

Review Article

An overview of the efficacy of topical corticosteroids in experimental human nickel contact dermatitis

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We review controlled trials of corticosteroid effect in experimentally elicited acute nickel contact dermatitis in man, in the hope of clarifying optimal efficacy for clinical use. To maximize discrimination and objectivity, we focus on data with 1 well-characterized allergen, nickel, in studies utilizing bioengineering documentation. Higher potency corticosteroids are effective (unlike in experimental irritant contact dermatitis), but optimum schedules still require definition.

Key words: allergic contact dermatitis; corticosteroids; man; colorimetry; echography; laser Doppler flowmetry; transepidermal water loss; bioengineering methods; nickel. © Munksgaard, 2000.

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Allergic contact dermatitis (ACD) is an inflammatory disease for which topical corticosteroid therapy is widely utilized. Corticosteroids inhibit antigen-specific activation and proliferation of lymphocytes although their exact mechanism of action remains unclear (1, 2). We review studies that utilized bioengineering techniques to evaluate the efficacy of topical corticosteroid in human experimental nickel contact dermatitis, in the hope that these highly controlled experiments might provide insight into optimum therapy.

Application of allergen in sensitized patients elicits a standardized allergic contact dermatitis. Bioengineering instrumentation, such as laser Doppler flowmetry (LDF), colorimetry and echography, is useful in quantifying the skin's allergic response. LDF evaluates the intensity of the inflammatory reaction (3). Colorimetry assesses the blanching effect of corticosteroids (4). Echography evaluates edema and inflammation (5).

Overview

De Lacharriere et al. studied the effects of clobetasol propionate 0.05%, hydrocortisone 1% and an emulsion control on experimentally elicited nickel

ACD in 10 nickel-allergic patients (6). ACD was elicited by 2-day (D) patch test application of 5% NiSO₄ to the upper back. 1D following removal of nickel patches, the corticosteroids were occlusively applied for 6 h, evaluation of their efficacy occurring upon corticosteroid patch removal and again 18 h later. The corticosteroids produced a significant decrease in LDF (as well as an increase in transcutaneous pressure of oxygen) when compared to involved skin. As this was an abstract only, we do not know if they could distinguish between the compounds; this abstract also did not include the mass per unit area of corticosteroid applied.

Queille-Roussel et al. (7) investigated the efficacy of clobetasol propionate 0.05% cream, hydrocortisone 1% cream and a cream vehicle on ACD, elicited by a 2-D patch application of 5% NiSO₄ on the lower back of 12 nickel-sensitive volunteers. Open application of 26 mg/cm² of corticosteroids 2× daily for 4D (D 3-6) and 1× on the morning of D7 followed nickel patch removal. The effect of corticosteroids was evaluated on the evening of D7. Clobetasol propionate 0.05% cream significantly decreased LDF, colorimetry and visual score values, when compared with untreated skin

Table 1. Efficacy of corticosteroids on nickel dermatitis: comparison of experimental design

	De Lacharriere et al. (6)	Queille-Roussel et al. (7)	Seidenari et al. (8)	Di Nardo et al. (9)	Seidenari et al. (10)
<i>n</i> sample size	10	12	10	22	16
patient population	nickel-allergic volunteers	nickel-allergic volunteers	nickel-allergic volunteers	nickel-allergic volunteers	nickel-allergic volunteers
age (years) distribution	?	21–38	18–45	18–45	avg age: 35±8
sex distribution	?	1 man 11 women	0 men 10 women	0 men 22 women	2 men 14 women
allergen utilized	5% NiSO ₄	50 mg 5% NiSO ₄	20 mg 5% NiSO ₄	40 mg 5% NiSO ₄	40 mg 5% NiSO ₄
duration of allergen application	48 h	48 h	16 h	16 h	16 h
method of exposure	Leucotest	large Finn Chamber (diameter 11 mm)	large Finn Chamber (diameter 11mm)	large Finn Chamber (diameter 11mm)	large Finn Chamber (diameter 11mm)
locus of exposure	upper back	lower back	right volar forearm	left volar forearm	both volar forearms
corticosteroid formulations tested	1. clobetasol propi- onate 0.05% 2. hydrocortisone 1% 3. W/H emulsion control	1. clobetasol propi- onate (CP) 0.05% cream 2. hydrocortisone 1% cream 3. skinbase cream vehicle	1. clobetasol propi- onate 0.05% cream 2. flucinolone ace- tonide 0.025% cream 3. clobetasone bu- tyrate 0.05% cream	1. hydrocortisone acetate 0.5% cream (HA) 2. clobetasone bu- tyrate 0.05% cream (CB) 3. clobetasol propi- onate 0.05% cream (CP) 4. mometasone fu- roate 0.1% cream (MF)	1. hydrocortisone acetate 0.5% cream (HA) 2. clobetasone bu- tyrate 0.05% cream (CB) 3. clobetasol propi- onate 0.05% cream (CP)
area of cortico- steroid application	unknown area	26 mg/cm ²	105 mg/cm ²	105 mg/cm ²	42 mg/cm ²
duration of corti- coid treatment	1 D 6 h	2× daily for 4 D 1 application on D5	1× daily for 2 D	1× daily for 2 D	1× daily for 2 D
method of exposure	occlusion	open application	occlusion	occlusion	occlusion
method of clinical evaluation	LDF TEWL tc PO ₂	LDF TEWL colorimetry visual grade	visual grade echography	echography	echography
	Compared with involved skin:	Compared with untreated skin and other formulations:	Compared with untreated skin:		
efficacy of cortico- steroid	• decrease in LDF and increase in tc PO₂ • decrease in TEWL at 6 h but higher than uninvolved skin	• decrease in LDF, colorimetry and visual score with CP • no change in TEWL with CP • no significant change of any parameter with other formulations	• graded decrease in visual score, hypoechogenic area and skin thickness* in accordance with potency of steroid at 64 h	• graded decrease in hypoechogenic area and skin thickness in accordance with potency of steroid at 64 h** for CB, CP and MF • no significant change for HA	• graded decrease in hypoechogenic area in accordance with potency of steroid at 6 h for CB and CP • no significant change for HA

* Values increased when compared with baseline measurements, but increased significantly less than the untreated site. Hypoechogenic area measurements were more sensitive in distinguishing between steroids of different potency than skin thickness measurements.

** no statistical difference when comparing MF and CB.

and with the other formulations. There was no significant change with application of hydrocortisone 1% cream or the cream vehicle. Transepidermal water loss (TEWL) did not significantly change with any of the formulations.

Seidenari et al. (8) studied the effectiveness of clobetasol propionate 0.05% cream, flucinolone acetone 0.025% cream and clobetasone butyrate 0.05% cream on ACD (8), elicited by 16-h patch application of 5% NiSO₄ on the right volar fore-

arm of 10 nickel-allergic volunteers. 105 mg per/cm² of corticosteroids were occlusively applied at 16 h and 40 h following nickel application. Evaluation using echography and visual score was performed 64 h after nickel application and 30 min after removal of patches. Significant decreases by both echography and visual score were observed when compared with untreated skin sites. The decreases positively correlated with the potency of the corticosteroid tested.

Di Nardo et al. (9) investigated the effectiveness of hydrocortisone acetate 0.5% cream, clobetasone butyrate 0.05% cream, clobetasol propionate 0.05% cream and mometasone furoate 0.1% cream on ACD, elicited by 16-h patch application of 5% NiSO₄ on the left volar forearm of 22 nickel-sensitive subjects. 105 mg/cm² of corticosteroids were occlusively applied at 16 h and 40 h following nickel application. Evaluation with echography was performed 64 h after nickel application and 30 min after removal of patches. Compared with untreated skin, they found significant decreases by echography for clobetasone butyrate, clobetasol propionate and mometasone furoate. The decreases positively correlated with the potency of corticosteroid tested. Hydrocortisone acetate did not differ from control.

In 1997, Seidenari et al. (10) applied 5% NiSO₄ to 16 nickel-sensitive patients to elicit ACD. 42 mg/cm² of corticosteroids were occlusively applied 16 h and 40 h following nickel application. Their efficacy was evaluated by echography 64 h following nickel application, 30 min after removal of patches. Clobetasone butyrate and clobetasol propionate produced significant decreases by echography, which correlated with the potency of the corticosteroids. Hydrocortisone acetate did not differ from control.

Discussion

The reviewed investigations occlusively applied NiSO₄ in nickel-sensitive patients to elicit ACD. Corticosteroids were applied only after the allergic reaction was elicited. Studies in which corticosteroids were applied before or concomitant with the allergic reaction were excluded (11–18). The studies differed in their duration of treatment, method of clinical evaluation and selection of controls.

15% of women and 1% of men are affected by nickel dermatitis (19–21). The higher prevalence of nickel dermatitis in women explains the heavily weighted sex distribution among the patient population in these studies. Testing individuals with ACD to haptens other than nickel would reduce this possible sex bias. Furthermore, it would assess

corticosteroid efficacy in the treatment of a variety of allergic reactions.

The studies exhibited great variation with regard to the amount of corticosteroid applied (range between 26 mg/cm² and 105 mg/cm²). Excessive or insufficient cream may affect corticosteroid efficacy. Further investigation is required to determine the optimal mass of corticosteroid per unit area.

De Lacharriere et al. (6), Seidenari et al. (8, 10) and Di Nardo et al. (9) compared the effect of corticosteroid to sensitized, untreated skin. They did not include a vehicle control. It is important to evaluate corticosteroid efficacy by comparing to vehicle as well as to untreated skin. The corticosteroid vehicle potentially affects the allergic response of the skin, as measured via bioengineering instrumentation and visual score (7, 38). Only Queille-Roussel et al. (7) compared to vehicle control and involved skin, and found a significant corticosteroid reduction in allergic response.

TEWL is a measure of skin water barrier function (22, 23). Though useful in irritant reactions focusing on the stratum corneum, it is not as sensitive a measure for evaluating allergic reactions. In a study by Serup & Staberg (24) there was no change in TEWL 24 h following elicitation of an allergic reaction (24), although TEWL increased significantly upon irritation. 48-h measurements indicated an increase in TEWL only in strongly allergic reactions. Additionally, in the study of De Lacharriere et al. (6), TEWL was an indiscriminate measure of ACD. Other testing modalities, such as laser Doppler flowmetry, colorimetry, and echography, are more appropriate.

Each of these bioengineering techniques has its limitations. Laser Doppler flowmetry shows decreased sensitivity in ranking the blanching potential of corticosteroids when compared to visual score (25, 26). As such, LDF may overestimate low-intensity reactions (27, 28). An improved reflectance spectroscopic (RS) technique allows separation of cutaneous hemoglobin content into arterial oxygenated and venous deoxygenated hemoglobin components. RS is equally sensitive to visual score in estimating the blanching effect of corticosteroids (3).

Colorimetry can be used to measure the blanching potential of corticosteroids. However, this technique does not evaluate the decrease in edema resulting from topical application of corticosteroid. Extending the vasoconstrictor assay to include clinical effect, several studies claim that the corticosteroid-provoked blanching quantified by LDF and colorimetry directly correlates with level of clinical efficacy (29–31). However, the vasoconstrictor assay may not allow detection of small

clinical differences in reduction of inflammation (32).

Echographic evaluation assumes that increased inflammation and edema will result in increased skin thickness and hypoechogenic area (8, 10). Accordingly, the decrease should be positively correlated with the potency of corticosteroid tested. However, echographic evaluation is not sensitive enough to evaluate the efficacy of low-potency corticosteroids: in the reviewed studies there was no significant difference between hydrocortisone acetate and untreated skin (9, 10). The echographic technique is also influenced by the timing of corticosteroid application and the test site (5, 33).

Occlusive application of corticosteroid in vivo is a widely employed method of evaluating experimentally elicited ACD. However, skin occlusion may result in pH change, moisture accumulation and bacterial growth (34, 35). Open application reduces these potential sources of error and provides a clinically more realistic environment.

Corticosteroid application may lead to adverse local and systemic side-effects, such as cutaneous atrophy, induction of allergic contact dermatitis, and potential reduction in response of the adrenal cortex and hypothalamic-pituitary axis to stress (2, 36). We should be motivated to find more selective treatments of ACD as we make advances regarding molecular events in the immune system. Meanwhile, open application testing of several corticosteroids on allergen-sensitive subjects would aid in determining the clinical efficacy of corticosteroid in relieving ACD in man. Examination of the clinical effect of corticosteroids using a combined approach – visual score, echography, colorimetric and blood flow measurements – would reduce bias associated with 1 device and would present a more accurate clinical picture. These controlled experiments show topical corticosteroids to be effective in the suppression of experimental ACD in man. This is opposed to what appears to be the case in irritant contact dermatitis (37).

We would not wish to overgeneralize the results of these experiments with 1 metal to all allergens and the more complex clinical situations seen in clinical practice (often with a combination of endogenous factors and irritation). Nevertheless, taken together, the experimental observations suggest that hydrocortisone (the standard over-the-counter corticosteroid) is ineffective in this model, while more potent corticosteroids are beneficial. The optimal dose (concentration), dosing schedule ($\times$ daily) and effect of time after onset of treatment require further elucidation. The experiments reviewed here provide the basis for refined experi-

mental design and power calculations for such investigations.

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