BIOAVAILABILITY AND ACTIVITY OF 0.1% AMCINONIDE PREPARATIONS: COMPARISON WITH PROPRIETARY TOPICAL CORTICOSTEROID FORMULATIONS OF DIFFERING POTENCIES

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ABSTRACT

The activity of a 0.1% amcinonide cream was compared with those of selected proprietary topical corticosteroid formulations of potencies differing according to the United Kingdom (U.K.) MIMS classification (very potent, potent and moderately potent) using a standard six-hour vasoconstrictor assay with multiple reading times. Statistical analysis indicated that 0.1% amcinonide cream fell within the category of a very potent preparation. Three 0.1% amcinonide formulations (cream, combination cream and combination ointment, the last two containing anti-infective agents) were equipotent in the skin-blanching test.

INTRODUCTION

A new topical fluorinated corticosteroid preparation, 0.1% amcinonide cream, has been reported to be as potent as 0.12% betamethasone 17-valerate cream in a vasoconstrictor assay and as effective as 0.1% betamethasone 17-valerate cream in a double-blind study involving various inflammatory dermatoses. On the other hand, other vasoconstrictor trials have shown a 0.1% amcinonide cream to be markedly superior to betamethasone 17-valerate creams of these concentrations. Experiments were, therefore, carried out to compare a) the blanching activity of 0.1% amcinonide cream with those of selected U.K. proprietary topical corticosteroid preparations of differing potency, and b) the bioavailability and activity of three formulations, each containing 0.1% amcinonide.

Seven corticosteroid creams were selected for comparison from MIMS, which classifies topical steroid preparations as mildly potent, moderately potent, potent and very potent. Representatives of the last three categories were employed.

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MATERIALS AND METHODS

Topical Preparations

Ten corticosteroid preparations were employed. Seven were proprietary formulations available in the U.K. (Betnovate cream, Dermovate cream, Halciderm, Metosyn cream, Synalar cream, Temetex cream and Ultradil cream). The other three were experimental preparations containing 0.1% of the new topical steroid, amcinonide (amcinonide cream, amcinonide combination cream and amcinonide combination ointment). The corticosteroid compositions are given in Table 1. All products were stored at room temperature for two weeks and approximately 5 grams of each preparation were removed and rejected before use.

Subjects

Twelve volunteers were selected from an experienced panel as those demonstrating consistency of response to a standard preparation (Betnovate cream) but without reference to their sex or steroid sensitivity. None had received topical corticosteroid application for at least three months prior to the study. The results from ten of those subjects were selected for statistical analysis.

Method

In the study, 5 mg of the preparations were applied to the washed flexor surface of each forearm. The application sites consisted of 7 x 7 mm areas punched out from double-sided adhesive Blenderm tape, to which the formulations were applied using a random design. The sites were sealed with impervious Melinex film and left occluded for 6 hours. The Melinex and tape were removed and the areas were washed with soap and water at body temperature and were dried. Readings were taken in a double-blind manner after 10 minutes (to allow transient erythema arising from washing to subside) and after 1, 2, 3, 6, 18, 26, 42, 66, 74 and 90 hours to provide data points for skin blanching at 6, 7, 8, 9, 12, 24, 32, 48, 72, 80 and 96 hours after application.

Assessment was made according to a 0-4 scale with half-point ratings for intermediate readings:

0 = Normal skin
1 = Slight vasoconstriction of indistinct outline
2 = More intense vasoconstriction
3 = General even vasoconstriction with a clear outline of the square
4 = More marked vasoconstriction with very distinct blanching

Ten volunteers provided a total of 200 application sites.

In order to assess approximately the retention of steroid in the skin, the sites in two volunteers were re-occluded with Melinex film for 12 hours eight days after commencement of the experiment. Pallor was estimated 5 hours later when blanching was maximal.

RESULTS

For each preparation the data for all volunteers were converted to percent of the total possible score at each time period: i.e., if the maximum score per site = 4, then for 2 arms and 10 volunteers, the maxi-
Table I — Blanching responses to corticosteroid preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Steroid and % w/w</th>
<th>(^a) Summed % Total Possible Score</th>
<th>(^b) Area Under the Curve % x Hours</th>
<th>(^c) Tm/10 Mean Value</th>
<th>(^d) % Total Possible Score on Re-occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermovate cream</td>
<td>Clobetasol propionate, 0.05</td>
<td>519</td>
<td>3100</td>
<td>6.41</td>
<td>53</td>
</tr>
<tr>
<td>Amcinonide cream</td>
<td>Amcinonide, 0.1</td>
<td>510</td>
<td>2770</td>
<td>6.34</td>
<td>44</td>
</tr>
<tr>
<td>Halciderm</td>
<td>Halcinonide, 0.1</td>
<td>504</td>
<td>2630</td>
<td>6.31</td>
<td>44</td>
</tr>
<tr>
<td>Amcinonide combination cream</td>
<td>Amcinonide, 0.1</td>
<td>501</td>
<td>2680</td>
<td>6.29</td>
<td>44</td>
</tr>
<tr>
<td>Amcinonide combination ointment</td>
<td>Amcinonide, 0.1</td>
<td>489</td>
<td>2760</td>
<td>6.20</td>
<td>53</td>
</tr>
<tr>
<td>Metosyn Cream</td>
<td>Fluocinonide, 0.05</td>
<td>414</td>
<td>2640</td>
<td>5.69</td>
<td>19</td>
</tr>
<tr>
<td>Betnovate cream</td>
<td>Betamethasone as valerate, 0.1</td>
<td>393</td>
<td>2570</td>
<td>5.55</td>
<td>19</td>
</tr>
<tr>
<td>Temetex cream</td>
<td>Diflucortolone valerate, 0.1</td>
<td>391</td>
<td>2220</td>
<td>5.51</td>
<td>25</td>
</tr>
<tr>
<td>Synalar cream</td>
<td>Fluocinolone acetonide, 0.025</td>
<td>370</td>
<td>2710</td>
<td>5.35</td>
<td>25</td>
</tr>
<tr>
<td>Ultradril cream</td>
<td>Fluocortolone pivalate, 0.1; Fluocortolone hexanoate, 0.1</td>
<td>217</td>
<td>1060</td>
<td>4.13</td>
<td>3</td>
</tr>
</tbody>
</table>

\(a\) The corrected % total possible scores summed for all volunteers over all reading times.

\(b\) Obtained by planimetry of the blanching profile.

\(c\) The Tm/10 mean value is the square root transformation of sum of corrected scores (Tm) divided by the number of volunteers (10). The minimum significant range value \(k = 0.54 (P = 0.05)\), i.e. if the Tm/10 value of two preparations differ by more than 0.54 there is a significant difference between those preparations (see Statistical Treatment of Results).

\(d\) Re-occluded for 12 hours, 8 days after commencement of the experiment.
mum score = 80. For example, amcinonide cream gave a 6-hour score of 19.5 out of 80 to provide a value of 24.4% total possible score. The data were then unified in terms of a standard preparation, Betnovate cream, as described previously in order to relate the results obtained in this trial to those obtained in previous studies employing both experimental amcinonide formulations and an extensive range of proprietary preparations. The unification correction factor for Betnovate cream in the present trial is given by: summed % total possible score for Betnovate cream as obtained by Barry and Woodford / summed % total possible score for Betnovate cream in this study = 1.41.

The % total possible score data were, therefore, multiplied by 1.41 and blanching curves of these results are shown in Figures 1 to 3. Experimental points have been omitted to aid clarity but all points lay on or near the curves as drawn. The profiles shown may be compared directly with those preparations previously studied.

Statistical Treatment

A computer-aided analysis of variance was performed on the results, the
Figure 2 — Blanching curves for preparations indicated.

computer program being written so that the data could be analysed without transformation or in one of five \( (x^{-1}, x^{-1/2}, \log x, x^{1/2} \text{ and } x^2) \) transformations.\(^8^,^4\) Tests for non-additivity\(^9\) indicated a preference for the “square root transformation” data and the randomised block design variance analysis was calculated using those values. Highly significant differences were found to exist between the preparations \( (F = 37.06, P < 0.01) \), while the minimum significant range value \( k \) in the Studentized range test\(^1^0^,^4\) at the 5% significance level was 0.54 (10 preparations and 81 degrees of freedom). Hence the non-significant range for \( e.g. \) amcinonide combination cream = 6.29 ± 0.54 = 6.83 to 5.75. If the Tm/10 mean values (Table I) of two preparations differ by more than 0.54 there is a significant difference between those formulations.

**Steroid Reservoir Formation in the Skin**

Re-occlusion of the application sites in two volunteers (statistical analysis was, therefore, inapplicable) provided an estimate of the steroid reservoir in the skin. These results are shown as % total possible score on re-occlusion (Table I).
DISCUSSION

All of the preparations studied in this trial produced obvious vasoconstriction, the shapes of the blanching curves for the amcinonide and proprietary formulations (Figures 1 to 3) being similar to those previously reported.4,6,7

In this trial the rather high value of the Betnovate cream correction factor was a little surprising. Examination of the individual volunteers' results suggested that this was due to rather low responses to Betnovate cream (and the other preparations) in three volunteers, thus producing a low total for Betnovate cream in this trial. However, the values of the corrected % total possible scores summed for all volunteers over all reading times (Table I) were very similar to those previously reported, e.g., amcinonide cream = 510 (509 in a previous trial).4 Dermovate cream = 519 (512 previously),6 Metosyn cream = 414 (409 previously.)6 An exception was amcinonide combination cream, which provided a value about 7% higher than in the previous study.4 This may have been due to the slight modification in the composition of the amcinonide combination cream compared to that employed in the 1977
Figure 4 — Histogram of sum of % total possible scores for preparations indicated.

Figure 5 — Histogram of areas under the blanching curve for preparations indicated.
The similarities in different trials noted for the proprietary preparations further inspires confidence in our standard vasoconstrictor test.

The corrected % total possible score values for the most active preparations (Dermovate cream, Halciderm cream and the amcinonide formulations) at the 12-hour reading time were somewhat greater than 100. Because the blanching curves were drawn to a maximum value of 100% (Figs. 1 to 3) the area under the curve values (Table I and Fig. 5) for the amcinonide, Halciderm and Dermovate preparations were rather lower, compared to the less potent formulations, than might otherwise be expected. A ranking based on the sum of the corrected % total possible score values (Fig. 4) suggested that the corticosteroid preparations comprised three potency groups: this was confirmed by statistical analysis (Table I).

Table II — Blanching responses to preparations containing 0.1% amcinonide

<table>
<thead>
<tr>
<th>Preparation</th>
<th>aBioavailability (i)</th>
<th>(ii)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amcinonide cream</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Amcinonide combination cream</td>
<td>0.98</td>
<td>0.97</td>
</tr>
<tr>
<td>Amcinonide combination ointment</td>
<td>0.96</td>
<td>1.00</td>
</tr>
</tbody>
</table>

aDefined by the relationships:

(i) summed % total possible score for preparation
(ii) summed % total possible score for most active preparation

"area under the curve" for preparation
"area under the curve" for most active preparation

Table III — Potency classification of topical corticosteroid creams

<table>
<thead>
<tr>
<th>Cream</th>
<th>aTm/10 Mean Value</th>
<th>bSignificance</th>
<th>cPotency Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermovate</td>
<td>6.41</td>
<td>No significant difference</td>
<td>very potent</td>
</tr>
<tr>
<td>Halciderm</td>
<td>6.31</td>
<td>difference between creams (P = 0.05)</td>
<td>—</td>
</tr>
<tr>
<td>Amcinonide</td>
<td>6.34</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Amcin. combination</td>
<td>6.29</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Metosyn</td>
<td>5.69</td>
<td>No significant difference</td>
<td>potent</td>
</tr>
<tr>
<td>Betnovate</td>
<td>5.55</td>
<td>difference between creams (P = 0.05)</td>
<td>&quot;</td>
</tr>
<tr>
<td>Temetex</td>
<td>5.51</td>
<td></td>
<td>&quot;</td>
</tr>
<tr>
<td>Synalar</td>
<td>5.35</td>
<td></td>
<td>&quot;</td>
</tr>
<tr>
<td>Ultradil</td>
<td>4.13</td>
<td>—</td>
<td>moderately potent</td>
</tr>
</tbody>
</table>

a Table I, k = 0.54 (P = 0.05)
b As determined by the blanching test. Significant differences exist between the three potency groups.
c MIMS classification for topical steroids

The three amcinonide formulations provided similar steroid bioavailability (Table II) and were statistically equivalent to each other and to
the Dermovate and Halciderm preparations (Table I). Table III lists the creams studied in decreasing Tm/10 mean values and shows that the hydrophilic amcinonide preparations were significantly more active in the 6-hour occluded blanching test than selected potent creams on the U.K. market: both amcinonide cream and amcinonide combination cream were apparently equivalent to the very potent products examined, and produced approximately similar reservoirs of steroid in the skin.

CONCLUSIONS

1. 0.1% amcinonide cream was significantly more active (P = 0.05) in a standard six-hour occluded vasoconstrictor assay than four "recognized as potent" U.K. proprietary topical corticosteroid creams (Betnovate, Metosyn, Synalar and Temetex).
2. 0.1% amcinonide cream was statistically equivalent to two very potent U.K. proprietary creams, Dermovate and Halciderm.
3. Three 0.1% amcinonide formulations (cream, combination cream and combination ointment, the last two containing anti-infective agents) were equipotent in the skin-blanching test.

Acknowledgements

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References:


