Potency Ranking of Two New Topical Corticosteroid Creams Containing 0.1 % Desonide or 0.05 % Halometasone Utilising the Human Skin Blanching Assay

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Summary: The human blanching assay was used to assess the potency of two new proprietary corticosteroid creams. The blanching abilities of 0.1 % desonide cream and 0.05 % halometasone cream were evaluated relative to the blanching elicited by 0.05 % clobetasol 17-propionate cream, 0.1 % betamethasone 17-valerate cream and 0.05 % clobetasone 17-butyrate cream. The results of the trial indicated that the 0.1 % desonide cream falls into the potent group of topical corticosteroid preparations and the 0.05 % halometasone cream falls into the moderately potent group.

Zusammenfassung: Wirkungsstärke von zwei neuen, 0.1 % Desonid oder 0.05 % Halometason enthaltenden Kortikosteroid-Cremes nach dem Bleichtest an menschlicher Haut
Key words: Corticosteroids, topical · Desonide, clinical studies · Halometasone, clinical studies · Skin, blanching

1. Introduction

The McKenzie/Stoughton [1] blanching assay has been extensively used since 1962 as a reliable method of assessing topical corticosteroid activity. The aim of this study was to investigate the blanching activities and, by inference, the clinical antiinflammatory efficacies of two corticosteroid-containing creams that were recently introduced onto the South African market. The two new proprietary creams, containing 0.1 % desonide or 0.05 % halometasone, were released onto the market without reference having been made to clinical efficacy, especially as compared to already available proprietary topical corticosteroid preparations.

The blanching activities of clobetasol 17-propionate cream [2-5] and betamethasone 17-valerate cream [2-7] have been extensively studied and reported and these two preparations have been classified in the United Kingdom Monthly Index of Medical Specialties (MIMS) [8] as very potent and potent, respectively. There do not appear to be any reports in the literature on the blanching ability of clobetasol 17-butyrate cream, although the ointment has been studied in blanching trials [9-12]. Clobetasol 17-butyrate cream has been used in numerous blanching trials in our laboratories and is classified as moderately potent in the United Kingdom MIMS [8]. The close correlation between the observed degree of blanching elicited by topical corticosteroids and their clinical antiinflammatory activities has been well documented [13-16] and it was therefore decided to mount a trial to investigate the comparative blanching abilities of the five abovementioned topical corticosteroid creams.

Desonide is a non-halogenated corticosteroid [14]. The absence of a halogen atom was for a time believed to produce topical corticosteroids with lower potential for side-effects, although this has since been refuted [17-20]. Clinical investigations have shown that 0.05 % desonide gave similar results to 0.025 % fluocinolone acetonide [21]. 0.1 % triamcinolone acetonide [14] and 0.1 % betamethasone 17-valerate [22], and that 0.1 % desonide cream was slightly more efficacious than 0.1 % betamethasone 17-valerate cream and equal to 0.1 % hydrocortisone 17-butyrate cream [23]. Blanching trials have further shown that desonide elicits a similar degree of blanching to triamcinolone acetonide [14, 22], fluocinolone acetonide [14], flurandrenolone [14] and betamethasone 17-valerate [14].

Halometasone is a relatively new trihalogenated corticosteroid [24]. There do not appear to be any reports in the literature referring to studies of the blanching activity of halometasone, although several clinical trials have been performed.

Halometasone ointment (0.05 %) was found to produce similar results to an ointment containing 0.25 % fluocortolone + 0.25 % fluocortolone caproate [25, 26], 0.025 % fluocortolone acetonide [26] and 0.05 % betamethasone dipropionate [26]. It is interesting to note that halometasone cream has been reported to be superior in clinical trials to 0.05 % clobetasol 17-propionate cream [27] while halometasone ointment was found to be less effective than 0.05 % clobetasol 17-propionate cream [26].

2. Materials, subjects and methods

The methodology of the McKenzie/Stoughton blanching assay [1] has been modified, discussed and reviewed by several researchers [28-31].

2.1. Topical preparations

All the creams used in this study were purchased shortly before the trial from a local pharmacy. Five creams were used, viz. 0.05 % clobetasol 17-propionate, 0.1 % betamethasone 17-valerate, 0.05 % clobetasol 17-butyrate, 0.1 % desonide and 0.05 % halometasone.

2.2. Subjects

A total of 12 healthy male and female Caucasian subjects were selected from a panel of volunteers known to show a response to a standard preparation (betamethasone 17-valerate cream) applied under occlusion for 6 h. All subjects had previously taken part in similar experiments and written informed consent was obtained from each subject. The volunteers were not using any form of systemic medication and had not received topical corticosteroids for at least 6 weeks prior to the investigation. Volunteers were further selected so that a range of blanching intensities could be observed within the group.

2.3. Method

The creams were applied to the flexor aspect of the forearm in four different arrangements, each application pattern being chosen randomly to avoid any bias during application and observation. Four stripes of the creams, equivalent to approximately 3.2 mg [6] were applied to fifteen 7 mm x 7 mm sites on each forearm of the volunteers in a double-blind fashion by means of 1 ml disposable syringes, the needles of which had been cut to about 5 mm in order to facilitate extrusion of the cream. The first gram of each cream of each tube was discarded so as to minimize any possible interaction between the closure and the formulation. The syringes were then filled immediately prior to application so as to minimize the possibility of any interaction between the corticosteroid and the plastic matrix of the syringe barrel. The 15 application sites were demarcated by applying self-adhesive labels, from which holes had been punched, onto each arm. The areas adjacent to the wrists and elbows were avoided, unless the subject had short forearms [28, 29]. The creams were evenly spread with a glass rod prior to occlusion or protection of the sites. All the sites on one arm of each volunteer were occluded while the sites on the other arm were left unoccluded. Occlusion was attained by means of individual strips of non-porous plastic tape (Blenderm Surgical Tape, 3M, Johannesburg, South Africa) placed over the self-adhesive labels and the sites that were left unoccluded were protected by plastic coverings designed so as to allow a free flow of air and held in place by Micropore Surgical Tape (3M). The residual cream, demarcating labels, plastic coverings and occlusive dressings were all removed 6 h after application. Assessment of the blanching responses was done independently by 3 experienced observers at several predetermined times which allowed the construction of blanching profiles and statistical analyses at a number of times over an extended period. Five creams applied to 15 sites on each forearm of 12 volunteers resulted in each cream being observed 108 times at each observation time in each mode of application. Observations were made at 7, 8, 9, 10, 12, 14, 16, 18, 28 and 32 h after application using a 0-4 scale where 0 = normal skin, 1 = slight blanching, 2 = more intense blanching, 3 = general even and distinct blanching and 4 = marked and very intense blanching.

The percentage of the total possible score (% TPS) was calculated [30] and plotted against time in h after application to produce the profiles shown in Fig. 1. The trapezoidal rule was employed to calculate the area under the blanching curve (AUC) values. The parameters used to obtain the AUC were the % TPS values and the time
3. Results and discussion

The blanching profiles of the 5 creams applied under occlusion are shown in Fig. 1 and the AUC values for both modes of application are given in Table 1. The blanching profiles for the unoccluded creams are not reproduced here, but were of similar shape to those seen in Fig. 1. The AUC values indicate a rank order of 0.05 % clobetasol 17-propionate > 0.1 % desonide > 0.1 % betamethasone 17-valerate > 0.05 % halometasone > 0.05 % clobetasone 17-butyrate, although these values should not be viewed in isolation, but rather with the blanching profiles and chi-squared analyses.

The main conclusions that can be drawn from this trial, with respect to the proprietary products used, are shown in Table 1. The 0.1 % desonide cream, in the occluded mode of application, elicited a similar blanching response to 0.1 % betamethasone 17-valerate cream, while in the unoccluded mode 0.1 % desonide cream elicited a superior blanching response to 0.1 % betamethasone 17-valerate cream. The results in the unoccluded mode showed statistically significant differences in favour of 0.1 % desonide cream throughout the period of the trial. The blanching profiles and %TPS values for 0.05 % clobetasol 17-butyrate and 0.05 % halometasone creams in both modes of application clearly indicated that 0.05 % clobetasol 17-butyrate cream had a more rapid onset of action than 0.05 % halometasone cream, which elicited a more intense blanching response in the latter half of the trial. Where significant differences were noted in the chi-squared analyses, they were in favour of the cream that showed more intense blanching (as depicted in Fig. 1).

4. Conclusions

The blanching profiles, AUC values and chi-squared analyses were not consistent between the two modes of analysis. Chi-squared analyses of the results in the unoccluded mode showed statistically significant differences in favour of 0.1 % desonide cream throughout the period of the trial. The blanching profiles and %TPS values for 0.05 % clobetasol 17-butyrate and 0.05 % halometasone creams in both modes of application clearly indicated that 0.05 % clobetasol 17-butyrate cream had a more rapid onset of action than 0.05 % halometasone cream, which elicited a more intense blanching response in the latter half of the trial. Where significant differences were noted in the chi-squared analyses, they were in favour of the cream that showed more intense blanching (as depicted in Fig. 1).

The importance of an extended observation period and of using more than one criterion to draw conclusions from the blanching elicited by topical corticosteroids is well illustrated in this trial. Several reports have recently appeared in the literature in which experimenters have drawn conclusions with respect to comparative blanching responses after a single observation of the degree of blanching. This practice disregards the rate of onset of blanching, the peak blanching response and the duration of action of the topical corticosteroid, and could therefore conceivably lead to an erroneous conclusion. The utilization of only one observation time would, in the comparison of 0.05 % clobetasol 17-butyrate and 0.05 % halometasone creams in this trial, have resulted in an inaccurate conclusion throughout the trial. The AUC is a useful biological parameter, but gives no indication of the rate of onset and the duration of action. It is therefore useful when assessing a blanching trial to utilize the AUC value (which cannot be obtained unless the trial is performed over an extended period) and some form of statistical analysis.

5. References

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