Can an imidazolidinyl urea-preserved corticosteroid cream be safely used in individuals hypersensitive to formaldehyde?

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Summary

Background A topical corticosteroid preparation on the Swedish market, Flutivate® cream, contains a fairly high concentration of formaldehyde.

Objectives To determine the clinical relevance of contact allergy to formaldehyde when treating an allergic eczema with the formaldehyde-containing topical corticosteroid preparation Flutivate® cream.

Methods In a randomized, dubble-blind study seven patients hypersensitive to both formaldehyde and nickel repeatedly applied Flutivate® cream containing formaldehyde or Betnovate cream not containing formaldehyde to areas of experimentally induced nickel

dermatitis. Seventeen controls allergic to nickel, but not formaldehyde went through the same procedure.

Results In twenty-nine per cent of the formaldehyde-allergic individuals the experimental dermatitis healed when treated with Flutivate® cream compared to seventy-two per cent of the controls. (P = 0·04, Fisher's exact test, one-sided).

Conclusion An individual hypersensitive to formaldehyde should not use Flutivate® cream on dermatitis skin.

Key words : Formaldehyde, Flutivate® cream, experimental eczema, pharmaceutical, contact allergy, imidazolidinyl urea, repetitive usage test

In the 1980s an investigation was conducted on the content of formaldehyde (FA) in corticosteroid preparations on the Swedish market.[1] In 2002 we undertook a similar study, where 73 topical corticosteroid preparations available on the Swedish Market (October 2002) were analyzed for the presence of FA.[2] We found FA in 5 creams and 1 ointment. The preparation that by far contained the highest concentration of FA was Flutivate® cream, i.e. 178 microgram/g (GlaxoSmithKline AB, Mölndal, Sweden). The reason for this is probably that Flutivate® cream contains a FA-releasing biocide, imidazolidinyl urea, even if some other FA sources also are possible.

The question whether the presence of FA in Flutivate® cream has any significance for individuals allergic to FA was raised by us, and as a consequence, a repetitive usage test was undertaken in a randomized and double-blind way. As corticosteroids are used on inflamed

skin therapeutically, a repetitive usage test with a relevant corticosteroid is best performed on such skin. In the present study, 24 individuals allergic to nickel, seven of whom were also allergic to FA, had a nickel allergic contact dermatitis experimentally induced, which was treated with either Flutivate® cream or Betnovate® cream (GlaxoSmithKline AB, Mölndal, Sweden), another corticosteroid of the same potency but not containing FA.

Materials and methods

Subjects

Twenty-four dermatitis patients, all women, hypersensitive to nickel sulphate, as demonstrated by patch testing with the European standard series, were included in the study. Seven of these were also hypersensitive to FA, as demonstrated previously by patch testing with the European standard series. None of the 24 was hypersensitive to chlorocresol, contained in Betnovate® cream or propylene glycol, contained in Flutivate® cream as demonstrated by negative patch testing to these 2 substances. The nickel-allergic individuals without FA allergy were chosen as controls.

The mean age of the patients without FA allergy was 45·7 years, median 46 years (range 26-69), while the corresponding figure for the patients with FA hypersensitivity was 49·9 years, median 55 years (range 27-64).

The study was approved by the Ethical Committee, Lund University, and the 24 patients gave written consent prior to inclusion.

Experimental allergic contact dermatitis

Prior to the provocation of the experimental allergic contact dermatitis, the patients were patch tested with a serial dilution of nickel sulphate to determine the degree of reactivity at the time. An aqueous stock solution of nickel sulphate ($NiSO_4 \cdot 6H_2O$; Merck, Darmstadt, Germany) at 12·5 % w/v was prepared, and further serially diluted 2·5-fold down to 0·0032 %

w/v. Each patient was tested with 10 consecutive serial dilutions of nickel sulphate from 12·5 to 0·0032 %.[3] Our department has long experience in testing aqueous nickel sulphate solutions at a concentration of 12·5 % w/v (in combination with the volume used, 15 µL, i.e. 30µL test solution/cm^2) without eliciting irritant reactions.[3] They were also patch tested to 4-chloro-3-cresol 1·0% petrolatum (pet) w/w and propylene glycol 5·0% pet w/w (both from Chemotechnigue Diagnostics, Tygelsjö, Sweden). The 7 patients allergic to FA were also patch tested to FA in serial dilutions. An aqueous stock solution of FA (ACROS Organics, Geel, Belgium) at 2·0 % v/v was prepared, and further serially diluted 2·0-fold down to 0.0156 % v/v. Each FA-allergic patient was tested with 8 consecutive serial dilutions of FA from 2·0 to 0·0156 %. Fifteen microlitres of the respective solution (nickel sulphate and FA) were micropipetted on to filter paper discs of small Finn Chambers (Epitest Ltd Oy, Tuusula, Finland) on Scanpor (Norgesplaster A/S, Vennesla, Norway). The petrolatum preparations were also tested in the same system. The tests were applied to the upper part of the back and left for 48 h. Tests were read by one of us (who did not participate at all in the reading of the repetitive usage tests) according to the guidelines of the International Contact Dermatitis research Group (ICDRG).[4]

Immediately after reading the serial dilutions of nickel sulphate, an experimental allergic contact dermatitis was provoked on the outer part of both upper arms. To this purpose, a 6 × 7 cm filter paper (Munktell Filter, Grycksbo, Sweden) was attached to the inner surface of a single 8 × 9 cm hydrocolloid wound dressing (Duoderm Hydroactive™ Bandage, Convatec Ltd., Deeside, UK). One milliliter of the nickel sulphate test solution with the lowest concentration resulting in a ++ reaction (according to ICDRG criteria) was micropipetted on to the filter paper, implying 23·8 µL test solution/cm^2. The hydrocolloid dressing test was then placed on the outer part of both upper arms in all 24 patients. An adhesive tape (Mefix, Mölnlycke, Sweden) secured the hydrocolloid dressing test and the test material was left on

the skin for 48 h. On day 3 the patient returned for evaluation. The reactions were scored according to ICDRG criteria with two classifications added between the three usual positive gradings: strong + and ++ reactions were graded as +(+) and ++(+), respectively. The different steps, including the intermediate steps were defined as follows: +, erythema, infiltration (referred to as weak in the text); +(+), erythema, infiltration, a few papules (referred to as moderately weak); ++, erythema, infiltration, papules (referred to as moderate); ++(+), erythema, infiltration, papules and a few vesicles (referred to as moderately strong); +++, intensive erythema, infiltration, vesicles (referred to as strong).

In 13 individuals both arms had the same grading before the repetitive usage test and in the rest, no systematic difference in the severity of the experimental eczema with reference to treatment with one or the other corticosteroid was seen.

The details of the study are shown in Table 1.

Repetitive usage test

The 24 patients were randomized to receive one of two different treatments with creams on each experimentally induced allergic contact dermatitis site. The treatment regimes are detailed in Table 1. The Flutivate® cream containing the potent corticosteroid fluticasone propionate 0·05% w/w contained FA whereas the Betnovate® cream containing the potent corticosteroid betamethasone valerate 0·1% w/w did not contain FA.

Both corticosteroids have the same potency and are intended to be used b.i.d. Betnovate® cream does not contain a FA-releasing preservative but contains 4-chloro-3-cresol. The corticosteroid tubes were blinded, i.e. creams intended for treatment of the eczema on the left arm were marked with red tape and the creams to be used on the right arm were marked with blue tape. Each patient thus received 2 tubes weighing 100g on day 6 when treatment started. Each tube was weighed before and after the repetitive usage test was finished. Each allergic contact dermatitis site was treated with the respective cream twice daily by the patient by

applying the cream with a bare fingertip, rubbing it in and covering the whole area. The patients were instructed to wash their hands thoroughly after each application session. They were evaluated twice weekly for 3 weeks by an observer who did not know to which group the patient was allocated, or whether the patient was allergic to FA or not. A final check-up was made after 4 weeks at the latest or one week after both dermatitis sites had healed. (The follow-up time was shorter than 4 weeks if both dermatitis sites of each patient had healed before the three weeks had passed.)

Statistical evaluations

Results were analyzed for statistical significance using Fisher's exact test and McNemar' s test and classified as significant when $P < 0{\cdot}05$.

Results

All 24 tested negatively to chlorocresol and propylene glycol. Table 1 shows the outcome of the repetitive usage test in the 24 patients. In two of seven patients hypersensitive to FA (29%) the nickel eczema healed completely when treated with Flutivate® cream compared to twelve of seventeen (72%) of the controls ($P = 0{\cdot}04$, Fisher's exact test, one-sided).

When comparing the healing of the experimental eczemas in the FA-allergic patients treated with either Betnovate® cream or Flutivate® cream, there was no statistical difference, ($P = 0{\cdot}24$, McNemar's test).

There was no deterioration of the experimental eczema in any of the patients or controls at any of the examination days or at the check-up one week after the final application of the respective corticosteroid cream. In Table 2 the results of the patch testing with FA in serial dilutions are shown. There was no correlation between the FA-reactivity and the tendency to healing in the FA-allergic patients treated with Flutivate® cream. The test reactivity for nickel

in the 24 individuals was calculated as the lowest concentration eliciting at least a + reaction and registered as the minimal eliciting concentration. There were no differences in patch test reactivity between those with and without FA-allergy.

The amount of applied cream varied inter-individually with a mean amount of 209 mg Flutivate® cream per application in the 17 controls (range 92-393), while the mean amount in the seven FA-allergic patients was 356 mg per application (range 30-1132). As there was one out-lineroutlier (pat. no. 5, 1132 mg), subtraction of this figure from the total sum of doses per application, will give a mean of 227 mg, i.e. no difference from the controls.

Discussion

Usage tests have two main applications: (i) in individual patients to determine if a demonstrated contact allergy is clinically relevant, particularly if a product containing the sensitizer patch tests negatively, and (ii) in the risk assessment of certain chemicals or products like perfume or methylchloroisothiazolinone/methylisothiazolinone when the usage test must be performed in a controlled way including many patients sensitized to the allergen under investigation and control patients not sensitized to the particular allergen. [5]

The repeated open application test (ROAT) was designed to be used on intact skin with the offending chemical.[6] In a study on deodorants and fragrance sensitivity, the importance of the anatomical site where such usage tests should be performed, was stressed, i.e. products should be tested in a manner that resembles the natural use situation as much as possible.[7] When dealing with corticosteroid treatment, the natural use situation is on compromised skin. A positive ROAT in an individual patient documents that the tested product can cause eczema, but not the mechanism of the adverse reaction,[6] and a negative use test indicates that the contact allergy and the exposure is not clinically relevant, at least with regard to the prevailing ROAT exposure conditions. On the other hand, a negative ROAT with a corticosteroid on intact skin does not exclude a clinically relevant contact allergy, as a corticosteroid is used

almost exclusively on diseased skin. Therefore, to perform usage tests with a corticosteroid you need (calls for) compromised skin and inducing an experimental eczema on sensitized patients is one such model. Any sensitizer could have been used to provoke an experimental dermatitis. The reason for choosing nickel sulphate was the accessibility of control patients with nickel allergy, previous experience with such experimental nickel sulphate eczemas,[8] and first and foremost the fact that the patients allergic to FA were also allergic to nickel sulphate. As a corticosteroid exerts its intrinsic anti-inflammatory action it may not be foreseeable to what extent this action will interact and influence a dermatitis in a FA-hypersensitive individual treated with the incriminating FA-containing corticosteroid cream for a prolonged time. Theoretically, there are three options even if the first is not very plausible: (i) the eczema may deteriorate and spread; (ii) the eczema may heal but the healing phase may be prolonged; or (iii) the eczema may heal in a way indistinguishable from the healing of eczema in a non-hypersensitive person. To enable assessment of these options, a moderate dermatitis was to be induced on both arms, because an experimental contact dermatitis should permit both an improvement and a deterioration when performing a repetitive usage test. To significantly substantiate an allergic mechanism behind a positive use test, we tested the sensitizer under investigation in a matched (gender and age) control group of non-sensitive eczema patients. The check-up one week after the final application of the respective cream was inserted to exclude a deterioration of any prevailing dermatitis or flare-up of a previously healed dermatitis in the FA-allergic patients once the anti-inflammatory effect of the corticosteroid had vanished.

The purpose of the study was to investigate whether a concentration around 200 ppm of FA present in a corticosteroid preparation is of any importance when treating compromised skin in a subject hypersensitive to FA. Furthermore, there is another question concerning the possible presence of FA in a corticosteroid preparation, as FA besides being a contact

sensitizer also is an irritant. To our knowledge, there have been no studies investigating this. However, the design of the present study, with a control group using two types of corticosteroids with and without FA, enables exploration of this issue. The results from the control group speak against this theory, required that the doses of Flutivate® cream applied did not significantly differ between the two groups, which they did not when correcting for the outlineroutlier.

The wide range of doses used among the different participants shows the difficulty in standardizing the application dose, even if each individual was told to use an amount of cream that would only cover the 6×7 cm dermatitis site in a way one would use a topical corticosteroid preparation. All 24 participants were dermatitis patients and as such they were used to applying corticosteroids. Instructions to use an exact string-length of each cream would probably have given a more even amount used, but as we wanted to mimic the normal use situation for each patient we did not apply that instruction. In an experimental provocation study using deodorants, significant interindividual differences in amounts used were seen, probably due to variations in application area and dose, as the patients were told to use the deodorants as they normally would normally.[7] Furthermore, there was no systematic difference between the two groups in the difference between the amount used of the respective corticosteroid cream used. In the seven FA-allergic patients, four individuals used more Flutivate® cream and three used more Betnovate® cream per application whereas in the control group, ten individuals used more Flutivate® cream and six used more Betnovate® cream per application and one used exactly the same amount of both corticosteroids.

Also, the patch test reactivity to nickel did not differ between the two groups, and even if they had, consideration of the test reactivity was taken when choosing the nickel concentration to induce the experimental eczema.

In the FA-allergic patients, we did not see any correlation between the FA-reactivity and the tendency to healing of the dermatitis treated with Flutivate® cream.

The present investigation is the 3rd randomized, double-blind study where a repetitive usage test has been performed on inflamed skin.[9] For products intended to be used on compromised skin, the only group that seems to have used this approach is our group. Using a common sensitizer like nickel to induce an experimental eczema in individuals sensitive to nickel worked well. From earlier experience we knew that an experimental nickel-allergic eczema will heal during treatment with a corticosteroid the patient tolerates as opposed to an experimental eczema induced by sodium laurylsulphate, which behaved differently when treated with a corticosteroid. Therefore we suggest, that whenever a repetitive usage test is planned on "sick skin" with a corticosteroid product containing a sensitizer, a simple allergen such as nickel, common to all study subjects, should be used instead of an irritant, even if it may be tempting to use the latter, since recruting patients with a common contact allergy always limits the amount of study subjects.

From this study we can conclude that Flutivate® cream should not be used on dermatitis skin in individuals allergic to FA. Even if not causing aggravation of the experimental eczemas when treatment with Flutivate® cream started, there was a prolonged/prevented healing.

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Legends

Table 1. The 24 patients and the gradings of their experimentally induced contact dermatitis from nickel sulphate on the left (L) and right (R) arm before the repetitive usage test (RUT), the RUT regimen, the number of treatments, the calculated mean amount of applied corticosteroid cream per application, and whether there was healing or not.

Patient	Treated side	Grading before RUT	RUT regimen	No. of treatments	Calculated mean amount per application (mg)	Healing
1	L	Moderate	B	49[a]	21	x
	R	Moderate	F	49	30	
2	L	Strong	B	31	351	x
	R	Strong	F	43	413	
3	L	Strong	B	43	180	
	R	Strong	F	43	173	
4	L	Moderate	B	43	149	
	R	Strong	F	43	371	
5	L	Weak	F	9	1132	x
	R	Moderately weak	B	9	1451	x
6	L	Strong	F	43	255	
	R	Strong	B	43	263	
7	L	Moderate	F	37	118	x
	R	Moderate	B	23	117	x
8	L	Strong	B	23	273	x
	R	Moderate	F	23	259	x
9	L	Moderate	B	23	118	x
	R	Moderate	F	23	240	x
10	L	Weak	B	17	121	x
	R	Moderate	F	43	393	

11	L	Moderate	B	17	94	x
	R	Moderate	F	17	96	x
12	L	Moderately weak	B	23	124	x
	R	Weak	F	23	92	x
13	L	Moderately strong	B	37	232	x
	R	Strong	F	42	204	
14	L	Weak	B	9	266	x
	R	Weak	F	17	196	x
15	L	Moderate	B	30	124	x
	R	Moderately weak	F	30	99	x
16	L	Moderate	B	23	126	x
	R	Moderate	F	23	157	x
17	L	Moderately strong	F	43	255	
	R	Moderately strong	B	43	175	
18	L	Strong	F	29	276	x
	R	Moderately weak	B	13	157	x
19	L	Moderate	F	31	240	x
	R	Weak	B	17	224	x
20	L	Moderate	F	17	163	x
	R	Moderate	B	29	97	x
21	L	Strong	F	43	144	x
	R	Strong	B	43	129	x
22	L	Strong	F	43	266	
	R	Strong	B	43	267	
23	L	Weak	F	17	242	x
	R	Moderate	B	45	223	
24	L	Strong	F	43	239	
	R	Moderately strong	B	43	239	

F, Flutivate® cream; B, Betnovate® cream; Patients 1-7 are those with hypersensitivity to FA.
[a]This patient did not appear after 3 weeks but came on the 4th week and the check-up was on the 5th week.

Table 2. Results of patch testing to FA in seven FA-allergic individuals.

Formaldehyde conc. %	Pat no.	1	2	3	4	5	6	7
2.0		+	+++	+++	++	+++	+++	+++
1.0		(+)	+++	++	(+)	+	+++	+++
0.5		-	++	(+)	(+)	(+)	+++	++
0.25			++	-	-	(+)	+++	++
0.125			-			(+)	+++	+
0.0625						(+)	(+)	-
0.0312						(+)	++	
0.0156						(+)	(+)	

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