17-butyrate and was a proof of concept study. It was considered that efficacy in a proof of concept study had to be evident within two weeks. At the time the study was planned sufficient data on cipamfylline to allow treatment on the whole body were not available. Therefore a left/right design involving application to the arms only and limited to two weeks was chosen. With a left/right design there is always the possibility of the patient using treatment on the non-designated side either accidentally or intentionally. Patients complied well with the treatments and there was good agreement between treatments on the amounts of medication used. The establishment of the diagnosis of atopic dermatitis was based on recognised criteria15 and the number of patients to be recruited was exceeded. The study was also effectively blinded and all available data were included in the efficacy analyses. The primary response criterion was the reduction in the Total Severity Score for atopic dermatitis, which was a modification of the SCORAD system18-20 whereby dryness and the area of affected skin were not assessed. These modifications are appropriate as dryness is assessed on unaffected skin and we evaluated only target lesions. The results of the study can be interpreted with confidence.

This is the first study to examine the efficacy of cipamfylline in atopic dermatitis. Cipamfylline cream was significantly more effective than cream vehicle. Efficacy was established in respect of the reduction in the Total Severity Score, reduction in the severity score for its individual components and by the assessment of the overall clinical response by both the investigator and the patient. Cipamfylline cream also reduced the score for pruritus to a significantly greater degree than did vehicle. However it has to be accepted that assessing pruritus in a left/right study may be problematic. It cannot be excluded that pruritus emanating from one side of the body would not influence the perception of pruritus on the other. However cipamfylline treatment was significantly more effective than vehicle in reducing the score for excoriation. Excoriation is likely to be a consequence of pruritus, thereby indicating that cipamfylline probably did in fact reduce the severity of pruritus.

The only other PDE4 inhibitor shown to have clinical activity in atopic dermatitis is CP 80,63314. Treatment was also given double-blind, but for up to 28 days. A scoring system based on only three signs, erythema,
induration/papulation and excoriation was used. It is, therefore, difficult to compare the results with CP 80,633 with those we achieved with cipamfylline. However, the results from both studies confirm that PDE4 inhibitors have clinically significant anti-inflammatory activity in the treatment of atopic dermatitis. Although we found cipamfylline had clinical activity in treating atopic dermatitis it was significantly less than that achieved with a moderately potent group II steroid, hydrocortisone 17-butyrate. Superiority of hydrocortisone 17-butyrate was apparent with all response criteria.

Adverse events contributed to treatment withdrawal in only two patients. One patient in the cipamfylline/vehicle group stopped treatment after 5 days due to flare up of dermatitis on the vehicle treated side and on areas outside the treatment areas. The other patient in the cipamfylline/hydrocortisone 17-butyrate group stopped treatment after 7 days due to flare up of dermatitis outside the treatment area. It can be concluded that overall cipamfylline cream is well tolerated. There was also no evidence of any adverse effect of cipamfylline treatment on the indices of haematology and blood chemistry monitored.

There is evidence of limited absorption of cipamfylline when applied topically. Detectable serum concentrations were recorded in around 25 percent of patients. These observations must however be treated with some caution. The highest concentration detected - 40 mg mL⁻¹ - was recorded 7 days after treatment was completed in one of three patients in whom cipamfylline serum levels were detected prior to receiving treatment. Interference with the HPLC assay by other compounds present in serum appears possible and the specificity of the assay for cipamfylline needs further investigation.

Topical corticosteroids are the mainstay of active treatment of atopic dermatitis. Although effective there is concern about their long term use and use of the more potent steroids particularly in children. There could be a place for topical non-corticosteroids such as cipamfylline in the management of atopic dermatitis and further studies with this compound are warranted.
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Chapter 10


