

## Possible Dosage Regimens for Topical Steroids, Assessed by Vasoconstrictor Assays Using Multiple Applications

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**Key Words.** Topical steroids · Bioavailability and activity · Corticosteroids · Vasoconstrictor · Amcinonide · Dosage regimens

**Abstract.** The bioavailabilities and activities of three amcinonide preparations and Betnovate cream were assessed using three multiple-dosage regimen vasoconstrictor assays in 10 volunteers. Applications were made once daily, twice daily and every alternate day with an initial three times daily loading dose applied on the first day only. Blanching responses first increased and then decreased due to tachyphylaxis. It is proposed that clinically the most advantageous dosage regimen is a once daily application with no loading dose.

Patients may become resistant to topical steroids after constant use [7]. Such tachyphylaxis has also been demonstrated in the vasoconstrictor assay for corticosteroids, with considerable recovery occurring if a 'rest period' intervenes in the dosage regimen [2, 4, 5]. The authors' previous studies using a non-occluded multiple-dosage regimen involved a three times daily application [2]: less frequent administration might produce less marked tachyphylaxis. Lack of clinical studies comparing the use of potent topical steroids in twice daily, daily and alternate-day regimens [3] prompted investigation of such regimens in the repeated-application skin-blanching test.

### Materials and Methods

#### *Corticosteroid Formulations*

Topical preparations (Cyanamid of Great Britain Ltd.) containing amcinonide (16 $\alpha$ , 17 $\alpha$ -cyclopentylidenedioxy-9 $\alpha$ -fluoro-11 $\beta$ , 21-dihydroxy-1,4-pregnadiene-3,20-dione 21-acetate) were amcinonide cream, 0.1%, amcinonide cream, 0.025%, and amcinonide ointment, 0.1%. The 0.1% formulations are marketed in Europe as Penticort. Betnovate cream (betamethasone velerate 0.1%) was employed as a standard preparation for comparative purposes.

#### *Volunteers*

10 volunteers were selected from an experienced panel as those demonstrating consistency of response to a standard preparation (Betnovate cream) in the vasoconstrictor test [1]. None had received topical corticosteroid application for at least 3 months prior to the study.

### Methods

**Dosage Regimens.** Each regimen included three applications on day 1, the loading dose (at 0, 4 and 7 h), the preparations thereafter being applied (days 2–5) in each of three modes: (a) twice daily at 9.30 h and 16.30 h; (b) once daily, at 9.30 h, and (c) on alternate days, at 9.30 h on days 3 and 5. Days 6 and 7 were rest periods. From day 8, the procedure was repeated at the same sites, omitting two of the applications of the loading dose.

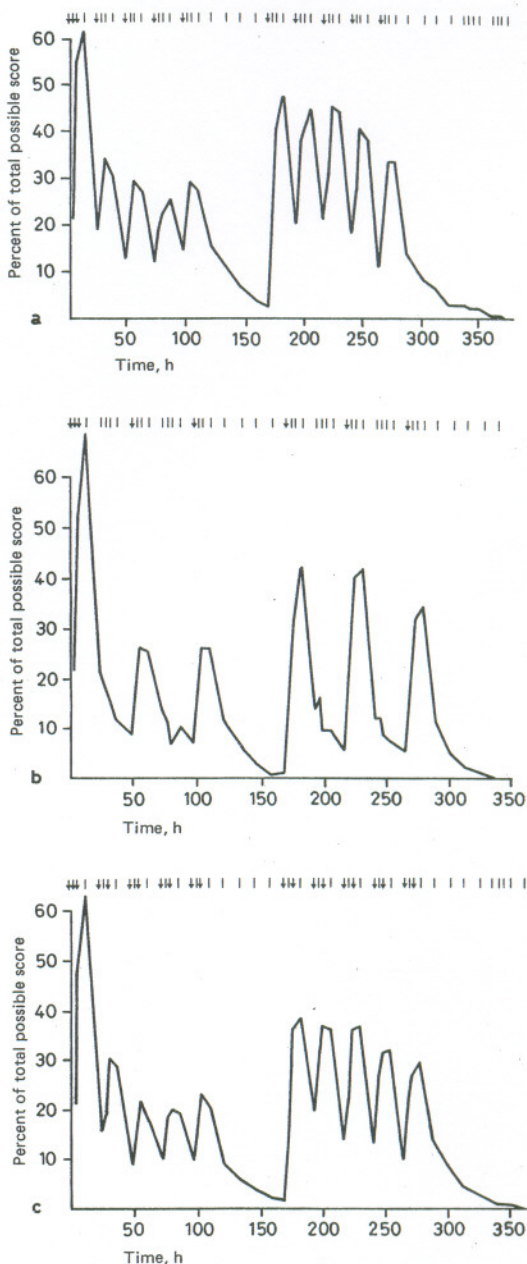
**Application Procedure and Result Assessment.**  $5 \pm 1$  mg of each formulation were rubbed (1 min) into a  $7 \times 7$  mm area on each forearm of 10 volunteers, using a glass rod, and with reference to a randomization chart. Holes in a plastic sheet located the application sites: indelible ink markers facilitated subsequent application. Blanching was estimated using a 0–4 scale with half-point ratings for intermediate readings: 0 = normal skin; 1 = slight vasoconstriction of indistinct outline; 2 = more intense vasoconstriction with at least two corners outlined; 3 = general even vasoconstriction with a clear outline of the square; 4 = more marked vasoconstriction with very distinct blanching.

Double-blind estimations of skin blanching were made at each application time immediately before re-applying the formulations and at additional times indicated on the figure. Sites were unguarded and volunteers lived normally so as to mimic domiciliary use of topical steroids.

### Results and Discussion

The results were summed for all volunteers at each time, expressed as a percentage of the total possible score [1] and were plotted as functions of time. Results for all four steroid preparations were similar therefore only those for amcinonide cream 0.1% are shown as an example (fig. 1).

The blanching responses are in table I. The results for the individual scores in each preparation/regimen were submitted to a computer-assisted analysis of variance followed by application of the Studentized range test on the preferred 'square root transformation' data [1, 10]. Statistically signifi-



**Fig. 1.** Blanching profiles for amcinonide cream 0.1% in daily (a) alternate-day (b) and twice daily (c) regimens. An arrow represents steroid application and a line indicates an additional reading time.



Table I. Blanching response to each preparation used in each regimen

Preparation and regimen <sup>1</sup>	Area under the curve (% × h) <sup>2</sup>	Total score <sup>3</sup>	Summed % total possible score <sup>4</sup>	T <sub>m</sub> /10 mean value <sup>5</sup>
HC/A	7,580	981	1,226	9.77
HC/B	6,170	798	998	8.84
HC/C	5,260	684	854	8.20
LC/A	4,980	637	796	7.90
LC/B	5,230	669	836	8.07
LC/C	3,920	494	619	6.97
O/A	6,210	799	998	8.84
O/B	5,750	740	925	8.46
O/C	5,040	629	786	7.86
BV/A	4,130	516	644	7.10
BV/B	4,870	625	781	7.78
BV/C	3,840	472	589	6.76

<sup>1</sup> HC = amcinonide cream, 0.1%; LC = amcinonide cream, 0.025%; O = amcinonide ointment, 0.1%; BV = Betnovate cream; A = daily application; B = twice daily; C = alternate day.

<sup>2</sup> Obtained by planimetry of the blanching profiles.

<sup>3</sup> The sum of the scores for all volunteers over all reading times.

<sup>4</sup> The sum of the % total possible scores for all volunteers over all reading times.

<sup>5</sup> The T<sub>m</sub>/10 mean value is the square root transformation of the sum of scores (T<sub>m</sub>) divided by the number of volunteers (10). The minimum significant range value  $k = 1.53$  ( $p = 0.05$ ), i.e. if two T<sub>m</sub>/10 values differ by more than 1.53 there is a significant difference between the two preparations/regimens [6].

cant differences existed between the values ( $F = 1.91$ ,  $p < 0.05$ ), the minimum significant range value  $k$  being 1.53 ( $p = 0.05$ , 12 means, 99 d. f.).

The three times daily application on day 1 produced a large blanching response and subsequent application caused tachyphylaxis, irrespective of potency or dosage regimen. Sites recovered over days 6 and 7 and the blanching profiles obtained during the second week showed a lower degree of tolerance than for days 1–5 (fig. 1). The incidence of tachyphylaxis in the second week was less than that demonstrated by Barry and Woodford [2] using the more drastic regimen of three times daily application. The areas under the blanching curves for

both weeks were similar, mean values for the first week being 49.1% (range 45.7–54.4%, depending on formulation/regimen) and for the second week, 50.9% (range 45.6–54.3%) of the total values (table I).

The rank order of blanching effectiveness for the application regimens was (a) amcinonide cream 0.025% and Betnovate cream: twice daily > daily > alternate day; (b) amcinonide cream 0.1% and ointment 0.1% daily > twice daily > alternate day. Statistical analysis suggested that the 0.1% cream was significantly more potent ( $p = 0.05$ ) (a) in the once daily regimen than when applied on alternate days, and (b) than amcinonide cream 0.025% and Betnovate cream applied in the once daily mode.

Amcinonide ointment was significantly more potent than Betnovate cream in the once daily regimen.

#### *Clinical Significance: Preferred Dosage Regimen*

Results suggest that once daily application should be preferred clinically to twice daily use for the following reasons.

(1) It was the only regimen permitting statistical differentiation at the 5% level between formulations, e.g. the apparent superiority of the 0.1% cream over the 0.025% preparation and Betnovate cream. This confirms potency classifications previously obtained in the single 6 hour occluded vasoconstrictor assay of (a) the 0.1% amcinonide preparations being 'very potent' by the United Kingdom Mims classification [8], and (b) the 0.025% and Betnovate creams as 'potent' [10, 11].

(2) Less total steroid would be applied, thus minimising unwanted side-effects of topical corticosteroid therapy.

(3) Once daily application should facilitate patient compliance and the use of smaller quantities is more economic.

(4) If therapy commenced with amcinonide cream 0.1% in a once daily regimen (this preparation/regimen produces the largest blanching parameters), once the condition was stabilised it could be maintained by changing to the 0.025% formulation. Because three times daily application on day 1 produced considerable tachyphylaxis not evident on day 8 it may be advantageous in the clinical situation to omit the loading dose.

The observation [9] that once daily application of 0.1% halcinonide cream was almost as effective as three times daily application in atopic dermatitis suggests that less

frequent use of very potent formulations in certain skin disorders may be preferable.

#### *Bioavailability of 0.1% Preparations*

Amcinonide ointment 0.1% was rather less effective than the corresponding cream in all dosage regimens (table I). This agrees with the formulation of these two preparations: both contain the steroid completely in solution, but whereas it is nearing saturation in the cream, the ointment system is less saturated [Cyanamid of Great Britain, personal commun.].

#### **Acknowledgement**

JMH acknowledges the award of a bursary from the South African Council for Scientific and Industrial Research.

#### **References**

- 1 Barry, B.W.; Woodford, R.: Comparative bioavailability of proprietary topical corticosteroid preparations; vasoconstrictor assays on thirty creams and gels. *Br. J. Derm.* 91: 323-338 (1974).
- 2 Barry, B.W.; Woodford, R.: Vasoconstrictor activities and bioavailabilities of seven proprietary corticosteroid creams assessed using a non-occluded multiple dosage regimen; clinical implications. *Br. J. Derm.* 97: 555-560 (1977).
- 3 Cornell, R.C.; Stoughton, R.B.: Use of glucocorticosteroids in psoriasis. *Pharmacol. Ther.* 11: 497-508 (1980).
- 4 Du Vivier, A.; Stoughton, R.B.: Tachyphylaxis to the action of topically applied corticosteroids. *Archs. Derm.* 111: 581-583 (1975).
- 5 Du Vivier, A.; Stoughton, R.B.: Acute tolerance to effects of topical glucocorticosteroids. *Br. J. Derm.* 94: suppl. 12, pp. 25-32 (1976).
- 6 Goldstein, A.: *Biostatistics: an introductory text* (Macmillan, New York 1964).
- 7 Miller, J.A.; Munro, D.D.: Topical corticosteroids: clinical pharmacology and therapeutic use. *Drugs* 19: 119-134 (1980).

- 8 Mims (Monthly Index of Medical Specialities) Feb., pp. 258-259 (1982).
- 9 Sudilovsky, A.; Muir, J.G.; Bocobo, F.C.: A comparison of single and multiple applications of halcinonide cream. *Int. J. Derm.* 20: 609-613 (1981).
- 10 Woodford, R.; Barry, B.W.: Activity and bioavailability of amcinonide and triamcinolone acetonide in experimental and proprietary topical preparations. *Curr. ther. Res.* 21: 877-886 (1977).
- 11 Woodford, R.; Haigh, J.M.: Bioavailability and activity of 0.1% amcinonide preparations: compar-

ison with proprietary topical corticosteroid formulations of differing potencies. *Curr. ther. Res.* 26: 301-310 (1979).

Received: September 1, 1980

Accepted: July 1, 1982

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