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# Bioavailability and Activity of Topical Corticosteroids from a Novel Drug Delivery System, the Aerosol Quick-Break Foam

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**Abstract** □ Experiments were conducted to: (*a*) compare the bioavailability of betamethasone benzoate in a quick-break aerosol foam and semisolid dosage forms, (*b*) compare the activity of betamethasone benzoate, betamethasone valerate, clobetasol propionate, triamcinolone acetonide, desonide, flumethasone pivalate, and hydrocortisone butyrate in foam concentrates, (*c*) assess steroid reservoir formation in skin, and (*d*) assess the effect of a natural moisturizer. Efficacy was determined by a graded response 6-hr occluded vasoconstriction test with subsequent reocclusion for reservoir demonstration. Moisturizer effect was assessed by a nonoccluded vasoconstriction test using "plain" and sodium 2-pyrrolidone-5-carboxylate-containing concentrates on arms pretreated with water or moisturizer. The activities of betamethasone benzoate concentrate, collapsed foam, ointment, and gel were similar and significantly better than the activity of the cream. Clobetasol propionate was significantly better than the other medicated concentrates, which were equivalent. Steroid-induced blanching decreased in the presence of a moisturizer.

**Keyphrases** □ Betamethasone benzoate—bioavailability and activity, quick-break aerosol foam and semisolid dosage forms, various corticosteroids in foam concentrates compared, effect of moisturizer □ Bioavailability—betamethasone benzoate, quick-break aerosol foam and semisolid dosage forms, effect of moisturizer □ Drug delivery systems—quick-break aerosol foam, betamethasone benzoate bioavailability and activity compared to semisolid dosage form, effect of moisturizer □ Aerosol foam, quick break—betamethasone benzoate bioavailability and activity compared to semisolid dosage form, effect of moisturizer □ Dosage forms—quick-break aerosol foam and semisolid, betamethasone benzoate bioavailability and activity compared, effect of moisturizer □ Moisturizers—effect on bioavailability and activity of betamethasone benzoate in quick-break aerosol foam and semisolid dosage forms □ Corticosteroids, topical—betamethasone benzoate, bioavailability and activity of quick-break aerosol foam and semisolid dosage forms, effect of moisturizer

Topical corticosteroid preparations are used widely to treat various dermatoses, and new formulations continue to be developed. While topical steroid aerosols have been advocated by dermatologists (1) and are commercially available, most new preparations are ointments, creams, or gels. Aerosols for clinical use are sprays or stable foams; although pharmaceutical quick-break foams offer possibilities (2), their medicinal application has apparently not been developed.

As a topical steroid dosage form, the quick-break aerosol foam offers the advantages of high activity (the steroid is in solution), ease of application, controlled dosage from a metering valve, economy in use, suitability for smooth or hairy skin, and reduced possibility of inhaling corticosteroid compared with aerosol sprays. Logical development involves devising suitable formulations and comparing them with current corticosteroid dosage forms.

This paper reports work performed to: (*a*) compare the activity and bioavailability of 0.025% (w/w) betamethasone benzoate formulated as an ointment, cream, gel, and quick-break aerosol foam, (*b*) compare the activity of 0.025% (w/w) betamethasone benzoate with that of other corticosteroids at the same concentration in quick-break foams, (*c*) assess steroid reservoir formation in the skin, and (*d*) assess the effect of sodium 2-pyrrolidone-5-carboxylate (a natural moisturizing factor) on the blanching response to steroid-containing quick-break foams.

The "activity" of a preparation is its ability to produce skin pallor (assumed to parallel anti-inflammatory activity), while the "bioavailability" of a formulation refers to the activity of a given corticosteroid in a particular base monitored as a function of time compared with this activity in different bases. Bioavailability is assessed from a pharmacological response rather than by measuring drug concentrations in tissues.

## EXPERIMENTAL

**Preparation of Quick-Break Foam**—A nonionic emulsifying wax[1] is a suitable foaming agent for quick-break foams, especially in the presence of dichlorodifluoromethane and dichlorotetrafluoroethane. An aqueous–alcoholic system incorporating these ingredients produces excellent quick-break foams provided that the ethanol–water ratio lies between approximately 50:50 and 70:30 (3). Quick-break foams may also be prepared using propylene glycol–water mixtures. Twelve preliminary formulations were investigated consisting of various combinations of ethanol, propylene glycol, and water: ethanol, 56.5–13.0% (w/w); propylene glycol, 75.0–3.9% (w/w); and water, 27.0–0% (w/w).

Four basic formulations were developed, and from these the following preparation was selected as the most satisfactory: 0.025 g of betamethasone benzoate, 5.50 g of propylene glycol BP, 55.475 ml of dehydrated alcohol BP, 26.50 ml of purified water BP, 2.0 g of nonionic

[1] Polawax A31, Croda Chemicals Ltd., Goole, Yorks., United Kingdom.

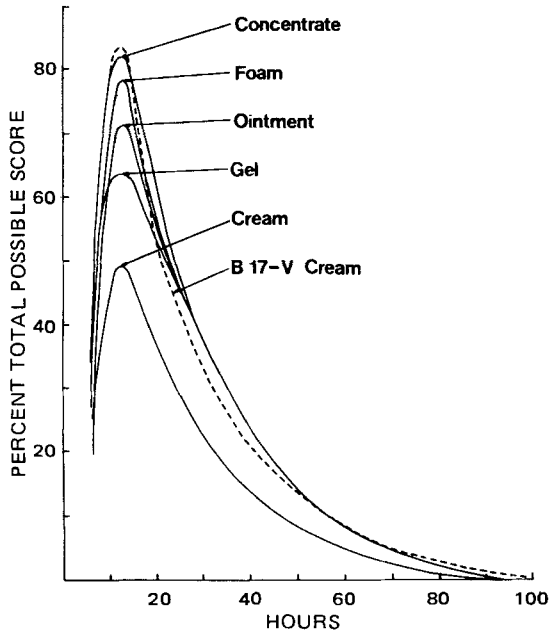


**Figure 1**—*Blanching response to betamethasone benzoate formulations containing 0.025% steroid and to 0.1% betamethasone valerate cream.*

emulsifying wax[1], 0.50 g of hydroxyethylcellulose[2], 4.0 g of dichlorodifluoromethane[3], and 6.0 g of dichlorotetrafluoroethane[4].

Water was added to the hydroxyethylcellulose with swirling. The mixture was gently heated to 60° until gelling commenced, and it was left to hydrate at room temperature for 1 hr with occasional swirling. Then propylene glycol was added with mixing. The corticosteroid was dissolved at room temperature in the alcohol, and this solution was added gradually with mixing. The nonionic emulsifying wax was added, and the system was warmed to approximately 60° with swirling until the wax dissolved. The homogeneous warm mixture was poured into a tin-plate aerosol container and cooled to below room temperature, and dichlorotetrafluoroethane was added. The valve system was crimped into place, and dichlorodifluoromethane was added *via* a transfer button.

Placebo formulations were prepared by replacing the steroid with dehydrated alcohol. Placebo foams were also produced using 5.0–6.0 g of a suitable mixture of hydrocarbons (propane, *n*-butane, and isobutane)[5] instead of the chlorofluorohydrocarbon propellent blend.

**Assessment of Betamethasone Benzoate Formulations**—Four formulations containing 0.025% (w/w) betamethasone benzoate were employed (quick-break foam, gel, cream, and ointment) together with the foam concentrate. A placebo foam and concentrate were also included. The carboxypolymethylene-based gel, oil-in-water cream, and white petrolatum-based ointment were used as received from the manufacturer[6].

Efficacy and bioavailability were assessed by a modified skin-blanching test (4, 5). Ten volunteers were selected without reference to their sex or steroid sensitivity. None had received topical corticosteroid therapy for at least 3 months prior to the study. Five milligrams of the semisolid preparations and 5 $\mu$l of the concentrates and expelled, collapsed foams were applied with reference to randomization charts to the washed flexor surface of each forearm. Application sites (7 × 7-mm areas punched out from double-sided polyethylene tape[7]) were occluded with polyester film[8] for 6 hr, the sites were washed with soap and water at skin temperature and dried, and readings were taken in a double-blind manner to provide data points for skin blanching at 6, 7, 8, 9, 12, 24, 32, 48, 72, 80, and 96 hr after application.

The degree of pallor was estimated on a 0–4 scale with half-point ratings (4). To assess steroid retention in the skin, the sites on selected volunteers were reoccluded with polyester film for 12 hr, 8 days after commencement of the experiment, and pallor was estimated 5 hr later when blanching was maximal.

**Assessment of Steroid-Containing Concentrates**—Seven corticosteroids (betamethasone benzoate, betamethasone valerate, clobetasol propionate, flumethasone pivalate, desonide, hydrocortisone 17-butyrate, and triamcinolone acetonide) were separately formulated as quick-break foam concentrates, and their activities were investigated as already described.

**Assessment of Effect of Natural Moisturizing Factor**—Five corticosteroids (betamethasone benzoate, betamethasone valerate, clobetasol propionate, flumethasone pivalate, and fluocinolone acetonide) were separately formulated in quick-break foam concentrates with and without 5% (w/w) of a 50% aqueous solution of sodium 2-pyrrolidone-5-carboxylate[9]. The "plain" concentrate contained 0.025 g of the corticosteroid, 5.0 g of propylene glycol BP, 55.475 ml of dehydrated alcohol BP, 25.0 ml of purified water BP, 2.0 g of nonionic emulsifying wax, and 0.50 g of hydroxyethylcellulose. The "moisturizing" concentrate was the same except that it contained 22.50 ml of purified water BP and 4.5 g of sodium 2-pyrrolidone-5-carboxylate (50% aqueous solution). The method of preparation was as previously described, the moisturizer being mixed with the hydrated hydroxyethylcellulose before the propylene glycol was added.

To accentuate any effect of the moisturizer, 0.7 ml of a 5% (w/w) aqueous solution of sodium 2-pyrrolidone-5-carboxylate was rubbed (3 min) into one arm of each of 10 volunteers twice a day for 7 days; the other arm was similarly treated with water as a control. A medical rubber finger-cot[10] was used, since experiments had shown that it was impermeable to water and sodium 2-pyrrolidone-5-carboxylate solutions. Five microliters of the plain and moisturizing concentrates were applied to each arm as described, and the polyethylene tape removed. The sites were left nonoccluded but protected by a perforated plastic guard for 6 hr (4) to avoid the hydrating effect of occlusion. Then the sites were washed and dried, and pallor was assessed as before.

In each blanching test, betamethasone valerate cream[11] was employed as a control "standard preparation" so that the results could be correlated with other investigations.

## RESULTS AND DISCUSSION

**Formulation of Quick-Break Foam**—The quick-break foam easily rubbed into glabrous or hairy skin, leaving the site soft and not sticky. The hydroxyethylcellulose increased the viscosity of the liquid remaining after foam collapse, facilitating application to a limited area. During application, some ethanol evaporated, tending to increase the concentration and thermodynamic activity of the steroid in the solvent mixture and thus promoting percutaneous absorption; the propylene glycol minimized precipitation of medicament as the amount of alcohol decreased. Experiments on a placebo formulation, packed in a glass bottle fitted with a metering valve[12] and foam actuator, showed that an undisturbed 180 mg of foam (mean of 10 determinations, range of 178–183 mg) collapsed on the ventral surface of the forearm in 6.5 sec (mean of 10 determinations, range of 6.1–7.0 sec).

A can aged for 1 week at room temperature (17–20°) had a vapor pressure of 24 psig, as did a sample consisting of 90 g of concentrate and 5.8 g of a hydrocarbon propellent blend. Foams produced using chlorofluorocarbon propellents and hydrocarbon propellents usually appeared equally satisfactory, although the hydrocarbon-containing foams were more flammable. Because of their possible adverse effect on the ozone layer, the continued use of halogen-containing propellents has been criticized (6). A suitable mixture of hydrocarbons is a possible alternative propellent for a corticosteroid quick-break foam.

**Betamethasone Benzoate Formulations**—With each formulation, the results for all volunteers were expressed as a percentage of the total possible score at each time period. The method of calculation was as follows: maximum score per site = 4; for two arms, 4 × 2 = 8; for 10 volunteers, 8 × 10 = 80 (*e.g.*, 6-hr reading for quick-break foam, score of 25 out of a possible 80 = 31.3%). To relate the results obtained with the betamethasone benzoate formulations to those obtained with proprietary

[2] Cellosize QP-4400-L, Union Carbide U.K. Ltd., Rickmansworth, Herts., United Kingdom.
[3] Arcton 12, Imperial Chemical Industries Ltd., Runcorn, Cheshire, United Kingdom.
[4] Arcton 114, Imperial Chemical Industries Ltd., Runcorn, Cheshire, United Kingdom.
[5] Calor Aerosol Propellent, Calor Gas Co., Weybridge, Surrey, United Kingdom.
[6] William R. Warner & Co. Ltd., Eastleigh, Hants., United Kingdom.
[7] Blenderm, 3M Medical Products, London, United Kingdom.
[8] Melinex S 12 $\mu$m, Imperial Chemical Industries Ltd., Welwyn Garden City, Herts., United Kingdom.
[9] Ajidew N-50, Ajinomoto Co., Tokyo, Japan.
[10] London Rubber Products, London, United Kingdom.
[11] Betnovate cream, Glaxo Laboratories Ltd., Greenford, Middlesex, United Kingdom.
[12] 5883/5618 R valve, Bespak Industries Ltd., Cheshunt, Herts., United Kingdom.

**Table I—Blanching Response to Betamethasone Benzoate Formulations Containing 0.025% (w/w) Steroid**

| Formulation | Area under Curve[a], % *TPS* × hr | Bioavailability[b] | Summed Percent Total Possible Score[c] | *Tm*/10 Mean Value[d] | $t_{1/2}$[e], hr | Percent Total Possible Score on Reocclusion[f] |
|---|---|---|---|---|---|---|
| Betamethasone benzoate concentrate | 2350 | 1.0 | 392 | 5.58 | 13.1 | 45 |
| Betamethasone benzoate foam | 2180 | 0.93 | 381 | 5.50 | 12.4 | 45 |
| Betamethasone benzoate ointment | 2010 | 0.85 | 297 | 4.84 | 12.5 | 28 |
| Betamethasone benzoate gel | 2000 | 0.85 | 357 | 5.32 | 13.2 | 37 |
| Betamethasone benzoate cream | 1290 | 0.55 | 240 | 4.30 | 14.0 | 14 |
| Betamethasone valerate cream, 0.1% | 2140 | — | 393 | 5.58 | 14.0 | 24 |

[a] Obtained by planimetry of the blanching profile to three significant figures; *%TPS* = percent total possible score. [b] The bioavailability of a betamethasone benzoate preparation is the area under its blanching curve divided by the area under the curve of the concentrate (the most active formulation). [c] The percent total possible scores summed for all volunteers over all reading times. [d] The *Tm*/10 mean value is the square root transformation of sum of scores (*Tm*) divided by the number of volunteers (10). The minimum significance range value $k = 0.75$ ($p = 0.05$); *i.e.*, if the *Tm*/10 values of two formulations differ by more than 0.75, there is a significant difference between those formulations. [e] Apparent vasoconstriction half-life = $0.693/K_{vc}$. [f] Reoccluded for 12 hr, 8 days after commencement of the experiment.

preparations (4, 5), the percentages of total possible score values were multiplied by the value: summed percent total possible score value for betamethasone valerate cream in Ref. 4/summed percent total possible score value for betamethasone valerate cream in the betamethasone benzoate study. By this means, the results obtained in the present work were comparable with those reported previously.

Blanching profiles for the betamethasone preparations are shown in Fig. 1; experimental points were omitted for clarity but all lay on or near the curves as drawn. All preparations gave curves with a peak in the 12-hr region and a marked fall-off thereafter. The blanching profile for each formulation was a measure of its activity as a function of time, involving: (*a*) release of corticosteroid from the base, (*b*) penetration of the medicament through the epidermis into the dermis, (*c*) onset and duration of corticosteroid-induced pallor at the vascular region, and (*d*) decline of pharmacological response and elimination of drug from the site of action.

A single numerical parameter that takes account of these four factors is the area under the blanching curve; therefore, it is the parameter most suitable for comparing the bioavailability of steroids in various bases. When arranged in an area under the curve rank order, the aerosol concentrate and foam were superior to the other preparations (Table I). The comparative bioavailability of a formulation was obtained by dividing its area under the curve by that of the most active preparation (*i.e.*, the concentrate). The order was not identical to that based on a summed percentage of the total possible score relationship (*i.e.*, the percentage of the total possible scores summed for all time periods).

The scores for each volunteer were summed over all reading times and analyzed statistically as the nontransformed data and as each of five transformations ($x^{-1}$, $x^{-1/2}$, $\log x$, $x^{1/2}$, and $x^2$) (4). Tests for nonadditivity (7) indicated a preference for the square root transformation, and the analysis of variance was calculated using those values. The differences between the preparations were highly significant ($F = 8.36$, $p < 0.01$), while those between the volunteers were significant ($F = 2.21$, $p < 0.05$).

Calculation of the minimum significance range value $k$ using the Student range test (8) permitted comparison of the betamethasone formulations. Significant differences between preparations occurred when their *Tm*/10 mean values (Table I) differed by a figure greater than the value of $k$. For example, the nonsignificance range for betamethasone benzoate concentration was $5.58 - 0.75 = 4.83$. Hence, the aerosol foam and concentrate were as active in the blanching test as the semisolid formulations with the exception of the betamethasone benzoate cream, which was significantly less active.

Linear plots of log percent total possible score against time over 24–72 hr permitted least-squares evaluation of the apparent vasoconstriction dissipation rate constant ($K_{vc}$) and the apparent vasoconstriction half-life ($t_{1/2}$) (9). The value of $K_{vc}$ quantifies the disappearance of blanching arising from steroid biotransformation, homeostasis, vascular removal, diffusion from the site of action, and tachyphylaxis. The overall elimination process was described by apparent first-order kinetics, and the values of $K_{vc}$, $t_{1/2}$ (Table I), and the slope of the regression line equation were similar for all betamethasone formulations. Thus, the equation for the linear plots may be written as:

$$\ln (\%\ TPS) = \ln (\%\ TPS)_0 - K_{vc}t \qquad \text{(Eq. 1)}$$

where $\ln (\%\ TPS)_0$ represents the extrapolated value of the response at time $t = 0$. Regression line equations (for four points) to three significant figures were:

| | |
|---|---|
| foam | $\ln (\%\ TPS) = 5.32 - 0.0560t$, $r = -0.999$ |
| foam concentrate | $\ln (\%\ TPS) = 5.27 - 0.0529t$, $r = -1.00$ |
| cream | $\ln (\%\ TPS) = 4.57 - 0.0494t$, $r = -0.997$ |
| gel | $\ln (\%\ TPS) = 5.22 - 0.0524t$, $r = -0.997$ |
| ointment | $\ln (\%\ TPS) = 5.31 - 0.0554t$, $r = -0.996$ |
| betamethasone valerate cream | $\ln (\%\ TPS) = 5.01 - 0.0495t$, $r = -0.997$ |

These results indicated that the disappearance of betamethasone benzoate-induced pallor proceeded at a rate essentially independent of the nature of the vehicle. Furthermore, the replacement of the benzoate group by valerate at the 17-position had little apparent effect on the dissipation of blanching due to the betamethasone derivative.

Reocclusion of the application sites in two volunteers (for which, therefore, statistical analysis was inapplicable) permitted estimation of steroid retention in the stratum corneum. Obvious reservoirs were established with the foam and concentrate, while the least pallor on reocclusion was produced by betamethasone benzoate cream (Table I). Subsequent reocclusion showed that the presence of steroids in the skin could not be demonstrated after 12 days. The placebo concentrate and foam failed to blanch following 6 hr application or after reocclusion.

**Steroid-Containing Concentrates**—The blanching scores for the steroid-containing concentrates were expressed as percent total possible scores as already described, and blanching curves are shown in Figs. 2 and 3. In all cases, the shapes of the graphs were similar; Table II ranks the concentrates on an area under the blanching curve basis. As with the previous experiment, this listing was not identical to that based on summed percent total possible scores. Least-squares evaluation of linear plots of log percent total possible score against time over 24–72 hr (Figs. 2 and 3) showed that similar steroids (triamcinolone acetonide and desonide and betamethasone benzoate and betamethasone valerate) gave similar values of $t_{1/2}$ and $K_{vc}$. Regression line equations (for four points) to three significant figures for the medicated concentrates were:

| | |
|---|---|
| clobetasol propionate | $\ln (\%\ TPS) = 5.02 - 0.0390t$, $r = -1.00$ |
| flumethasone pivalate | $\ln (\%\ TPS) = 5.34 - 0.0596t$, $r = -1.00$ |
| triamcinolone acetonide | $\ln (\%\ TPS) = 5.13 - 0.0463t$, $r = -0.999$ |
| desonide | $\ln (\%\ TPS) = 5.12 - 0.0472t$, $r = -0.999$ |
| hydrocortisone 17-butyrate | $\ln (\%\ TPS) = 5.61 - 0.0731t$, $r = -1.00$ |
| betamethasone benzoate | $\ln (\%\ TPS) = 5.27 - 0.0529t$, $r = -0.999$ |
| betamethasone valerate | $\ln (\%\ TPS) = 5.06 - 0.0530t$, $r = -1.00$ |
| betamethasone valerate cream | $\ln (\%\ TPS) = 5.01 - 0.0497t$, $r = -1.00$ |

A ranking of steroid concentrates using $t_{1/2}$ values was similar to that based on area under the curve data (Table II).

Statistical analysis showed that the medicated concentrates were as effective in inducing pallor as the standard (betamethasone valerate cream) with the exception of that containing clobetasol propionate, which was significantly more active ($p < 0.05$). Similar steroid reservoirs were produced in the skin with all concentrates (Table II); subsequent reoc-

Table II—Blanching Response to Quick-Break Foam Concentrates Containing 0.025% (w/w) Steroid

| Steroid or Formulation | Area under Curve[a], % *TPS* × hr | Summed Percent Total Possible Score[b] | *Tm*/10 Mean Value[c] | $t_{1/2}$[d], hr | Percent Total Possible Score on Reocclusion[e] |
|---|---|---|---|---|---|
| Clobetasol propionate | 3070 | 568 | 6.74 | 17.8 | 28 |
| Desonide | 2610 | 441 | 5.89 | 14.7 | 24 |
| Triamcinolone acetonide | 2580 | 453 | 6.00 | 15.0 | 24 |
| Betamethasone benzoate | 2350 | 392 | 5.58 | 13.1 | 45 |
| Flumethasone pivalate | 2250 | 445 | 5.92 | 11.6 | 37 |
| Betamethasone valerate | 2020 | 409 | 5.70 | 13.1 | 34 |
| Hydrocortisone 17-butyrate | 1970 | 394 | 5.56 | 9.5 | 28 |
| Betamethasone valerate cream, 0.1% | 2140 | 393 | 5.58 | 13.9 | 24 |

[a] Obtained by planimetry of the blanching profile to three significant figures; *%TPS* = percent total possible score. [b] The percent total possible scores summed for all volunteers over all reading times. [c] The *Tm*/10 mean value is the square root transformation of sum of scores (*Tm*) divided by the number of volunteers (10). The minimum significance range value $k = 0.53$ ($p = 0.05$); *i.e.*, if the *Tm*/10 values of two formulations differ by more than 0.53, there is a significant difference between those formulations. [d] Apparent vasoconstriction half-life = $0.693/K_{VC}$. [e] Reoccluded for 12 hr, 8 days after commencement of the experiment.

clusion showed that the presence of medicament could not be demonstrated after 12 days with the exception of clobetasol propionate, which disappeared after 14 days.

The area under the blanching curve, summed percent total possible score, and percent total possible score on reocclusion values obtained with the foam concentrates were often higher than the values obtained previously with the corresponding commercial creams and ointments (4, 5), although the concentration of steroid in the semisolid formulations was usually two to four times greater than that of the concentrates. For flumethasone pivalate, the concentration of steroid in the ointment and cream was 0.02% (*i.e.*, approximately the same as that in the concentrate). However, the foam concentrate gave blanching values three to four times those of the commercial preparations, depending on the parameter employed (area under the curve or summed percent total possible score). No attempt was made to optimize fully the release and subsequent blanching activity of corticosteroid from each concentrate. It is thus possible that, by careful selection of the ethanol–propylene glycol–water ratio for each steroid (within the limits for quick-break foam production), a further enhanced vasoconstrictor efficacy for the concentrate could be achieved.

**Assessment of Effect of Moisturizer**—Hydration of the stratum corneum usually facilitates penetration of corticosteroid. To increase skin hydration, a moisturizer was employed both in the formulations and in pretreatment of the arms.

Steroid-induced blanching in the presence and absence of sodium 2-pyrrolidone-5-carboxylate is shown in Table III. Statistical examination by a three-way analysis of variance (10) followed by the Student range test showed significant differences ($p < 0.05$) between moisturizer- and water-treated arms for clobetasol propionate, fluocinolone acetonide, and betamethasone valerate, whereas only clobetasol propionate (the most potent steroid examined) showed a significant difference between concentrates with and without moisturizer on either arm.

The corticosteroids gave values that decreased in the order: control (moisturizer-free) concentrate on control (water-treated) arm > moisturizer-containing concentrate on control arm > control concentrate on moisturizer-treated arm > moisturizer-containing concentrate on moisturizer-treated arm. This sequence was surprising, and the reason

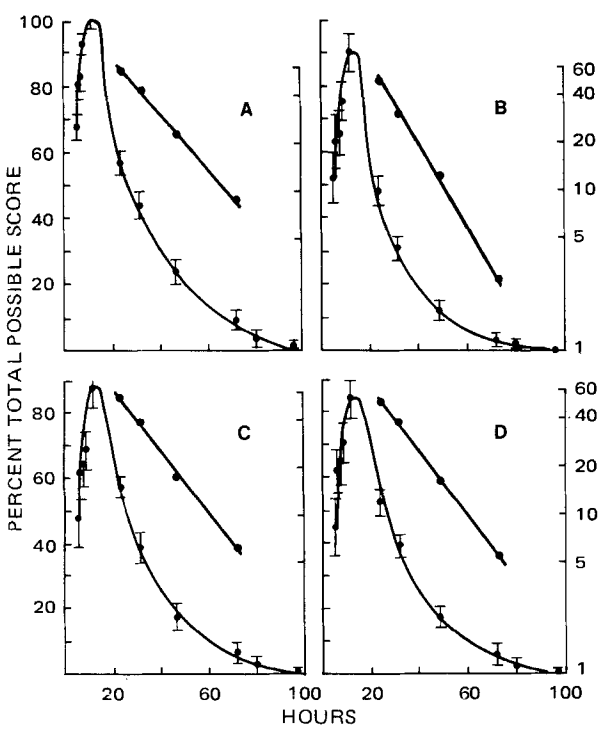


**Figure 2**—*Blanching response to quick-break foam concentrates containing 0.025% steroid. Curves are the arithmetic plots ± SEM; n = 10 (bar lines were omitted from occasional points for clarity). Straight lines are the percent total possible score logarithmic plots. Key: A, clobetasol propionate; B, flumethasone pivalate; C, triamcinolone acetonide; and D, desonide.*

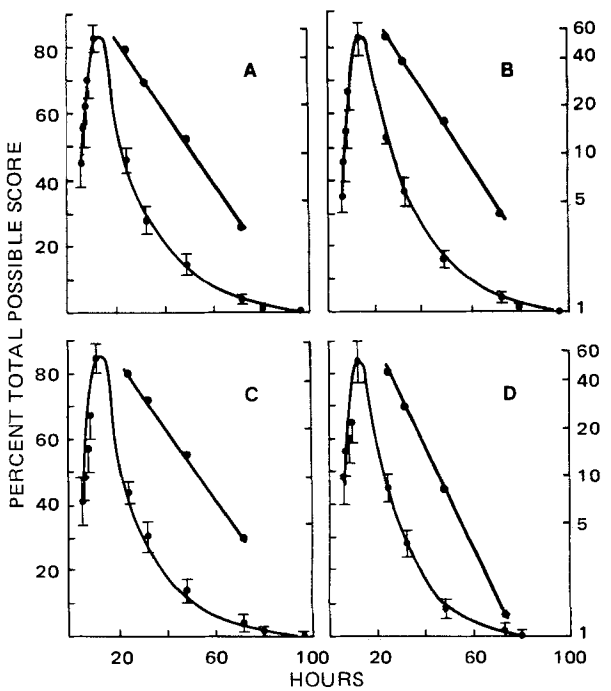


**Figure 3**—*Blanching response to quick-break foam concentrates containing 0.025% steroid and to 0.1% betamethasone valerate cream. Curves are the arithmetic plots ± SEM; n = 10 (bar lines were omitted from occasional points for clarity). Straight lines are the percent total possible score logarithmic plots. Key: A, betamethasone valerate; B, betamethasone benzoate; C, betamethasone valerate cream, 0.1%; and D, hydrocortisone 17-butyrate.*

Table III—Blanching Response to Quick-Break Foam Concentrates Containing 0.025% (w/w) Steroid in the Presence and Absence of Moisturizer[a]

| | *Tm*/10 Mean Value[b] | |
|---|---|---|
| | Moisturizer-Treated Arm | Water-Treated Arm |
| Clobetasol propionate plus moisturizer | 5.15 | 11.70 |
| Fluocinolone acetonide plus moisturizer | 1.70 | 6.90 |
| Betamethasone valerate plus moisturizer | 0.90 | 5.50 |
| Betamethasone benzoate plus moisturizer | 1.10 | 3.70 |
| Flumethasone pivalate plus moisturizer | 1.15 | 3.10 |
| Clobetasol propionate | 9.85 | 15.60 |
| Fluocinolone acetonide | 4.05 | 10.75 |
| Betamethasone valerate | 4.40 | 8.60 |
| Betamethasone benzoate | 3.25 | 6.90 |
| Flumethasone pivalate | 3.00 | 5.65 |

[a] Moisturizer was sodium 2-pyrrolidone-5-carboxylate, 5% (w/w) of concentrate. [b] Sum of scores (*Tm*) divided by number of volunteers (10). The minimum significance range value $k = 3.86$ ($p = 0.05$); *i.e.*, if two formulations differ by more than 3.86, there is a significant difference between those formulations. Betamethasone valerate cream, 0.1%, gave total scores of 38 (moisturizer-treated arm) and 78.5 (water-treated arm).

for the diminution of steroid-induced blanching in the presence of sodium 2-pyrrolidone-5-carboxylate remains unresolved. This result could have been due to the effects of moisturizer within the vehicle and/or within the skin.

For example, sodium 2-pyrrolidone-5-carboxylate may have increased the solubilities of the steroids in the vehicle and/or reduced their thermodynamic activities by complexation, thus lowering the skin–vehicle partition coefficients, with consequent reduction in flux through the skin. (Preliminary work[13] indicated that the water solubility of the parent steroid, hydrocortisone, increased approximately twofold in the presence of 2-pyrrolidone-5-carboxylic acid.) The moisturizer may have altered the diffusional properties of corticosteroid molecules in the skin (*e.g.*, by an effect on skin structure, by binding of water, or by complex formation with the steroid).

In addition, sodium 2-pyrrolidone-5-carboxylate may have had an effect on shunt diffusion; it was suggested[14] that if the corticosteroids penetrated significantly *via* the hair follicles and/or down the ducts of the sweat glands, lower blanching responses in the presence of moisturizer might have been caused by partial constriction of the shunt routes by sodium 2-pyrrolidone-5-carboxylate. To investigate this possibility for sweat glands, a 5% (w/w) aqueous solution of the moisturizer was rubbed into one side of the forehead of one volunteer twice a day for 7 days, the other side being similarly treated with water. After 1 week, the volunteer exercised vigorously to perspire. There was no apparent difference in sweating between the moisturizer-treated and control halves of the forehead. However, when the procedure was repeated using undiluted moisturizer (*i.e.*, 50% aqueous solution of sodium 2-pyrrolidone-5-carboxylate), there seemed to be some reduction in the sweat flow. These results indicate that large amounts of moisturizer may have some vehicle effect on shunt pathways. However, more sophisticated techniques are required to elucidate the reduction of corticosteroid-induced blanching in the presence of sodium 2-pyrrolidone-5-carboxylate.

The present work investigated the possible pharmaceutical use of an aerosol quick-break foam. The foam concentrate together with the propellent gave a homogeneous system at room temperature. When the product was discharged from the container, the propellent vaporized; the foaming agent (nonionic emulsifying wax) crystallized due to a loss of solubilizer (*i.e.*, propellent) and a reduction in temperature to below that at which the foaming agent deposited. The precipitation of the wax from solution produced a foam that collapsed on the skin as the wax redissolved at skin temperature, foam destruction being accelerated by shearing.

In use, the product is expelled onto a limited skin area; the resultant foam breakage brings the homogeneous liquid into intimate contact with the skin surface. The liquid may be rubbed into the skin to leave a site that is dry, soft, and not sticky. The present work indicates that quick-break foams containing corticosteroids are highly active preparations as assessed by the blanching test. Drug bioavailability is good, so the steroid is readily available to the skin from a controlled-dosage, esthetically attractive, economic preparation. It should be possible to modify the basic formulation to optimize release of drug or moisturizer or to control the breaking characteristics of the foam. The quick-break foam should be a suitable vehicle for a wide range of topical corticosteroids and may be a useful delivery system for other medicaments, offering the prospect of a sterile preparation that will remain so during use.

[13] A. Cripps, School of Pharmacy, Portsmouth Polytechnic, Portsmouth, Hants., United Kingdom, unpublished observations.

[14] B. Poulsen, Syntex Research, Palo Alto, Calif., personal communication.

## REFERENCES


(1) H. I. Maibach and R. B. Stoughton, *Med. Clin. N. Am.*, **57**, 1253 (1973).

(2) J. J. Sciarra, *J. Pharm. Sci.*, **63**, 1815 (1974).

(3) J. F. L. Chester, *Soap Perfum. Cosmet.*, **40**, 393 (1967).

(4) B. W. Barry and R. Woodford, *Br. J. Dermatol.*, **91**, 323 (1974).

(5) *Ibid.*, **93**, 563 (1975).

(6) *Drug Cosmet. Ind.*, **116** (2), 36 (1975).

(7) H. L. Harter and M. D. Lum, Aeronautical Research Laboratories, USAF ARL 62-313, 1962, p. 1.

(8) A. Goldstein, "Biostatistics: An Introductory Text," Macmillan, New York, N.Y., 1964, p. 63.

(9) B. W. Barry and A. R. Brace, *J. Pharm. Pharmacol., Suppl.*, **26**, 67P (1974).

(10) K. A. Brownlee, "Statistical Theory and Methodology in Science and Engineering," Wiley, New York, N.Y., 1965, p. 504.


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