

Relevance and reproducibility of patch-test reactions to corticosteroids

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We present our patch test findings with dermatocorticosteroids during the period 1995–1999. We retrospectively studied the % of doubtful and positive reactions to each allergen in our corticosteroid series and assessed the relevance of these reactions. To assess reproducibility, we retested 15 patients with doubtful or positive reactions in 1999. The % of + or ++ reactions on D2–D3 and D7 ranged from 0.0% to 0.9% for most of the compounds tested. Hydrocortisone acetate 1% alc.abs./DMSO 50/50 showed a much higher % of positive reactions. Most of these reactions were not relevant and therefore probably due to the irritant nature of the vehicle. An overall reproducibility of 47.2% was obtained. 100.0% of the non-reproducible patch test reactions were not relevant. Definite relevance was much higher in the reproducible + or ++ reactions than in the reproducible doubtful reactions: 100.0% and 18.2%, respectively. We conclude that the mean % of + and ++ reactions to the corticosteroid series on D2–D3 is 0.5%, with an overall reproducibility of 47.2%. Tixocortol pivalate and budesonide proved to be important markers for dermatocorticosteroid allergy.

Key words: corticosteroids; patch-testing technique; reproducibility; retesting; clinical relevance; medicaments; tixocortol pivalate; budesonide; cross-sensitivity; contact allergy. © Munksgaard, 2001.

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Contact sensitization to dermatocorticosteroids is considered to be a relevant clinical problem (1, 2). The prevalence of positive patch tests is high, though varies between studies (3). Retesting of positive reactions shows concordance depending on the score of the positive reaction (4). In contact allergy to topical corticosteroids, not only the patch test reactions but also the clinical picture can be deceptive. We studied the relevance of doubtful and positive patch test reactions to corticosteroids, in order to interpret the patch test results better. Moreover, we studied the reproducibility by retesting positive tests, and related (non)concordance to the relevancy of the tests.

Materials and Methods

The clinical relevance of doubtful and positive patch test reactions to dermatocorticosteroids tested from 1995 till 1999 in the Department of Dermatology of the University Medical Center Nijmegen, The Netherlands, was assessed by interviewing the tested patients. Special emphasis was put on the question whether avoiding the specific

(putative) allergen (and cross-reacting chemicals) had made any difference to the severity of their dermatitis. We categorized the relevance of the positive patch test reactions as definite, probable, possible or none (5). The corticosteroids that tested during that period are listed in Table 1. The patch test vehicle for hydrocortisone acetate (DMSO/alc.abs. 50/50) was also patch tested, because of the reported high rate of positive reactions, probably caused by the irritant nature of the vehicle (6).

We also retested 15 patients with positive reactions in 1999, to assess the reproducibility of doubtful and positive reactions. Patch testing was done using Van der Bend chambers affixed with Fixomull stretch tape. Tests were removed after 2 days (D) and results read according to ICDRG guidelines at D2, D3 and D7.

Results

Table 2 shows the dermatocorticosteroids tested, the number of patients tested with each substance (budesonide and tixocortol pivalate are also tested

Table 1. Dermatocorticosteroids tested in the period 1995–1999

Test compounds:

betamethasone dipropionate 1% alc. abs.
 budesonide 0.1% pet.
 clobetasol-17-propionate 1.0% pet.
 desoximetasone 1% alc. abs.
 dexamethasone 1% alc. abs.
 hydrocortisone 1.0% pet.
 hydrocortisone acetate 1% DMSO/alc.abs. 50/50
 hydrocortisone-17-butyrate 0.1% pet.
 prednisone 1% alc. abs.
 prednisolone 1.0% pet.
 tixocortol pivalate 1.0% pet.
 triamcinolone acetonide 0.1% pet.
 betamethasone-17-valerate 0.12% pet.
 DMSO/alc.abs. 50/50

in our additional series, explaining the higher number of tested patients), the number and % of doubtful reactions and + or ++ positive reactions on D2-D3 and on D7. The number and % of estimated relevancy is also shown. The % of + or ++ reactions on D2-D3 and D7 ranged from 0.0% to 0.9% for most of the compounds tested. 2 out of the 14 compounds tested produced significantly higher %s of positive reactions: hydrocortisone acetate 1% DMSO/alc.abs. 50/50 and the vehicle

DMSO/alc.abs. 50/50: 6.1% and 5.2%, respectively, on D2-D3.

We found cross-reactions primarily within certain groups of corticosteroids: 4 cross-reactions between hydrocortisone, tixocortol pivalate and budesonide; 1 cross-reaction between betamethasone dipropionate, dexamethasone and budesonide and 1 cross-reaction between clobetasol-17-propionate, hydrocortisone-17-butyrate and budesonide. We had 2 cross-reactions between budesonide and tixocortol pivalate; 1 cross-reaction between budesonide and prednisone and 1 cross-reaction between budesonide and triamcinolone acetonide.

After retesting the 15 patients with positive reactions in 1999, we compared the sequential test results (Table 3). If a doubtful or positive reaction to a test substance was obtained in 1999, but not in 2000, the result was regarded as nonreproducible. We found an overall reproducibility of 47.2% (17 of the 36 reactions in 1999 were reproducible).

We found 100.0% of the nonreproducible patch test reactions to be not relevant. The definite relevance was much higher in the reproducible + or ++ reactions than in the reproducible doubtful reactions: 100.0% and 18.2%, respectively.

On retesting we found 5 new doubtful reactions,

Table 2. Our corticosteroid series, the number of patients tested with each allergen, the number and % of doubtful reactions and + or ++ positive reactions on D2-D3 and on D7 and the number and % of estimated relevance

Test compound	Tested patients	Doubtful reactions on D2-D3		+ or ++ reactions on D2-D3		+ or ++ reactions on D7		Estimated relevancy of + or ++ reactions			
		#	%	#	%	#	%	definite	probable	possible	none
betamethasone dipropionate 1% alc.abs.	220	9	4.1	1	0.5	2	0.9	2/2 (100.0%)	—	—	—
budesonide 0.1% pet.	1760	26	1.5	11	0.6	4	0.2	5/11 (45.4%)	5/11 (45.4%)	—	1/11 (9.2%)
clobetasol-17-propionate 1.0% pet.	215	8	3.7	1	0.5	1	0.5	—	1/1 (100.0%)	—	—
desoximetasone 1% alc.abs.	210	11	5.2	0	0.0	0	0.0	—	—	—	—
dexamethasone 1% alc.abs.	213	7	3.3	1	0.5	1	0.5	—	1/1 (100.0%)	—	—
hydrocortisone 1.0% pet.	218	3	1.4	2	0.9	2	0.9	—	2/2 (100.0%)	—	—
hydrocortisone acetate 1% DMSO/alc.abs. 50/50	294	22	7.5	18	6.1	10	3.4	2/18 (11.1%)	2/18 (11.1%)	2/18 (11.1%)	12/18 (66.7%)
hydrocortisone-17-butyrate 0.1% pet.	216	4	1.9	1	0.5	1	0.5	—	—	1/1 (100.0%)	—
prednisone 1% alc.abs.	216	1	0.5	1	0.5	1	0.5	1/1 (100.0%)	—	—	—
prednisolone 1.0% pet.	216	1	0.5	0	0.0	0	0.0	—	—	—	—
tixocortol pivalate 1.0% pet.	1760	6	0.3	8	0.5	4	0.2	2/8 (25.0%)	4/8 (50.0%)	—	2/8 (25.0%)
triamcinolone acetonide 0.1% pet.	343	2	0.6	1	0.3	1	0.3	—	—	1/1 (100.0%)	—
betamethasone-17-valerate 0.12% pet.	157	5	3.2	0	0.0	0	0.0	—	—	—	—
DMSO/alc.abs. 50/50	289	36	12.4	15	5.2	7	2.4	—	—	—	15/15 (100.0%)

Table 3. Sequential test results of our corticosteroid series in 15 patients with doubtful or positive patch test reactions in 1999, retested in 2000

	Number	Estimated relevancy				Overall reproducibility
		definite	probable	possible	none	
reproducible doubtful reactions	11	2/11 (18.2%)	3/11 (27.2%)	4/11 (36.4%)	2/11 (18.2%)	17 reproducible reactions
reproducible + or ++ reactions	5	5/5 (100.0%)				
doubtful reaction becoming + or ++	1	1/1 (100.0%)				
nonreproducible doubtful reactions	16				16/16 (100.0%)	19 non-reproducible reactions
nonreproducible + or ++ reactions	3				3/3 (100.0%)	
new doubtful reactions to the corticosteroid series	5			2/5 (40.0%)	3/5 (60.0%)	8 new reactions
new + or ++ reactions to the corticosteroid series	3	3/3 (100.0%)				

all of which were irrelevant. In contrast, 3 new + or ++ reactions were found that were definitely relevant.

Discussion

Considering our results, we can state that the mean % of + and ++ reactions to the corticosteroid series on D2-D3 is 0.5%, with a significantly higher % of doubtful reactions at the same reading time. In addition, the relevance of the + and ++ reactions is estimated as higher than that of the doubtful reactions. None of the nonreproducible reactions were relevant.

Bircher et al. found a frequency of positive patch tests to corticosteroids ranging from 0.2 up to 5% in a multicentre study of patients undergoing routine patch tests in Switzerland. This is in agreement with our results. However, we found an overall reproducibility of 47.2%, whereas Bircher et al. found a concordance of 70–98% on retesting, depending on the corticosteroid and the score of the positive reaction (4).

Of the 14 compounds tested, only hydrocortisone acetate 1% DMSO/alc.abs. 50/50 and the vehicle DMSO/alc.abs. 50/50 produced significantly higher %s of positive reactions on D2-D3, with a significant lower % of estimated relevance. These are presumably irritant patch test reactions. Moreover we could find no cross-reactions with other compounds tested.

We found 11 reproducible doubtful reactions, of which 5 (45.5%) had probable or definite relevance. This could be due to the 'edge' effect. False-negative or doubtful patch test reactions can be due to the anti-inflammatory effect of the corticosteroid itself, the effects of vasoconstriction and vasodilatation and the 'edge' effect (7). This is an eczema-

tous reaction apparent only at the edge of the patch test site, particularly at the 1st reading. The inflammation is probably still suppressed in the middle of the site where the concentration of the corticosteroid is the highest, while around the edges of the site, the corticosteroid diffuses through the skin, and the low concentrations allow the allergenic effect to prevail (8). This implies that these doubtful reactions would also be relevant and hence reproducible.

Boffa et al. (9) states that at least 90% of individuals with a reaction on patch testing to budesonide are allergic to another corticosteroid. This is true of 50% of those allergic to tixocortol pivalate, the other proposed marker of corticosteroid allergy. We can indeed come to this conclusion: 10 of the 11 patients (90.8%) with + or ++ reactions to budesonide also had positive patch test reactions to other corticosteroids tested. The same can be said of 6 of the 8 patients (75.0%) with + or ++ reactions to tixocortol pivalate. Tixocortol pivalate and budesonide proved to be important markers for dermatocorticosteroid allergy (2).

The available evidence suggests that, with corticosteroids, the allergen is not the steroid itself but a degradation product. Degradation within the skin might therefore be a factor that influences the development of cross-reactivity (10). The pattern of cross-reacting corticosteroids in our tested patients is, accordingly, to the groups of cross-reacting corticosteroids described by Coopman et al. (11).

In contrast to what is generally accepted, the reading on D7 was of minor importance in our series. Only 1 additional + reaction was found on D7. It was a reaction to betamethasone dipropionate and it was considered to be definitely relevant. This is in contrast to the findings of Isaksson et al.

(12), who state that without a late reading (D7) up to 30% of contact allergy to corticosteroid markers is missed.

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