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Allergic contact dermatitis to inhalation corticosteroids

Inhaled and intranasal corticosteroids (CS) are used to treat various inflammatory or allergic diseases of the upper and lower respiratory tract. Despite their wide use, only a few reports about their sensitization potential have been published. We determined the frequency, clinical signs and molecules responsible for skin allergic reactions following inhalation of corticosteroids amongst patients with identified and investigated "contact allergy" to corticosteroids. We reviewed clinical data, patch test results and sensitization sources in patients who reacted positively to corticosteroids tested in the K.U.Leuven Dermatology department during an 18-year period. 12 subjects (out of 315 with contact allergy to CS) presented with allergic manifestations due to nasal or orally inhaled corticosteroids, 11 of which were due to budesonide and one to tixocortol pivalate. Amongst patients with "contact allergy" to corticosteroids, very few were found with allergic manifestations due to inhaled corticosteroids. Budesonide was the major allergen found. Other inhalation corticosteroids such as beclomethasone, mometasone and fluticasone derivatives may, in most cases, still be used, since they do not cross react with budesonide.

Key words: allergy, budesonide, corticosteroids, hypersensitivity, inhalation, nasal, oral, respiratory

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Despite the wide use of inhalation corticosteroids, only a few cases of allergic reactions have been reported [1-18]. Isaksson and co-workers [3], who examined patients suffering from asthma or allergic rhinitis treated with tixocortol pivalate, observed a corticosteroid sensitization rate of 1.4%; among non-asthmatic patients, however, the rate of sensitization was 0.9%, the difference being not statistically significant.

When a respiratory condition fails to improve or worsens following treatment by inhaled corticosteroids, an allergic phenomenon could be suspected among other causes of failure, including non-adherence or refractory disease.

After (oral) inhalation, several adverse effects have been reported: worsening of airway obstruction, expressed as a severe asthma attack/bronchospasm and/or a marked reduction in VEMS (forced expiratory volume in one second) [19-21], or as dry cough [6] or odynophagy/dysphagy [5, 8]. However, skin and mucosal reactions may also arise: eczematous eruption around the orifices (nostrils, nose, lips), with possible locoregional extension *i.e.*, eyelids, cheeks, neck, and thorax [1, 4-6]; erythema and/or oedema of the oral mucosa [5-8]; stomatitis [5, 6, 9]. Sometimes the patient may simply complain of pruritus, a dry or burning sensation [5, 6], but systemic reactions have also been observed, such as urticaria and generalized eczematous eruptions [22, 23].

With regard to nasal administration, the following symptoms have occurred: nasal congestion, nose bleed, inflammation of the nasal fossae and/or sinus cavity, chronic rhinitis [3, 5], and perforation or ulceration of the nasal

septum [7]. Also, painful, nodular intranasal lesions have been reported following the administration of flunisolide and beclomethasone dipropionate aerosols, the latter evolving into superficial haemorrhagic ulcerations [24]. Sometimes, subjects who are not themselves being treated by budesonide-containing aerosols but who are taking care of/or living together with patients who use them because of a chronic respiratory affection, have been sensitized by airborne exposure and/or have presented with airborne allergic contact dermatitis from them [25-28].

Materials and methods

We reviewed the 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, *i.e.* from January 1, 1990 to June 30, 2008. All patients attending the Contact Allergy Unit were examined clinically and routinely patch tested with a baseline (standard) series containing tixocortol pivalate 0.1% pet., included to detect allergic reactions to CS molecules such as hydrocortisone, methylprednisolone and prednisolone, and budesonide 0.01% pet., a marker for CS such as triamcinolone acetonide and amcinonide [29], as well as with hydrocortisone 17-butyrate and prednisone caproate, both diluted 0.1% in ethanol. Moreover, those patients who had been exposed to CSs were, in most cases, also tested with the respective molecules used. Patients with a proven contact allergy to a CS and some, presumed to have such a reaction from the his-

Table 1. Corticosteroid series with the concentration of the test solution

	Name	Vehicle/Concentration	CAS
1	Alclometasone dipropionate	0.5% ethanol	66734-13-2
2	Amcinonide	0.1% ethanol	51022-69-6
3	Beclomethasone dipropionate	0.1% ethanol	5534-09-8
4	Betamethasone	0.1% ethanol	378-44-9
5	Betamethasone dipropionate	0.1% ethanol	5593-20-4
6	Betamethasone sodium phosphate	0.1% saline	151-73-5
7	Betamethasone 17-valerate	0.1% ethanol	2152-44-5
8	Budesonide	0.01% petrolatum 0.002% ethanol	51333-22-3
9	Clobetasol propionate	0.1% ethanol	25122-46-7
10	Clobetasone butyrate	0.1% ethanol	25122-57-0
11	Cloprednol	0.1% ethanol	5251-34-3
12	Cortisone acetate	0.5% ethanol/DMSO	50-04-4
13	Desonide	0.1% ethanol	638-94-8
14	Desoxymethasone	0.1% ethanol	382-67-2
15	Dexamethasone	0.1% ethanol	50-02-2
16	Dexamethasone acetate	0.1% ethanol	1177-87-3
17	Dexamethasone sodium phosphate	0.1% ethanol	2392-39-4
18	Dichlorisone acetate	0.1% ethanol	79-61-8
19	Diflorasone diacetate	0.1% ethanol	33564-31-7
20	Diflucortolone valerate	0.1% ethanol	59198-70-8
21	Difluprednate	0.1% ethanol	23674-86-4
22	Flucloronide	0.1% ethanol	3693-39-8
23	Fludrocortisone acetate	0.1% ethanol	514-36-3
24	Flumethasone pivalate	0.1% ethanol	2002-29-1
25	Flumoxonide	0.1% ethanol	60135-22-0
26	Flunisolide	0.1% ethanol	3385-03-3
27	Fluocinolone acetonide	0.1% ethanol	67-73-2
28	Fluocinonide	1% ethanol	356-12-7
29	Fluocortin butyl	0.1% ethanol	41767-29-7
30	Fluocortolone	0.1% ethanol	152-97-6
31	Fluocortolone caproate	0.1% ethanol	303-40-2
32	Fluocortolone pivalate	0.1% ethanol	29205-06-9
33	Fluorometholone	0.1% ethanol	426-13-1
34	Fluprednidene acetate	0.1% ethanol	1255-35-2
35	Fluprednisolone	0.1% ethanol	53-34-9
36	Fluticasone propionate	0.1% ethanol	80474-14-2
37	Halcinonide	0.1% ethanol	3093-35-4
38	Halometasone	0.1% ethanol	50629-82-8
39	Hydrocortisone	0.5% ethanol/DMSO	50-23-7
40	Hydrocortisone aceponate	1% ethanol	74050-20-7
41	Hydrocortisone acetate	0.1% ethanol	50-03-3
42	Hydrocortisone-17-butyrate	0.1% ethanol	13609-67-1
43	Hydrocortisone-21-butyrate	0.1% ethanol	6677-99-2
44	Hydrocortisone hemisuccinate	0.1% ethanol	2203-97-6
45	Isofluprednone acetate	0.1% ethanol	338-98-7
46	Mazipredone	0.1% ethanol	13085-08-0
47	Medrysone	0.1% ethanol	2668-66-8
48	Meprednisone	0.1% ethanol	1247-42-3
49	Methylprednisolone aceponate	0.1% ethanol	86401-95-8
50	Methylprednisolone acetate	0.1% ethanol	53-36-1
51	Methylprednisolone hemisuccinate	0.1% ethanol	2921-57-5
52	Mometasone furoate	0.1% ethanol	83919-23-7
53	Pivalate tixocortol	0.1% petrolatum	55560-96-8
54	Prednicarbate	1% ethanol	73771-04-7

(continued)

Table 1 (continued)

	Name	Vehicle/Concentration	CAS
55	Prednisolone	0.1% ethanol	50-24-8
56	Prednisolone caproate	0.1% ethanol	69164-69-8
57	Prednisolone sodium metasulphobenzoate	0.1% ethanol	630-67-1
58	Prednisolone pivalate	0.1% ethanol	1107-99-9
59	Prednisolone hemisuccinate	1% ethanol	2920-86-7
60	Prednisone	0.1% ethanol	53-03-2
61	Procinonide	0.1% ethanol	58497-00-0
62	Progesterone	2% ethanol	57-83-0
63	Testosterone propionate	2% ethanol	57-85-2
64	Triamcinolone	0.1% ethanol	124-94-7
65	Triamcinolone acetonide	0.1% ethanol	76-25-5
66	Triamcinolone benetonide	0.1% ethanol	31002-79-6
67	Triamcinolone diacetate	0.1% ethanol	67-78-7
68	Triamcinolone hexacetonide	1% ethanol	5611-51-8
69	Ethanol	70% water	64-17-5
70	Ethanol/DMSO	50/50% water	64-17-5/67-68-5
71	Glutaraldehyde	1% water	111-30-8
72	Glyoxal	2% water	107-22-2

tory, were later tested with an extended CS series in order to study simultaneous positive (and cross) reactions. Sixty-six CSs, including those from the baseline series, were thus tested (table 1). All corticosteroids (except for the 2 screening agents once officially added to the baseline series, 4) were compounded in the Contact-allergy Unit by a laboratory technician; the substances used for these preparations had been obtained from the pharmaceutical companies marketing them. Dexamethasone Naphosphate was introduced from November 1990 and difluprednate (Sicor, Milan, Italy), a corticosteroid only recently (2008) marketed to treat ocular pain [30], was included from October 1994 onwards.

Ethanol was the vehicle used to test all corticosteroid molecules except for tixocortol pivalate and budesonide for which petrolatum works well [31, 32]. Due to their weak trans-epidermal penetration, hydrocortisone and cortisone acetate were diluted in an equal mixture of ethanol and dimethyl sulfoxide (DMSO) [31]. Both ethanol and ethanol/DMSO were included as controls in the extended series. The concentrations of the test solutions were defined according to the studies of Isaksson and co-workers [33, 34] (table 1). 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 to 12 months. Although CSs are unstable in ethanol and may degrade after just one month of storage in a refrigerator, it has been shown that skin tests carried out with fresh and preserved solutions give comparable results [35]. This might relate to the fact that the actual allergen is a degradation product rather than the CS itself, therefore instability in the solution should not affect the sensitivity of the test. We did, however, not check the stability of the aged preparations. 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 clearly positive tests (at least palpable erythema) were taken into account in this study. Although, in general, dubious reactions 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.

The results were collected from a computer database containing the following information: sex, birth date, occupation, personal and familial atopic history, localization and lesion types, use of CSs, 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 well as according to the follow-up of the patients in whom the dermatitis got better, *e.g.* in the case of an underlying disease such as atopic or seborrheic dermatitis, or which 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 nonparametric tests of one-dimensional probability distributions used to compare a sample with a reference probability distribution or to compare two independent samples.

The study and data accumulation were conducted with the approval of the Institutional Ethical Committee, Commission d'Éthique Biomédicale Hospitalo-Facultaire de l'Université Catholique de Louvain (NCT 340320084407).

Results

12 (3.8%) out of 315 corticosteroid allergic patients (table 2) presented reactions following orally and/or nasally inhaled corticosteroids. Most of them (10/12) (nrs. 1, 2, 3, 4, 5, 6, 7, 9, 10, 12) presented with facial eczema most pronounced around the orifices, *i.e.* eyes, nose and mouth. Figures 1A, B provide an example of an eczematous flare-up reaction during patch-testing with the budesonide-

Table 2. List of patients with delayed allergic hypersensitivity following inhalation of corticosteroids

	Sex	Age	Occupation	Lesion location	Date cons.	Positive tests to CS	Other positive tests	Corticosteroids exposure
1	F	39	Office work	Face	04/2005	Budesonide+++, amcinonide++, desonide+, flumoxonide ++, triamcinolone+, hydrocortisone aceponate++, maziapredonum+, alclomethasone dipropionate++, prednicarbate++, methylprednisolone aceponate++, difluprednate+, hydrocortisone 17-butyrate++, ethanol+, ethanol DMSO+	Fragrance mix I, myroxyton pereirae, nickel, cobalt chloride, paraphenylenediamine	Buccal inhalation of budesonide
2	F	48	Housewife	Eyelids – eyes (conjunctivitis)	02/2004	Budesonide+, tixocortol pivalate+	Neomycin	Buccal inhalation of budesonide
3	F	43	Office work	Nose and perinasal areas	06/2000	Budesonide+, methylprednisolone aceponate+		Buccal and nasal inhalation of budesonide and nasal inhalation of prednisolone
4	F	43	Housekeeping	Face – eyelids – arms	05/1998	Budesonide++, amcinonide++, hydrocortisone hemisuccinate++, medrysone++, prednisolone metasulpho-benzoate+, triamcinolone++, hydrocortisone aceponate+, prednicarbate++, methylprednisolone aceponate++, hydrocortisone 17-butyrate++, ethanol++, testosterone propionate++	Propylene glycol, wool alcohols, amercol L101, euxyl K400™	Nasal inhalation of prednisolone and buccal inhalation of beclomethasone dipropionate, fluticasone propionate and budesonide
5	F	46	Housekeeping	Nose – eyelids – face	12/1998	Budesonide++, amcinonide++, cortisone acetate+, hydrocortisone aceponate+, alclomethasone dipropionate ++, methylprednisolone aceponate+, prednisolone caproate+	Fragrance mix I, colophonium	Nasal inhalation of budesonide
6	F	13	Student	Nose and perinasal areas	03/2000	Budesonide++, tixocortol pivalate+, amcinonide++, prednicarbate+	Fragrance mix I, colophonium	Nasal inhalation of budesonide
7	F	60	Housekeeping	Face	02/1997	Tixocortol pivalate++, cloprednol++, fludrocortisone acetate++, methylprednisolone acetate++, prednisolone sodium metasulphobenzooate++, prednisolone succinate+ +, hydrocortisone aceponate++, maziapredonum++, prednicarbate+++, methylprednisolone aceponate+++, prednisolone caproate+		Nasal inhalation of tixocortol pivalate
8	M	57	Office work	Generalized	01/1995	Budesonide++, tixocortol pivalate++, amcinonide++, beclomethasone dipropionate+, betamethasone+, betamethasone dipropionate+, betamethasone 17-valerate+, clobetasol propionate+, clobetasone butyrate+ +, cloprednol+, desonide++, dexamethasone acetate+, flucoronide++, fludrocortisone acetate+, flumoxonide+, fluprednidene acetate+, halcinonide++, methylprednisolone acetate+, momethasone furoate++, prednisone+, progesterone+, triamcinolone+, triamcinolone diacetate+, triamcinolone hexacetone+, flucocinonide+, triamcinolone benetonide+, fluticasone propionate+, hydrocortisone aceponate+, alclomethasone dipropionate+, triamcinolone acetoneide++, prednicarbate	Myroxyton pereirae	Buccal inhalation of budesonide

(continued)

Table 2 (continued)

Sex	Age	Occupation	Lesion location	Date cons.	Positive tests to CS	Other positive tests	Corticosteroids exposure
9	F	42	Education	12/1995	++, methylprednisolone aceponate+, prednisolone caproate+, ethanol+ Budesonide+++, amcinonide+++, beclomethasone dipropionate+, betamethasone++, cortisone acetate+++, desonide+++, desoxymethasone++, dexamethasone+, flunisolide++, fluocinolone acetoneide++, fluocortin butyl ++, halcinonide++, hydrocortisone 21-butyrate++, hydrocortione hemisuccinate++, medrysone++, methylprednisolone hemisuccinate++, momethasone furoate++, hydrocortisone+, prednisone++, procinonide+, progesterone++, triamcinolone+++, triamcinolone diacetate++, triamcinolone hexacetoneide++, fluocinonide ++, triamcinolone benetonide++, hydrocortisone aceponate++, hydrocortisone 17-butyrate++, prednisolone caproate+, glyoxal ++, ethanol+ Budesonide+++, cloptrenol +++, prednisolone metasulpho benzoate++, prednisone++, hydrocortisone aceponate++, prednicarbate++, methylprednisolone aceponate+++, hydrocortisone aceponate++, prednisolone caproate++ Budesonide++, amcinonide+++, desonide++, flunisolide +, fluocinolone acetoneide+, triamcinolone+, fluocinonide +, triamcinolone acetoneide+, hydrocortisone 17-butyrate+ Budesonide++, amcinonide++	Potassium dichromate, cobalt chloride, paraphenylenediamine	Buccal inhalation of flunisolide and budesonide
10	F	34	Office work	03/1996	Face – generalized	Potassium dichromate, cobalt chloride, paraphenylenediamine	Nasal inhalation of budesonide
11	F	63	Housekeeping	11/1996	“Décolleté” – generalized	Budesonide++, amcinonide+++, desonide++, flunisolide +, fluocinolone acetoneide+, triamcinolone+, fluocinonide +, triamcinolone acetoneide+, hydrocortisone 17-butyrate+	Buccal and nasal inhalation of budesonide
12	F	57	Housekeeping	03/1993	Face – lips – tong	Paraphenylenediamine, diaminodiphenylmethane	Buccal inhalation of budesonide



Figure 1. A) Eczematous flare-up reaction during patch-testing with the budesonide-containing nasal preparation used. B) Positive patch test to the budesonide-containing preparation used.

containing nasal preparation used. One patient (nr. 12) also presented with stomatitis and another (nr. 2) with conjunctivitis. 3 patients (nrs. 8, 10, 11) developed a generalized eczematous or maculo-papular eruption. *Figure 2* illustrates a generalized maculo-papular eruption caused by inadvertent nasal use of budesonide during patch-testing; this woman was previously sensitized by a budesonide-containing aerosol. All patients (except case nr. 7) had used nasal sprays and/or aerosols containing budesonide, with some of them also other inhalation CSs, *i.e.* fluticasone propionate (nr. 4), beclomethasone dipropionate (nr. 4), prednisolone (nr. 3), tixocortol pivalate (nr. 7), and flunisolide (nr. 9).

Some patients (nrs. 1, 5 and 6) also tested positive to other potentially responsible allergens, such as fragrance-mix, but avoidance of this allergen did not relieve the symptoms; in fact, they only improved when exposure to the particular aerosols was stopped.

All patients (except nr. 7) tested positively to budesonide, most of them with concomitant or cross-reactions with corticosteroids with an acetonide structure (group B following the Coopman *et al.* [36] classification) (nr. 1, 4, 5, 6, 8, 9, 11, 12) and to CSs esters that are metabolized in the skin (group D2) [37], *i.e.* the “labile esters” (nr. 1, 3, 4, 5, 8, 9, 10, 11). This is ascribed to the acetal function in budesonide, with its R and S diastereoisomers, the R-sensitive subjects reacting to group B, the S-sensitive ones to group D2 corticosteroids [38, 39]. Patient nr. 9 also tested positive to flunisolide, which he had used as well. Patient nr. 7 reacted to tixocortol pivalate (also used as a marker for other group A corticosteroids to which he reacted) which was present in the nasal spray he had used; cross-reactions with labile D2 esters group were also observed.

Discussion and conclusion

Patients allergic to inhalation corticosteroids mainly present with loco-regional eruptions *i.e.* eczema around the nose, mouth and/or eyes with possible spreading to the face and neck. However, sometimes generalized eruptions also occur.



Figure 2. Generalized maculo-papular eruption caused by inadvertent nasal inhalation of budesonide during patch-testing; this woman was previously sensitized by a budesonide-containing oral aerosol.

Amongst patients with identified and investigated “contact allergy” to corticosteroids, very few presented with an “allergic contact dermatitis” or other allergic manifestations when using inhaled corticosteroids. Budesonide, the molecule most frequently used in liquid aerosols, is the principal allergen involved, while other corticosteroids seem only exceptionally responsible for allergies. Patients often present multiple positive reactions to corticosteroids which may be due to simultaneous or subsequent sensitization, or to cross-reactivity [36, 37, 40], (although an adjustment of these classifications has recently been proposed, [41]). However, patients allergic to budesonide can in most cases still be treated by aerosols containing CSs, such as beclomethasone, fluticasone, or mometasone derivatives (belonging to group D1 esters, [37]), since they are not cross reacting. Contact-allergic reactions to the latter, as observed in patients nrs. 8 and 9, are indeed extremely rare.

This study also highlights the need to inform patients and those who are taking care of them about the possibility of allergic reactions to inhalation corticosteroids, which may appear paradoxical in the context of the treatment of inflammatory/allergic diseases of the upper and/or lower airways. Budesonide is the main culprit, but following a careful history and appropriate drug testing, an alternative treatment can be proposed. ■

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