

Delayed hypersensitivity to corticosteroids in a series of 315 patients: clinical data and patch test results

MARIE BAECK¹, JULIE-ANNE CHEMELLE³, RAPHAËL TERREUX³, JACQUES DRIEGHE² AND AN GOOSSENS²

¹Department of Dermatology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium,

²Department of Dermatology, University Hospital, K.U. Leuven, Belgium, and ³Institut de Biologie et Chimie des Protéines (UMR5086), CNRS, University of Lyon 1, IFR 128 BioSciences, Lyon-Gerland, France

Background: Corticosteroids may cause immediate or delayed hypersensitivity. In 1989, based on structural and clinical characteristics, we put forward a classification of corticosteroids into four cross-reacting groups, namely group A, B, C, and D, the latter later subdivided into two subgroups, i.e. D1 and D2. The constituents on the D-ring of the corticosteroid-molecule are considered to have a central role for binding to skin proteins and for cross-reactions patterns; however, halogenation of the molecules is also interfering.

Objective: To study the clinical data and analyse simultaneous positive reactions obtained in a large group of corticosteroid-allergic patients.

Methods: Patch tests were performed with the baseline series, to which hydrocortisone butyrate and prednisolone caproate were added, as well as with the corticosteroids to which the patients had been exposed. Three hundred and forty subjects with a presumed or proven corticosteroid allergy were further investigated with an extended series containing 72 molecules.

Results: Out of 11 596 patients investigated, 315 subjects reacted positively to at least 1 corticosteroid-molecule, with most of them presenting with multiple positive reactions.

Conclusion: A prevalence of corticosteroid allergy of 2.7% was found. Despite validity of the ABCD (sub)classification in many cases, possible adjustments may have to be considered.

Key words: allergic contact dermatitis; classification; concomitant reactions; cross-reactions; corticosteroids; delayed hypersensitivity. © John Wiley & Sons A/S, 2009.

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It may appear as paradoxical that corticosteroids, potent anti-inflammatory agents and immunomodulators used in the treatment of allergic reactions (in the broad sense), are capable of producing allergic immediate or delayed hypersensitivity reactions.

When patients are investigated for contact allergy, they often give multiple positive reactions to corticosteroids. Although the existence of cross-reaction phenomena has been proven, e.g. by positive skin tests to synthetic corticosteroids to which a patient could *never* have been exposed (simply because they had not been marketed), simultaneous or

subsequent sensitization can never be entirely ruled out. Indeed, it is often extremely difficult to determine which corticosteroids a patient has been exposed to in the past. As Isaksson emphasizes, in general it is more appropriate to discuss *concomitant sensitization*, which may include cross-reactivity (1). Beside patch test data, statistical arguments and three-dimensional structural analysis can also address the question of cross-reactivity.

In 1989, based on structural and clinical characteristics, Coopman et al. (2) classified corticosteroids into four reacting groups, namely group A, B, C, and

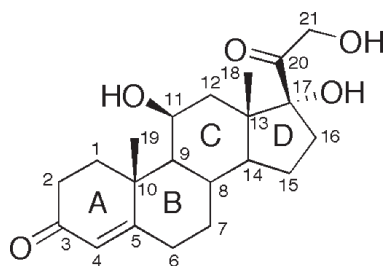


Fig. 1. Chemical structure of hydrocortisone with the conventional numbering of carbon atoms.

D. In 1995, Lepoittevin et al. (3) carried out conformational analysis of the observed cross-reactions, which supported this classification and the central role of constituents of the D-ring (Fig. 1: chemical structure of hydrocortisone with the conventional numbering of carbon atoms).

Further clinical data led Matura and Goossens to further subdivide group D into two subgroups, i.e. D1 and D2 (4, 5) (Table 1). Beside the recognition site of the D-ring influenced by C16, C17 substitutions, Wilkinson et al. considered the A-ring to be a second immune recognition site, and halogenation of the corticosteroid structure (C6 and/or C9) to be of utmost importance as to the cross-sensitivity patterns observed with corticosteroids (6).

The allergen does not seem to be the corticosteroid itself but a metabolite from its skin metabolism; assuming that all corticosteroids interact with proteins in the same manner, steroid glyoxals or 21-dehydrocorticosteroids (aldehydes), being the principal metabolites, are most probably the haptens that bind to nucleophilic protein residues (7, 8). It has been shown that steroid glyoxals can bind to any amino acid except proline and hydroxyproline. The arginine reaction, however, is clearly predominant – and also irreversible (9, 10): Wilkinson et al. (9) showed that corticosteroids with a greater capacity to bind to arginine do have stronger allergenic properties, and recently, Berl et al. (10) confirmed that steroids were indeed selectively reacting with arginine to form important adducts.

With regard to immunogenicity and cross-reactivity, the respective role of the different substitutions (the methyl function at C16 and halogen groups, in particular) that are attached to the basic steroid structure, still remains unclear.

Patients, Materials, and Methods

We reviewed clinical data and the results of patch testing to an extended corticosteroid series in the Dermatology department at the K.U. Leuven University Hospital during an 18-years' study period.

From January 1990 to June 2008, all patients attending the Contact Allergy department were examined clinically and routinely patch tested with a

baseline series including tixocortol pivalate, budesonide, as well as hydrocortisone 17-butyrate and prednisone caproate. Moreover, those patients with a history of corticosteroids use were, in most cases, also tested with the respective molecules. Patients with a proven contact allergy to a corticosteroid and some, presumed to have such a reaction from the history, were later tested with an extended corticosteroid series in order to study simultaneous positive (and cross) reactions.

Sixty-six corticosteroids, including those from the baseline series, as well as two sex hormones, i.e. progesterone and testosterone, were thus tested (Table 2). All corticosteroids [except for the two screening agents in the baseline series, (11)] were diluted in the Contact Allergy department by a laboratory technician; the substances used for these preparations had been obtained from the pharmaceutical companies marketing them. Dexamethasone sodium phosphate was introduced from November 1990 and difluprednate (Sicor, Milan, Italy), a corticosteroid recently (2008) marketed to treat ocular pain (12), was included from October 1994.

Ethanol (eth.) was the vehicle used to test all corticosteroid molecules except for tixocortol pivalate and budesonide for which petrolatum (pet.) works well (13, 14). Because of their weak *trans*-epidermal penetration, hydrocortisone, and cortisone acetate were diluted in an equal mixture of ethanol and dimethyl sulfoxide (DMSO) (13). Besides ethanol and ethanol/DMSO as controls, also glutaraldehyde and glyoxal were included in the extended series.

The concentrations of the test solutions were defined according to the studies of Isaksson and co-workers (15, 16) (Table 2). Particularly for budesonide, lower concentrations were also tested, i.e. 0.01% pet. and 0.002% eth.

The test solutions were freshly prepared every 6–12 months. Although corticosteroids are unstable in ethanol and may degrade after just 1 month of storage in a refrigerator, it has been shown that skin tests carried out with fresh and preserved solutions give comparable results (17). This might relate to the fact that the actual allergen is a degradation product rather than the corticosteroid itself, therefore instability in the solution should not affect the sensitivity of the test.

The patch test materials used were van der Bend chambers (van der Bend, Briele, The Netherlands) on Mepore® (3M, USA), covered on the upper back with Mefix® (Mölnlycke, Sweden). The patches were removed after 2 days and the patch test reactions were evaluated at D2, D4, and in many cases also after 7 days, according to the ICDRG criteria. All clear positive tests were taken into account in this study. Although, in general, dubious reactions

Table 1. Classification of corticosteroids according to the classification of Coopman et al., and Matura and Goossens

Group	Characteristics of the group	Typical members	Possible cross-reactions outside the group
A	No substitution on the D-ring except a short chain ester or a thioester on C21	Cloprednol Cortisone acetate Dichlorisone acetate Fludrocortisone acetate Fluorometholone Fluprednisolone acetate Hydrocortisone Hydrocortisone acetate Hydrocortisone 21-butyrate Hydrocortisone hemisuccinate Isofluprednone acetate Mazipredone Medrysone Methylprednisolone acetate Methylprednisolone hemisuccinate Prednisolone Prednisolone sodium metasulphobenzoate Prednisolone succinate Prednisolone pivalate Prednisolone caproate Prednisone Tixocortol pivalate	D2
B	C16, C17 <i>cis</i> Ketal or diol structure Possibly a side chain on C21	Amcinonide Budesonide Desonide Fluchloronide Flumoxonide Flunisolide Fluocinolone acetonide Fluocinonide Halcinonide Triamcinolone Triamcinolone diacetate Triamcinolone hexacetonide Triamcinolone benetonide Triamcinolone acetonide	
C	C16 methyl substitution on the D-ring Halogen substitution No side chain on C17 Possibly a side chain on C21	Betamethasone Betamethasone sodium phosphate Desoxymethasone Dexamethasone Dexamethasone acetate Dexamethasone sodium phosphate Diflucortolone valerate Flumethasone pivalate Fluocortin butyl Fluocortolone Fluocortolone caprylate Fluocortolone pivalate Fluprednidene acetate Halometasone Meprednisone	
D1	Methyl substitution on C16 Halogen substitution Side chain ester on C17 Possibly a side chain on C21	Alclometasone dipropionate Beclomethasone dipropionate Betamethasone dipropionate Betamethasone 17-valerate Clobetasol propionate Clobetasone butyrate Diflorasone diacetate Fluticasone propionate Mometasone furoate	
D2	No methyl substitution on C16 No halogen substitution Side chain ester on C17 Possibly a side chain on C21	Difluprednate Hydrocortisone 17-butyrate Hydrocortisone aceponate Methylprednisolone aceponate Prednicarbate	A Budesonide (S isomer)

Table 2. Corticosteroid series, along with their test concentrations and vehicles, and positive reaction rates for each corticosteroid

	Molecules	Vehicle /Concentration	CAS	Number of positive tests (315 subjects in total)
1	Alclometasone dipropionate	0.5% eth	66734-13-2	57
2	Amcinonide	0.1% eth	51022-69-6	91
3	Beclomethasone dipropionate	0.1% eth	5534-09-8	22
4	Betamethasone	0.1% eth	378-44-9	36
5	Betamethasone dipropionate	0.1% eth	5593-20-4	19
6	Betamethasone sodium phosphate	0.1% normal saline	151-73-5	9
7	Betamethasone 17-valerate	0.1% eth	2152-44-5	19
8	Budesonide	0.01% pet 0.002% eth	51333-22-3	191
9	Clobetasol propionate	0.1% eth	25122-46-7	16
10	Clobetasone butyrate	0.1% eth	25122-57-0	25
11	Cloprednol	0.1% eth	5251-34-3	61
12	Cortisone acetate	0.5% eth/DMSO	50-04-4	67
13	Desonide	0.1% eth	638-94-8	59
13	Desoxymethasone	0.1% eth	382-67-2	18
14	Dexamethasone	0.1% eth	50-02-2	27
15	Dexamethasone acetate	0.1% eth	1177-87-3	18
16	Dexamethasone sodium phosphate	0.1% eth	2392-39-4	9
17	Dichlorisone acetate	0.1% eth	79-61-8	30
18	Difflorasone diacetate	0.1% eth	33564-31-7	10
19	Difflocortolone valerate	0.1% eth	59198-70-8	6
20	Diffuprednate	0.1% eth	23674-86-4	15
21	Ethanol	70% water	64-17-5	24
22	Ethanol DMSO	50/50% water	64-17-5/67-68-5	38
23	Fluocinonide	1% eth	356-12-7	29
24	Flucloronide	0.1% eth	3693-39-8	15
25	Fludrocortisone acetate	0.1% eth	514-36-3	25
26	Flumethasone pivalate	0.1% eth	2002-29-1	6
27	Flumoxonide	0.1% eth	60135-22-0	14
28	Flunisolide	0.1% eth	3385-03-3	35
29	Fluocinolone acetonide	0.1% eth	67-73-2	27
30	Fluocortin butyl	0.1% eth	41767-29-7	42
31	Fluocortolone	0.1% eth	152-97-6	7
32	Fluocortolone caproate	0.1% eth	303-40-2	13
33	Fluocortolone pivalate	0.1% eth	29205-06-9	9
34	Fluorometholone	0.1% eth	426-13-1	13
35	Fluprednidene acetate	0.1% eth	1255-35-2	10
36	Fluprednisolone	0.1% eth	53-34-9	15
37	Fluticasone propionate	0.1% eth	80474-14-2	14
38	Glutaraldehyde	1% water	111-30-8	17
39	Glyoxal	2% water	107-22-2	11
40	Halcinonide	0.1% eth	3093-35-4	11
41	Halometasone	0.1% eth	50629-82-8	6
42	Hydrocortisone aceponate	1% eth	74050-20-7	86
43	Hydrocortisone-17-butyrate	0.1% eth	13609-67-1	96
44	Hydrocortisone acetate	0.1% eth	50-03-3	48
45	Hydrocortisone-21-butyrate	0.1% eth	6677-99-2	66
46	Hydrocortisone hemisuccinate	0.1% eth	2203-97-6	15
47	Hydrocortisone	0.5% eth/DMSO	50-23-7	99
48	Isofluprednone acetate	0.1% eth	338-98-7	14
49	Mazipredone	0.1% eth	13085-08-0	67
50	Medrysone	0.1% eth	2668-66-8	23
51	Meprednisone	0.1% eth	1247-42-3	24
52	Methylprednisolone acetate	0.1% eth	53-36-1	58
53	Methylprednisolone hemisuccinate	0.1% eth	2921-57-5	17
54	Methylprednisolone aceponate	0.1% eth	86401-95-8	105

were excluded from our analysis, weak irritant reactions to the DMSO/eth. (even in the presence of hydrocortisone) could not always be ruled out with certainty.

Sometimes, 'edge effects' could be observed at early readings, a phenomenon generally disappearing at later readings when the entire test site becomes eczematous (18).

The results were recorded on a database containing the following information: sex, date of birth, occupation, personal, and familial atopic history, site and type of lesions, use of corticosteroids (names and classes), and patch test results. The relevance of the reactions was considered on the basis of a history of known or likely contact of the affected skin area with products containing the allergen, as

Table 2. (Continued)

	Molecules	Vehicle /Concentration	CAS	Number of positive tests (315 subjects in total)
55	Mometasone furoate	0.1% eth	83919-23-7	15
56	Pivalate tixocortol	0.1% pet	55560-96-8	135
57	Prednisolone pivalate	0.1% eth	1107-99-9	46
58	Prednisolone caproate	0.1% eth	69164-69-8	70
59	Prednicarbate	1% eth	73771-04-7	111
60	Prednisolone	0.1% eth	50-24-8	55
61	Prednisolone sodium metasulphobenzoate	0.1% eth	630-67-1	48
62	Prednisolone hemisuccinate	1% eth	2920-86-7	13
63	Prednisone	0.1% eth	53-03-2	43
64	Procinonide	0.1% eth	58497-00-0	29
65	Progesterone	2% eth	57-83-0	31
66	Testosterone propionate	2% eth	57-85-2	38
67	Triamcinolone	0.1% eth	124-94-7	65
68	Triamcinolone diacetate	0.1% eth	67-78-7	27
69	Triamcinolone hexacetone	1% eth	5611-51-8	39
70	Triamcinolone benetonide	0.1% eth	31002-79-6	42
71	Triamcinolone acetone	0.1% eth	76-25-5	51

well as according to the follow-up of the patients of whom the dermatitis got better, e.g. in the case of an underlying disease such as atopic or seborrheic dermatitis, or disappeared when stopping the use of the incriminated corticosteroid.

The data were analysed using statistical methods i.e. the Kolmogorov–Smirnov test and the Chi-square test, with a significance level of 95% and 99%. These are non-parametric goodness of fit tests of one-dimensional probability distributions used to compare a sample with a reference probability distribution or to compare two independent samples.

Results

Patient data

From 1/1/1990 until 30/06/2008, 11 596 patients, i.e. 4009 men (35%) and 7587 (65%) women attended the Contact Allergy department. The MOAHLFA index was: M (male): 34.6%, O (occupational dermatoses): 16.9%, A (personal atopy): 21.2%, H (hand eczema): 38.7%, L (leg ulcer/stasis dermatitis): 3.6%, F (face): 34.0%, A (age 40+): 46.4%.

6509 (56%) in total, i.e. 1775 (27%) men and 4734 (73%) women reacted to at least one allergen tested. Three hundred and forty patients with a presumed or known corticosteroid allergy were patch tested with an extended corticosteroid series and 315 presented at least one reaction. This represents a prevalence of corticosteroid allergy of 2.7% considering all the patients attending the Contact Allergy department and 4.8% of those with at least one positive patch test reaction. Out of 315 patients 267 reacted to more than one molecule in the corticosteroid series, which represent 85%.

Among the 315 positive-reacting patients, 74 were men (24%) and 241 woman (76%). There is

no statistical difference with the positive-reacting patients though. Their mean age was 48 years.

The most frequent occupations of the corticosteroid-allergic patients were: housewife (18%), office work (17%), retired (7%), housekeeping (6%), education (5%), student (5%), and health care (4%). Only two patients suffered from occupational dermatitis, i.e. nurses with acute contact dermatitis on the hands, who had treated patients with a methylprednisolone infusion to which they became sensitized.

A personal atopic history was found in 108/315 patients (34%) (atopic eczema 23%, asthma 11%, and rhino-conjunctivitis 19%) and familial atopy in 119/315 patients (38%) (atopic eczema 19%, asthma 16%, and rhino-conjunctivitis 20%); 73/315 (23%) presented with both a personal and a familial atopic background. The difference in personal atopy with the population attending the contact allergy unit was significant ($P < 0.01$).

As to the exposure, taking Coopman's classification into consideration, the following classes of corticosteroids present in the corticosteroid preparations used, in decreasing order, were observed as follows: Group D1, group A, group B, Group D2, and finally group C. The history revealed that the individual corticosteroids most frequently used were betamethasone valerate, betamethasone dipropionate, clobetasol propionate, and mometasone furoate (class D1), hydrocortisone, methylprednisolone, or prednisolone (class A), triamcinolone acetone (class B), and hydrocortisone 17-butyrate (class D2).

With regard to the sensitization route, despite the ignorance of the exact exposure patterns in all patients and the different contacts with multiple preparations, the skin revealed to be the most frequent sensitization site, i.e. in 235 of the 315 patients

(75%). Twenty-two patients (7%) probably became sensitized by inhalation corticosteroids of whom 15, not themselves treated by aerosols, were taking care of, or living together with patients who used them regularly, appeared to have been sensitized by airborne exposure, to budesonide in particular; 19 (6%) became sensitized by ophthalmic preparations. In some cases, the sensitization route could not be determined, however.

Forty-five patients (14%) had been previously exposed to systemic corticosteroids from the group to which they were reacting but, of course, they may have become sensitized through other exposures.

Two hundred and twenty-five patients (71%) presented positive reactions to corticosteroids that were considered clinically relevant: 197 patients (63%) presented with a skin reaction following skin application of corticosteroids, 21 (7%) after contact with inhalation corticosteroids, of whom 9 suffering from 'by proxy' airborne dermatitis, 18 (6%) after ocular application, 7 (2%) after intra-lesional injection, and 10 (3%) after systemic administration. Some of these patients reacted to different types of exposure.

The affected skin sites were hands (25%), legs (21%), face (20%), feet (17%), generalized (14%), arms (14%), eyes (14%), trunk (5%), and neck (5%).

Most patients applying corticosteroid to their skin suffered from chronic eczema or reported to respond poorly or not at all to corticosteroid treatment. Associated 'classical' side effects of corticosteroids were sometimes predominant with clinical symptoms, such as steroidal rosacea, periocular and perinasal, or perioral dermatitis.

Patients reacting to corticosteroids administered by the ophthalmological route generally presented with conjunctivitis, a periorbital eruption, and oedema or eczema on the eyelids.

In the case of reactions following nasal or oral inhalation of corticosteroids, the clinical signs were facial eczema (particularly perinasal, perioral, or on the cheeks), with or without loco-regional extension (ears, chest, neck); also cheilitis and stomatitis were observed.

Out of seven patients reacting to intra-lesional or intra-articular injection of corticosteroids, five presented with a generalized eruption, one of them also suffering from systemic symptoms such as hypotension and malaise. One presented with facial oedema and in a further one the type of skin reaction that had occurred, could not be specified.

A generalized maculo-papular or eczematous eruption was observed in 8 out of 10 patients presenting reactions following systemic corticosteroid administration. For the other 2, the exact nature of the skin 'rash' could not be determined.

Patch test results

Positive reactions. The molecules causing allergic reactions and the reaction rates for each of them are listed in Table 2.

The results with the corticosteroid markers in our baseline series were as follows: out of the 315 patients testing positively to corticosteroids, 191 (61%) reacted to budesonide, 135 (43%) to tixocortol pivalate, 96 (31%) to hydrocortisone 17-butyrate, and 70 (22%) to prednisolone caproate; 57 patients (18%) with a positive test to tixocortol pivalate had a negative test to budesonide or hydrocortisone 17-butyrate; 84 patients (27%) with a positive test to budesonide had a negative test to tixocortol pivalate or hydrocortisone 17-butyrate. A positive test to hydrocortisone 17-butyrate with negativity of the other screening markers was found among 12 patients (4%) and in 0 patients to prednisolone caproate. Twenty-four patients (7.5%) reacting to a corticosteroid in the extended series had negative tests to all four corticosteroids included in the baseline series. 109/135 (81%) patients allergic to tixocortol pivalate, 174/191 (91%) to budesonide, and 95/96 (99%) to hydrocortisone 17-butyrate presented at least one positive test to another corticosteroid.

In the corticosteroid series, the highest rate of positive reactions was found for molecules from group A, i.e. cortisone acetate, cloprednol, hydrocortisone 21-butyrate, methylprednisolone acetate, prednisolone, mazipredone (not marketed in Belgium), and hydrocortisone; followed by group B, i.e. amcinonide, desonide, triamcinolone, and triamcinolone acetonide; and group D2, i.e. methylprednisolone aceponate, hydrocortisone aceponate and prednicarbate (the latter two not marketed in Belgium).

266/315 patients (84%) also reacted to others allergens: the most frequent being fragrance mix (29%), nickel (23%), *Myroxylon pereira* (19%), lanolin (wool alcohols) (17%), amerchol L101® (also added to the Belgian baseline series) (16%), colophonium (15%), neomycin (15%), cobalt chloride (14%), p-phenylenediamine (13%), potassium dichromate (11%), propylene glycol (11%), and sorbitane sesquioleate (7%) (the latter two also present in the Belgian baseline series).

Simultaneous positive tests in the corticosteroid series. Among patients reacting to more than one molecule, 89 patients (28%) presented simultaneous positive tests only to corticosteroids belonging to the same group and no reactions to corticosteroids from other groups according to Coopman's et al. classification: 50 patients had reactions exclusively within group A corticosteroids, 32 within group B among whom 16 exclusively to budesonide, 3 within group

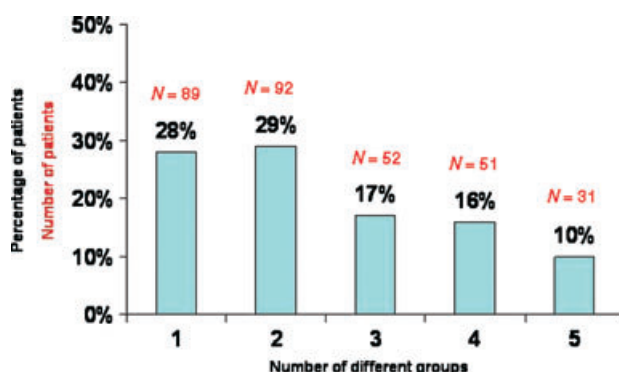


Fig. 2. Results according to the classification of Coopman et al.

D2, 4 within group D1, while none within group C; 31 patients (10%) had positive tests to corticosteroids from all five groups (Fig. 2).

Taking into account the R and S diastereoisomers of budesonide and the subclassification into D1 ('stable') and D2 ('labile' esters) corticosteroids (3–5, 19), 35 patients (11%) presented simultaneous positive tests exclusively to corticosteroids belonging to group A and D2, 11 to A, budesonide and D2, and 6 to A, budesonide, D2 and alclomethasone dipropionate, which, according to the present results, co-reacts more often with D2 than with D1 (as previously put forward, 5); 30 (10%) patients reacted to budesonide and D, among which 23 reacted to budesonide and D2 and 6 to budesonide, D2 and alclomethasone dipropionate.

Statistical analysis permits identification of concomitant reactions (including cross-reactions) between corticosteroids by coupling (association of one corticosteroid to another) and clustering (grouping of different corticosteroids). The results, with a significance of $P < 0.05$, are given in Table 3 (coupling) and Table 4 (clustering) (with a minimal association frequency of 12).

Coupling and clustering confirm the individualization of the group A corticosteroids, the 'labile ester group' (D2), the B and the D1 group. Clobetasol propionate, mometasone fuorate and fluticasone propionate (also D1) are also statistically associated, although, because of the very low number of positive reactions, not significantly.

Regarding molecules from group C, we could observe significant associations between betamethasone, dexamethasone, and molecules from the B group.

Thirty-one patients (10%) with corticosteroid allergy presented with a positive test to progesterone and 38 (12%) to testosterone propionate, two molecules between which a significant association was found. Specific associations with particular corticosteroids could not be observed because, in most

cases, these patients reacted to molecules from different groups.

Twenty-four patients (8%) reacted to the ethanol control, 38 (12%) to DMSO/ethanol, 17 to glutaraldehyde (5%) and 11 (4%) to glyoxal. Compared to the population attending the Contact Allergy department, there is a significant difference in positive reactions for the 3 former molecules ($P < 0.001$). Concerning glyoxal, the results could not be compared with the general population because it was tested only in 317 patients, among which 315 to the corticosteroid series. Since only a minority of the corticosteroid-allergic subjects reacted to the aldehydes and the ethanol controls, and the morphological appearance was allergic in nature, the reactions were not considered to be irritant.

Discussion

Prevalence

During this 18-year period a mean of 20 patients/year were recruited, the frequency of corticosteroid allergy being somewhat higher before (25 patients/year) than after 2000 (15 patients/year), for which there could be several explanations. Before 2000, because of the preparation of Matura's doctoral thesis (4, 5), more corticosteroid-allergic patients had been referred to our centre to be investigated; some allergenic topical corticosteroid preparations such as those containing alclomethasone dipropionate, but particularly budesonide, have been withdrawn since from the market; moreover, the introduction of tixocortol pivalate and budesonide in the baseline series in 2000 (11) has allowed general dermatologists to detect corticosteroid allergy themselves, who also became more aware about the molecules that more easily induce sensitization and which they try to avoid when prescribing.

Since 1990 a prevalence of corticosteroid allergy of 2.7% was observed, which is within the range reported from the literature, i.e. 0.2–5% (20–22).

Tixocortol pivalate was positive among 1.1%, budesonide among 1.6%, and hydrocortisone 17-butyrate among 0.8% of the patients tested. The sensitization rate to tixocortol pivalate in the literature varies from 1.5% to 5% (11, 23, 24) and to budesonide from 1 to 2% (11, 21). The rate of contact allergy to hydrocortisone 17-butyrate ranges from 0.5% to 1% (21, 25).

Corticosteroid markers

Sixty per cent (191/315) of the patients allergic to corticosteroids had a positive test to budesonide and 43% (135/315) to tixocortol pivalate. Furthermore, more than 80% of the tixocortol pivalate- and even more than 90% of the budesonide-positive

Table 4. Clustering ($P < 0.05$, with a minimal association frequency of 12), along with the Group to which these clustered corticosteroid molecules belong

Molecule name						Group
Cloprednol	Methylprednisolone acetate	Prednisolone				A
Amcinonide	Desonide	Triamcinolone				B
Desonide	Flunisolide	Triamcinolone hexacetonide	Triamcinolone benetonide	Triamcinolone acetonide		B
Flunisolide	Fluocinolone acetonide	Procinnonide	Triamcinolone hexacetonide	Fluocinnonide	Triamcinolone benetonide	B
Triamcinolone	Triamcinolone hexacetonide	Triamcinolone benetonide	Triamcinolone acetonide			B
Beclomethasone dipropionate	Betamethasone dipropionate	Betamethasone 17-valerate				D1
Hydrocortisone aceponate	Prednicarbate	Methylprednisolone aceponate				D2
Prednicarbate	Methylprednisolone aceponate	Hydrocortisone 17-butyrate				D2
Betamethasone	Desonide	Flunisolide	Triamcinolone hexacetonide	Triamcinolone benetonide	Triamcinolone acetonide	B-C
Desoxymethasone	Dexamethasone	Procinnonide				B-C
Dexamethasone	Fluocinolone acetonide	Procinnonide	Fluocinnonide			B-C

patients reacted to other corticosteroid molecules. Together, these two markers detect 88.5% (279/315) of the corticosteroid-allergic patients, which is in accordance with the literature (26). Addition of hydrocortisone 17-butyrate to the baseline series allow to detect another 4%, while prednisolone caproate had no additional benefit. Only 7.5% were not detected with those markers, which still prove the utility to test with the particular corticosteroids used.

Factors influencing sensitization to corticosteroids

We found three times more woman than men with corticosteroid allergy, which differ significantly from the total population of patients tested but not from those presenting with a positive test to at least one allergen. This was in accordance with a previous study (21).

Comparing to all patients attending the Contact Allergy department, we did observe significant differences in the prevalence of a personal atopic background, being higher in the group of corticosteroid-allergic patients. It is not clear whether atopy is a risk factor for the development of a corticosteroid allergy, or whether its occurrence might be due to a selection bias because this group of patients is more likely to apply corticosteroids on their skin or to use aerosols with corticosteroids (27–29).

Most of the patients suffered from chronic eczema on the hands or feet, stasis dermatitis, leg ulcers, and chronic facial dermatitis, confirming that long-standing dermatological diseases, because of the application of numerous corticosteroids over a long period, is a determining factor to develop

corticosteroid sensitivity (30). Sometimes classical side effects masked contact allergy.

According to the literature and as expected, corticosteroid allergy is only in exceptional cases occupationally induced (31, 32).

Sensitization routes

Most patients were sensitized by the cutaneous route, which is in agreement with the literature (33). Airborne contact dermatitis (34, 35) and sensitization due to 'by proxy' (connubial or consort) dermatitis was also observed (results to be published in detail elsewhere). Patients who themselves administer inhalation corticosteroids, despite their wide use, rarely develop corticosteroid sensitization, and if it occurs, nasal seems to be more frequently involved than oral inhalation. This is also in accordance with the literature (36–39).

Concomitant and cross-reactions patterns

The results confirm the evidence that cross-reactions occur between corticosteroids, since patients also reacted to corticosteroid not marketed in Belgium: cloprednol, dichlorisone acetate, prednisolone succinate, fluprednisolone acetate, isofluprednone acetate, mazipredone, and medrysone within group A; fluchloronide, flumoxonide, halcinnonide, procinnonide, triamcinolone diacetate, triamcinolone hexacetonide, and triamcinolone benetonide within group B; desoxymethasone, fluocortolone, and meprednisone within group C; diflorasone diacetate within group D1, and prednicarbate and hydrocortisone aceponate within group D2.

Recent data from Claudel, Lepoittevin and collaborators (40) confirm that binding to skin proteins,

i.e. arginine, is taking place at C21 after oxidation of the corticosteroid-molecule. The positive patch test results obtained with both corticosteroids and aldehydes (glutaraldehyde and glyoxal) support the hypothesis that such degradation products or metabolites play a role in sensitization (7, 8, 41). In addition, our study confirmed simultaneous positive reactions between corticosteroids and ethanol, which is metabolized by dehydrogenase into acetaldehyde (42, 43).

Wilkinson et al. (6) put forward that corticosteroids without fluorine substitution experience more rapid metabolic degradation and therefore bind more easily to arginine than their fluorinated derivatives, and are thus more likely to induce allergic reactions. This hypothesis could be confirmed for corticosteroids of the D1, D2, most of the C, and also some of the group A corticosteroids. For example, difluprednate, a molecule from the D2 group, despite no methyl substitution in C16 but fluorinated in C6 and C9, gave fewer positive reactions in contrast to other 'labile' esters. However, the halogenated cloprednol, belonging to group A and most corticosteroids of group B, despite halogenation, such as amcinonide, triamcinolone, and triamcinolone acetonide, were often positive. Also betamethasone and dexamethasone, with fluorine substitution on C9 and C6, respectively, produced positive reactions relatively frequently. The influence of halogenation thus remains unclear.

As shown in this study and despite possible concomitant reactions, there is an indisputably significant association between betamethasone and/or dexamethasone (both belonging to group C) and corticosteroids from the acetonide group (B). Already in earlier studies (3) the position of group C was unclear. As mentioned earlier, this group contains more allergenic molecules such as betamethasone and dexamethasone, which is in contrast to their ester derivatives, such as betamethasone –valerate or –propionate, diflucortolone valerate, flumethasone pivalate, that produced only very few positive reactions; this may be due to the fact that they convert less rapidly into aldehydes, because of steric hindrance by the presence of these (stable) esters. It seems more and more evident that this group has to be subdivided into two different subgroups, i.e. esterified and non-esterified molecules. Also fluocortin butylester is a particular molecule that often gives isolated positive reactions within the C group; if considered separately, the total amount of patients reacting only within one group would still be higher.

This study confirms that budesonide, based on the acetal function, being actually an equal mixture of the R and S diastereoisomers (3, 19), is able to cross-react within the acetonide group and also with the ester molecules, i.e. the 'bridged' C16-C17 with

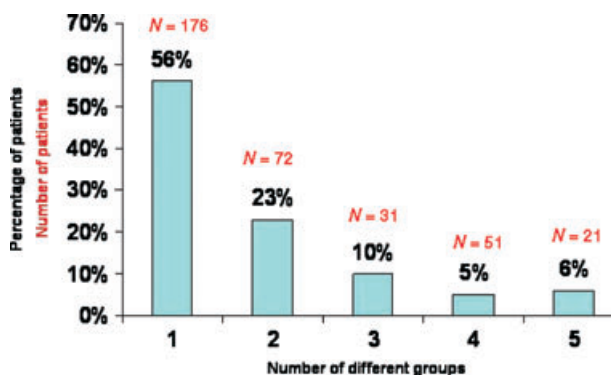


Fig. 3. Results according to the adjusted classification.

group B and the hydrophobic cavity of the S isomer with the ester group.

Taking into account both the Coopman and Matura (clustering A and D2) classifications, the particular position of budesonide, and the subdivision of group C into esterified and non-esterified molecules, 56% of patients reacted only within one group (Fig. 3). Hence, an adjustment of the previous classifications is proposed (Table 5).

Our study showed that more than 1 out of 10 corticosteroid-allergic patients also reacted to sex-hormonal steroids, which has been reported earlier (44, 45). Wilkinson and Beck (46) estimated the prevalence of 17-hydroxyprogesterone allergies in patients reacting positively to hydrocortisone to be 19–26% and considered them to be the expression of cross-sensitivity, without clinical consequences in the majority of the cases. However, corticosteroid allergy may induce an allergy to, e.g. endogenous progesterone, for which the clinical presentation is a generalized eczematous eruption that gets worse during the premenstrual period, the so-called autoimmune progesterone dermatitis (47). On the other hand, any patient presenting symptoms compatible with autoimmune progesterone dermatitis should be tested for corticosteroid allergy as well.

Conclusion

Contact allergy to corticosteroid is an important problem in patients suffering from (chronic) dermatitis and certain molecules such as those belonging to A, B, and D2 (the labile esters) are more apt to induce sensitization than others (e.g. group D1, despite being among the molecules most frequently prescribed in our patient population).

Testing with corticosteroid allergy markers in the baseline series is necessary, since both budesonide and tixocortol pivalate detect 89% of the corticosteroid-allergic patients. However, this study emphasizes the importance to test with the particular corticosteroids used as well.

Most patients (85%) present with multiple positive reactions to corticosteroid which may be due to

Table 5. The adjusted classification of corticosteroids

Group	Characteristics of the group	Typical members	Possible cross-reactions outside the group
A ‘labile esters’ <i>Highest rate of positive reactions</i>	Non-esterified or short C21 esters Labile C17 and/or C21 esters Diastereoisomer S of budesonide No halogen substitution except for cloprednol and budesonide <i>Group A</i> <i>Former group D2</i> <i>Former member of group D1</i> <i>S diastereoisomer</i>	Tixocortol pivalate Cloprednol Cortisone acetate Hydrocortisone Hydrocortisone acetate Hydrocortisone 21-butyrate Hydrocortisone hemisuccinate Mazipredone Medrysone Methylprednisolone acetate Methylprednisolone hemisuccinate Prednisolone Prednisolone metasulpho benzoate Prednisolone succinate Prednisolone pivalate Prednisolone caproate Prednisone Dichlorisone acetate Fludrocortisone acetate Fluorometholone Fluprednisolone acetate Isofluprednone acetate Hydrocortisone 17-butyrate Hydrocortisone aceponate Methylprednisolone aceponate Prednicarbate Difluprednate Alclomethasone dipropionate (particular position) Budesonide	B via budesonide
B <i>Second highest rate of positive reactions</i>	C16, C17 <i>cis</i> ketal or diol structure Diastereoisomer R of budesonide <i>Group B</i> <i>R diastereoisomer</i>	Amcinonide Desonide Fluchloronide Flumoxonide Flunisolide Fluocinolone acetonide Halcinonide Triamcinolone Triamcinolone diacetate Triamcinolone hexacetonide Fluocinonide Triamcinolone benetonide Triamcinolone acetonide Budesonide	A via budesonide

Table 5. (Continued)

Group	Characteristics of the group	Typical members	Possible cross-reactions outside the group
D 'stable esters'	C16 methyl substitution on the D-ring	Beclomethasone dipropionate	
Rarely sensitizing	Side chain ester on C17	Betamethasone dipropionate	
	Possibly a side chain on C21	Betamethasone 17-valerate	
	Halogen substitution	Clobetasol propionate	
		Clobetasone butyrate	
		Difflorasone diacetate	
		Mometasone fuorate	
	Formerly D1	Fluticasone propionate	

concomitant but certainly also to cross-sensitivity; the majority (84%) also react to other allergens.

Binding to skin proteins takes place at C21 after oxidation. In this regard, by steric hindrance, ester derivatives could in certain cases protect the corticosteroid molecules from sensitization, such as in the case of group C and D1 esters. In contrast, in group A and D2 the esters penetrating more easily into the skin and which are rapidly metabolized, promote sensitization. However, the influence of halogenation still remains unclear.

Despite some inconsistent results and unanswered questions, the ABCD classification with its subclassification into D1 and D2 (4, 5), the latter resulting in clustering of both esters from group A and the 'labile' esters from D2, seems to be valid in many cases. However, this study points out some particular observations such as distinction between esterified and non-esterified molecules of group C, and indisputable significant association between betamethasone and/or dexamethasone (group C) and corticosteroids from the acetonide group (B); hence, the previous classifications needed to be adjusted. Indeed, it seems more and more evident that the immune recognition site of the corticosteroid [recognition by the ceramide monohexoside/T cell receptor (CMH/TCR) after protein binding], as Wilkinson (6) suggested, also depends of other parts of the molecule.

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Address:
Marie Baeck
Department of Dermatology
Cliniques Universitaires Saint-Luc, U.C.L.
Avenue Hippocrate, 10
B-1200 Brussels
Belgium
Tel: 00 32 2 764 14 72
Fax: 00 32 2 764 80 27
e-mail: marie.baeck@uclouvain.be