

Prevalence of and factors influencing sensitization to corticosteroids in a Danish patch test population

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Summary

Background. Corticosteroids are used to treat dermatoses, including allergic contact dermatitis, but can also cause contact allergy. The frequency of corticosteroid allergy varies between studies and is influenced by treatment traditions and availability.

Aim. To estimate the prevalence of tixocortol-21-pivalate, budesonide and hydrocortisone-17-butyrate allergy in a Danish patch test population and characterize individuals with corticosteroid allergy.

Materials/methods. Three thousand five hundred and ninety-four patients were patch tested with tixocortol-21-pivalate, budesonide, and hydrocortisone-17-butyrate. Characterization was performed according to the MOAHLFA index and duration of disease.

Results. Two per cent had a steroid allergy: 0.8% had a tixocortol-21-pivalate allergy, 1% a budesonide allergy, and 1% a hydrocortisone-17-butyrate allergy. Tixocortol-21-pivalate and budesonide allergy were associated with atopic dermatitis in crude analyses, but only tixocortol-21-pivalate allergy and atopic dermatitis remained associated in adjusted analyses. Leg dermatitis was uniquely associated with tixocortol-21-pivalate allergy. Hydrocortisone-17-butyrate allergy was associated with duration of disease in both crude and adjusted analyses.

Discussion/conclusion. Chronic dermatoses (atopic dermatitis and leg dermatitis) were identified as risk factors for group A corticosteroid allergy, probably because of more pronounced exposure to group A steroids resulting from ease of access that is exploited by patients with a chronic dermatosis. The duration of disease rather than the dermatosis itself seemed to be important for group B and D2 corticosteroid allergy.

Key words: allergic contact dermatitis; budesonide; contact allergy; corticosteroids; hydrocortisone-17-butyrate; tixocortol-21-pivalate.

It is paradoxical that corticosteroids, which are widely used to treat various dermatoses, including allergic contact dermatitis, are capable of causing delayed

hypersensitivity (type IV) reactions themselves (1). Corticosteroids are categorized into one of four groups [A, B, C, or D (with subgroups of D: D1 and D2)], depending on the molecular structure and chemical properties (2, 3). Cross-reactivity occurs among steroids belonging to the same group (1, 3, 4). Steroids of groups A, B and D2 most frequently induce type IV reactions, in contrast to group C and D1 steroids, which rarely cause allergy. Hence, useful screening markers have been identified for steroid groups A, B, and D2. Tixocortol-21-pivalate is a marker of group A, budesonide of group B, and hydrocortisone-17-butyrate of group D2.

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Tixocortol-21-pivalate and budesonide detect almost 90% of the corticosteroid type IV reactions (5), and were introduced into the European baseline series in the year 2000 (6). Hydrocortisone-17-butyrate is included in a supplementary patch test series.

The prevalence of corticosteroid allergy varies from one centre to another, and is influenced by factors such as the types of corticosteroid available on the pharmaceutical market, the treatment traditions, and the test and detection methods for corticosteroid sensitivity. Previous studies have shown that, among all individuals patch tested, corticosteroid allergy to tixocortol-21-pivalate occurs in 2–5%, allergy to budesonide occurs in 1–2%, and allergy to hydrocortisone-17-butyrate occurs in 2% (1).

The aim of this study was to estimate the prevalence rates of, respectively, tixocortol-21-pivalate, budesonide and hydrocortisone-17-butyrate allergy in a Danish patch test population, and to characterize the allergic population in terms of the internationally used MOAHLFA index and duration of disease. MOAHLFA is the acronym for male (M), occupational dermatitis (O), atopic dermatitis (A), hand dermatitis (H), leg dermatitis (L), face dermatitis (F), and age >40 years (AA).

Materials and Methods

From January 2005 to December 2008, 3594 patch tests were performed consecutively at the Department of Dermato-Allergology, Copenhagen University Hospital, Gentofte, Denmark. Finn Chambers® of 8 mm (Epitest Ltd Oy, Tuusula, Finland) were applied on the back with Scanpor® tape (Norgesplaster A/S, Amphora, As, Norway) and TROLAB® allergens (Hermal, Reinbek, Germany) for 48 hr. Readings were performed on D2, D3 or D4 and D7, according to the guidelines from the International Contact Dermatitis Research Group (7). A +1, +2 or +3 reaction was regarded as a positive reaction.

Fifty-three individuals had been tested twice. Only one person changed status from negative to positive in the second test performed. The last patch test performed was included in the analysis to avoid duplication, giving a total study population of 3541 individuals. Of the 3541 individuals, 34.5% (1222) were male, 65.5% (2320) were older than 40 years, 20.9% (740) had occupational dermatitis, 16.9% (597) had atopic dermatitis, 40.9% (1450) had hand eczema, 6.2% (221) had leg dermatitis, and 22.5% (797) had facial dermatitis. Of the 3541 individuals patch tested, 0.4% (14), 0.6% (23) and 0.4% (14) were not tested with tixocortol-21 pivalate, hydrocortisone-17-butyrate, and budesonide, respectively.

Data analysis was performed with the statistical software programme SPSS® version 15.0 (SPSS, Chicago, IL, USA). Comparisons of the MOAHLFA parameter frequencies between corticosteroid-allergic and non-allergic individuals were performed with the χ^2 -Square test. A χ^2 -square trend test was used to evaluate the association between duration of dermatitis and a corticosteroid allergy. Logistic regression analyses were performed for each specific corticosteroid allergy in order to adjust for confounding factors (MOAHLFA variables and duration of dermatitis). For all analyses, a *p*-value < 0.05 was considered to be significant.

Results

In total, 72 individuals, corresponding to 2.0% of the study population, had a corticosteroid allergy. In the entire population, 0.8% (30) had a tixocortol-21-pivalate allergy, 1% (34) a budesonide allergy, and 1% (34) a hydrocortisone-17-butyrate allergy. Twenty-three people (31.9%) had more than one corticosteroid allergy. Four individuals were positive for both tixocortol-21-pivalate and hydrocortisone-17-butyrate, 16 individuals were positive for both budesonide and hydrocortisone-17-butyrate, and 3 individuals had positive reactions to all three corticosteroids. The MOAHLFA index for individuals with a tixocortol-21-pivalate, budesonide or hydrocortisone-17-butyrate allergy, respectively, is presented in Tables 1–3.

For tixocortol-21-pivalate allergy, crude analyses showed no association between this allergy and sex, dermatitis of the face and hands, age >40 years, or duration of disease. However, significantly more patients with a tixocortol-21-pivalate allergy had atopic dermatitis (*p* = 0.02) and leg dermatitis (*p* = 0.01). Both atopic dermatitis and leg dermatitis remained associated in an adjusted logistic regression model. A trend towards a negative association between tixocortol-21-pivalate allergy and occupational dermatitis was observed in the crude analyses, but this association did not persist in the adjusted logistic regression analysis.

For budesonide allergy, crude analyses showed that occupational dermatitis, atopic dermatitis and age >40 years were significantly associated with this allergy. However, only the occupational dermatitis remained negatively associated in an adjusted logistic regression model. No association was found between leg dermatitis or duration of disease and budesonide allergy.

For hydrocortisone-17-butyrate allergy, crude analyses showed that occupational dermatitis, age >40 years and duration of dermatitis were significantly associated with this allergy. However, only the occupational

Table 1. Tixocortol-21-pivalate

	Tixocortol-21-pivalate allergy (n = 30), % (no.)	No tixocortol-21-pivalate allergy (n = 3497), % (no.)	Chi-square test (crude) <i>p</i> -value	Logistic regression [OR (95% CI)]*
M	23.3 (7)	34.7 (1214)	0.19	0.56 (0.24–1.34)
O	6.7 (2)	21.0 (736)	0.054	0.32 (0.07–1.45)
A	33.3 (10)	16.7 (584)	0.02	3.09 (1.31–7.30)
H	36.7 (11)	41.0 (1435)	0.63	1.10 (0.49–2.44)
L	20.0 (6)	6.1 (214)	0.01	3.96 (1.54–10.2)
F	26.7 (8)	22.4 (784)	0.58	0.99 (0.42–2.34)
AA	73.3 (22)	65.5 (2290)	0.37	1.68 (0.69–4.08)
Duration of dermatitis [†]	—	—	0.23 [‡]	1.14 (0.90–1.44)

Significant associations are presented in bold.

A, atopic dermatitis; AA, age above 40 years; F, facial dermatitis; H, hand eczema; L, leg dermatitis; M, male; O, occupation; CI, confidence interval; OR, odds ratio.

*Adjusted for remaining MOAHLFA variables and duration of dermatitis.

[†]Only ordinal data were available for the parameter duration of dermatitis since debut; therefore, no average values of duration of dermatitis for individuals with and without tixocortol-21-pivalate allergy can be presented.

[‡]Trend test crude.

Table 2. Budesonide

	Budesonide allergy (n = 34), % (no.)	No budesonide allergy (n = 3493), % (no.)	Chi = square test (crude) <i>p</i> -value	Logistic regression [OR (95% CI)]*
M	38.2 (13)	34.6 (1208)	0.66	1.21 (0.59–2.47)
O	5.9 (2)	21.1 (736)	0.03	0.22 (0.05–0.97)
A	2.9 (1)	17.0 (593)	0.03	0.17 (0.02–1.31)
H	38.2 (13)	41.0 (1433)	0.74	1.55 (0.74–3.24)
L	5.9 (2)	6.2 (218)	1.00	0.70 (0.16–2.99)
F	29.4 (10)	22.4 (782)	0.33	1.61 (0.74–3.50)
AA	85.3 (29)	65.4 (2283)	0.02	2.19 (0.83–5.77)
Duration of dermatitis [†]	—	—	0.79 [‡]	0.97 (0.78–1.21)

Significant associations are presented in bold.

A, atopic dermatitis; AA, age above 40 years; F, facial dermatitis; H, hand eczema; L, leg dermatitis; M, male; O, occupation; CI, confidence interval; OR, odds ratio.

*Adjusted for remaining MOAHLFA variables and duration of dermatitis.

[†]Only ordinal data were available for the parameter duration of dermatitis since debut; therefore, no average values of duration of dermatitis for individuals with and without budesonide allergy can be presented.

[‡]Trend test crude.

dermatitis and duration of disease remained associated in an adjusted logistic regression model. No association between atopic dermatitis or leg dermatitis and hydrocortisone-17-butyrate allergy was found.

Neither tixocortol-21-pivalate, hydrocortisone-17-butyrate nor budesonide allergy was associated with having dermatitis at a specific anatomical site (data not shown).

Discussion

Two per cent of individuals had a corticosteroid allergy, in good agreement with previously reported frequencies in other patch test populations (8, 9). The risk of inducing a contact allergy is influenced by the nature of exposure; that is, dose, duration and frequency of

exposure, simultaneous occlusion and inflammation, the condition of the skin, and potency of the allergen (10). Corticosteroids are not potent allergens, but are used to treat dermatoses with inflammation and broken skin barriers. Chronic dermatoses such as atopic dermatitis and leg dermatitis are treated with corticosteroids, and the treatment is frequently long-lasting. For leg dermatitis in particular, such corticosteroid treatment often occurs with simultaneous occlusion, which increases the risk of inducing a contact allergy. Associations between corticosteroid allergy and leg dermatitis/atopic dermatitis have previously been reported (8, 11). It is therefore interesting that only tixocortol-21-pivalate allergy was associated with atopic dermatitis and leg dermatitis in adjusted analyses. For budesonide allergy, the association with atopic dermatitis disappeared in the

Table 3. Hydrocortisone-17-butyrate

	Hydrocortisone-17-butyrate allergy (n = 34), % (no.)	No hydrocortisone-17-butyrate allergy (n = 3484), % (no.)	Chi-square test (crude) <i>p</i> -value	Logistic regression [OR (95% CI)]*
M	35.3 (12)	34.5 (1203)	0.93	0.96 (0.47–1.98)
O	5.9 (2)	21.1 (736)	0.03	0.20 (0.05–0.89)
A	11.8 (4)	16.9 (590)	0.42	0.85 (0.28–2.59)
H	47.1 (16)	40.9 (1424)	0.47	1.92 (0.94–3.91)
L	11.8 (4)	6.2 (217)	0.16	1.60 (0.55–4.70)
F	17.6 (6)	22.6 (786)	0.50	0.80 (0.32–2.01)
AA	85.3 (29)	65.3 (2275)	0.02	2.53 (0.94–6.84)
Duration of dermatitis [†]	—	—	0.01[‡]	1.30 (1.05–1.62)

Significant associations are presented in bold.

A, atopic dermatitis; AA, age above 40 years; F, facial dermatitis; H, hand eczema; L, leg dermatitis; M, male; O, occupation; CI, confidence interval; OR, odds ratio.

*Adjusted for remaining MOAHLFA variables and duration of dermatitis.

[†]Only ordinal data were available for the parameter duration of dermatitis since debut; therefore, no average values of duration of dermatitis for individuals with and without hydrocortisone-17-butyrate allergy can be presented.

[‡]Trend test crude.

logistic regression analysis, where confounding factors (duration of disease and remaining MOAHLFA variables) were accounted for. The lack of association between budesonide allergy and atopic dermatitis in the adjusted analysis may be explained by the fact that only 1 of 34 individuals with budesonide allergy had atopic dermatitis. However, it may also reflect the fact that it is not the disease in itself but the duration of disease that is crucial for the development of budesonide allergy. Furthermore, hydrocortisone-17-butyrate allergy was not associated with either atopic dermatitis or leg dermatitis, but was associated with duration of dermatitis. This suggests that it is the duration of disease, rather than the chronic dermatosis, for example atopic dermatitis and leg dermatitis, in itself, that is a risk factor for corticosteroid allergy. One study has also reported an increased prevalence of budesonide allergy with increasing duration of dermatitis (12).

Tixocortol-21-pivalate allergy was, however, associated with both leg dermatitis and atopic dermatitis, even after adjustment for duration of disease in the logistic regression analysis. Tixocortol-21-pivalate allergy is a marker of corticosteroid group A allergy, budesonide a marker of group B allergy, and hydrocortisone-17-butyrate a marker of group D2 allergy. In Denmark, group A corticosteroids are mainly found in topical treatments that can be purchased without prescription, but are also found in frequently used topical combination products containing antibiotics and antifungal substances. Group A corticosteroids in topical treatments in Denmark include only low-potency grade 1 corticosteroids. In Denmark, group B and group D2 corticosteroids are found only in prescription-required topical medicaments with stronger potency than group A steroids, and in

some nasal and aerosol preparations. The easy access to group A corticosteroids may very well explain why only tixocortol-21-pivalate allergy is uniquely associated with atopic dermatitis and leg dermatitis, despite controlling for duration of disease in regression analyses. It is likely that individuals with these dermatoses have purchased such non-prescription medicaments on their own at an early stage of their disease, before consulting a doctor. The fear of corticosteroid side effects combined with the easy access may also be a motivating factor for individuals to choose to self-treat their dermatosis with low-potency group A corticosteroids. Such unsupervised self-treatment with low-potency corticosteroids might result in unnecessarily long exposure to steroids, and could explain the unique association between tixocortol-21-pivalate allergy and atopic dermatitis and leg dermatitis.

All three corticosteroid allergies were negatively associated with occupational dermatitis; for tixocortol-21-pivalate allergy, this was only borderline significant. Corticosteroid allergy is a treatment-related contact allergy that is not found in occupational settings, and this explains these findings.

Conclusion

Chronic dermatoses such as atopic dermatitis and leg dermatitis were identified as individual risk factors for group A corticosteroid allergy, and this can be explained by more pronounced exposure to group A steroids resulting from easy access being exploited by patients with a chronic dermatosis. The duration of disease rather than the dermatosis in itself seems to be more important for group B and D2 corticosteroid allergy.

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