

Patients with airborne sensitization/contact dermatitis from budesonide-containing aerosols ‘by proxy’

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Background: Inhalation corticosteroids (CSs), despite their wide use, rarely cause sensitization in subjects administering them.

Objective: To determine the cause of sensitization and/or of allergic contact dermatitis which occurred in air-exposed body areas of patients reacting to corticosteroids and to budesonide, in particular.

Methods: We reviewed the 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.

Results: Fifteen subjects, not themselves treated by budesonide-containing aerosols, but taking care of/or living together with patients who used them because of a chronic respiratory affection, appeared to have been sensitized by airborne exposure and/or presented with airborne allergic contact dermatitis from them.

Conclusion: Air exposure to inhalation corticosteroids used ‘by proxy’ and to budesonide, in particular, needs to be taken into account as a potential cause of primary sensitization and/or airborne allergic contact dermatitis, sometimes also in an occupational context.

Key words: airborne; allergic contact dermatitis; budesonide; ‘by proxy’; connubial; consort; corticosteroid; inhaled corticosteroids; primary sensitization. © John Wiley & Sons A/S, 2009.

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Despite the wide use of inhaled corticosteroids (CSs), few cases of asthmatic patients experiencing allergic reactions have been reported (1–18). Isaksson et al. (3), who examined patients suffering from asthma or allergic rhinitis treated with tixocortol pivalate, observed a corticosteroids sensitization rate of 1.4%; among non-asthmatic patients, however, the rate of sensitization was 0.9%, the difference being not statistically significant.

Raison-Peyron et al. (19) were the first authors to describe connubial or consort contact dermatitis from an inhalation corticosteroid-containing budesonide in the mother of a 3-year old boy treated for asthma. Moreover, Ponten (20) and also more recently Corraza (21) reported on airborne contact dermatitis from occupational exposure to such

aerosols, notwithstanding the extremely low concentrations involved (20).

Materials and methods

We reviewed the patch test results and sensitization sources in patients who reacted positively to corticosteroids obtained during an 18-year study period, i.e. from January 1, 1990 to June 30, 2008. All patients attending the Contact Allergy Unit at the Dermatology department, K.U. Leuven, were patch tested with a baseline series containing tixocortol pivalate and budesonide (22), to which hydrocortisone 17-butyrate and prednisone caproate, both diluted to 0.1% in ethanol, were added. Those patients having been exposed to corticosteroids

were, in most cases, also tested with the respective corticosteroid molecules, and 315 patients were tested with an extended corticosteroid series (the details of which will be published separately), of whom most reacted positively to several corticosteroids.

A total of 66 corticosteroids, including 4 in the baseline series, and two sex hormones, i.e. progesterone and testosterone, were thus tested (Table 1). All corticosteroids (except the two screening agents in the baseline series) 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. The test solutions were freshly made every 6–12 months.

Although petrolatum works well for tixocortol pivalate and budesonide, ethanol was the vehicle used to test all other corticosteroid molecules (23–24). Owing to their weak trans-epidermal penetration, hydrocortisone and cortisone acetate are exceptions to this rule and optimally require an equal mixture of ethanol and dimethyl sulfoxide (DMSO) for their preparation (23). Besides ethanol and ethanol/DMSO as controls, glutaraldehyde and glyoxal were also included in this series. Dubious reactions were excluded, weak irritant reactions to the DMSO/eth. (even in the presence of hydrocortisone) could not always be ruled out with certainty.

The concentrations of the test solutions were defined according to the studies of Isaksson et al. (25–26). Particularly, for budesonide, lower concentrations were also tested, i.e. 0.01% pet. and 0.002% eth.

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 D2, and the patch test reactions were evaluated at D2, D4, and in many cases also after D7, according to the ICDRG criteria. To interpret the results, all positive tests in this study were considered, irrespective of the test concentration.

The results were collected from a database containing the following information: sex, birthday, occupation, personal and familial atopic history, localization and lesions' type, exposure to corticosteroids (names and classes, according to Coopman et al. (27)), patch test results, and sensitization sources. 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 of whom the dermatitis got better or disappeared when stopping the use of the incriminated corticosteroid.

Results

With regard to the sensitization route of the corticosteroid, despite the ignorance of the exact exposure patterns in all patients and the different contacts with multiple preparations, 15 (14 women and 1 man) out of 315 corticosteroid-allergic patients (5%) who were not themselves treated by aerosols, but who took care and/or lived together with patients using them regularly, appeared to have been sensitized by airborne exposure, in particular to budesonide. Nine of them also presented clinical signs of airborne contact dermatitis. Figures 1 and 2 provide an example of an airborne contact dermatitis on the face with flare-up reactions of previously affected sites that had been treated with a budesonide-containing topical product, i.e. hands. The dermatitis occurred following the treatment of her child for asthma with an inhalation corticosteroid-containing budesonide. Table 2 lists all patients with airborne sensitization to and/or contact dermatitis 'by proxy' from budesonide aerosols.

Twelve out of the 315 patients (4%) presented with a skin reaction due to the personal use of nasal or oral inhalation corticosteroids, the patch test results of whom will not be discussed here.

Likely primary sensitization through airborne exposure (six patients)

Three women (nos 4, 10 and 13, Table 2) presented with a positive patch test reaction to budesonide only, but no obvious clinical relevance was found since they had never used themselves budesonide nor other Group B corticosteroids in the past. Only one patient (no. 13) had previously applied a preparation containing hydrocortisone 17-butyrate (Locoid®, Astellas Pharma, Tokyo, Japan) that may cross react with budesonide (28), but which tested negatively.

The patients consulted for dermatitis on the scalp, legs and axillae, respectively, the latter localization sometimes observed with airborne exposure (29). However, all three had been exposed to the budesonide-containing aerosol Pulmicort® (AstraZeneca, London, UK): one by taking care of a child, one of whom her husband regularly inhaled it, and a further one, a nurse, who had contact with budesonide, both through occupational (patients treated by aerosols) and personal exposure (father asthmatic, daily treated by inhalation). Patient no. 10 had also been exposed to beclometasone dipropionate-containing aerosol, the CS remaining negative on patch testing.

Two women (nos 7 and 12, Table 2) tested positively to budesonide and also to other corticosteroid molecules from Group B. They had never used preparations containing such corticosteroids, but had

been treated with hydrocortisone that belongs to Group A, which classically does not cross-react with budesonide nor with other molecules from the B group (27–28). However, they both lived in the same room with patients inhaling budesonide, i.e. the mother in the first and son in the second case, respectively. However, these two patients consulted for hand and feet eczema and had no clinical signs related to the corticosteroid airborne exposure.

One man (no. 5, Table 2), who presented with foot eczema, reacted positively to budesonide and to other corticosteroid from Groups B and C, all of which he had never used. He had only been exposed to a topical preparation containing hydrocortisone 17-butyrate, which tested negatively. However, his father and girlfriend were both asthmatic and daily treated with corticosteroid

aerosols containing budesonide and fluticasone propionate, the latter of which remained negative on patch testing.

Airborne allergic contact dermatitis (nine patients)

Nine patients (nos 1, 2, 3, 6, 8, 9, 11, 14 and 15, Table 2), all females, presented with eyelid and/or facial eczema suspected to be contact or airborne contact dermatitis. All had daily contact with patients treated with budesonide-containing aerosols. Patch tests data showed positive tests to at least one corticosteroid, i.e. budesonide, and sometimes also to others corticosteroid molecules. Some of them were also exposed to aerosols containing fluticasone propionate (nos 2 and 11) or beclomethasone dipropionate (no. 15), however, patch tests with the respective molecules remained negative. Other aerosols components, i.e. salmeterol (Seretide®),

Table 1. CS series with the concentration of the test solution and reaction rates for each CS

	INN English	Vehicle/concentration	CAS	Number of positive tests (314 subjects in total)
1	Ethanol	70% water	64-17-5	24
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 Na-phosphate	0.1% saline	151-73-5	9
7	Betamethasone 17-valerate	0.1% eth	2152-44-5	19
8	Clobetasol propionate	0.1% eth	25122-46-7	16
9	Clobetasone butyrate	0.1% eth	25122-57-0	25
10	Cloprednol	0.1% eth	5251-34-3	61
11	Cortisone acetate	0.5% eth/DMSO	50-04-4	67
12	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 Na-phosphate	0.1% eth	2392-39-4	9
17	Diflorasone diacetate	0.1% eth	33564-31-7	10
18	Diflucortolone valerate	0.1% eth	59198-70-8	6
19	Fluchloronide	0.1% eth	3693-39-8	15
20	Fludrocortisone acetate	0.1% eth	514-36-3	25
21	Flumethasone pivalate	0.1% eth	2002-29-1	6
22	Flumoxonide	0.1% eth	60135-22-0	34
23	Flunisolide	0.1% eth	3385-03-3	15
24	Fluocinolone acetonide	0.1% eth	67-73-2	27
25	Fluocortin butyl	0.1% eth	41767-29-7	42
26	Fluocortolone	0.1% eth	152-97-6	7
27	Fluocortolone caproate	0.1% eth	303-40-2	13
28	Fluocortolone pivalate	0.1% eth	29205-06-9	9
29	Fluorometholone	0.1% eth	426-13-1	13
30	Fluprednidene acetate	0.1% eth	1255-35-2	10
31	Fluprednisolone acetate	0.1% eth	53-34-9	15
32	Halcinonide	0.1% eth	3093-35-4	11
33	Halomethasone	0.1% eth	50629-82-8	6
34	Hydrocortisone acetate	0.1% eth	50-03-3	48
35	Hydrocortisone 21-butyrate	0.1% eth	6677-99-2	66
36	Hydrocortisone hemisuccinate	0.1% eth	2203-97-6	15
37	Isofluprednone acetate	0.1% eth	338-98-7	14
38	Medrysone	0.1% eth	2668-66-8	23
39	Meprednisone	0.1% eth	1247-42-3	24
40	Methylprednisolone acetate	0.1% eth	53-36-1	58
41	Methylprednisolone hemisuccinate	0.1% eth	2921-57-5	17
42	Momethasone fuorate	0.1% eth	83919-23-7	15
43	Prednisolone	0.1% eth	50-24-8	55
44	Hydrocortisone	0.5% eth/DMSO	50-23-7	99
45	Prednisolone metasulfate benzoate	0.1% eth	3694-41-5	48

Table 1. (Continued)

	INN English	Vehicle/concentration	CAS	Number of positive tests (314 subjects in total)
46	Prednisolone succinate	1% eth	2920-86-7	13
47	Prednisone	0.1% eth	53-03-2	43
48	Procionide	0.1% eth	58497-00-0	29
49	Progesterone	2% eth	57-83-0	31
50	Testosterone propionate	2% eth	57-85-2	38
51	Triamcinolone	0.1% eth	124-94-7	65
52	Triamcinolone diacetate	0.1% eth	67-78-7	27
53	Triamcinolone hexacetonide	1% eth	5611-51-8	39
54	Dichlorisone acetate	0.1% eth	79-61-8	30
55	Fluocinonide	1% eth	356-12-7	29
56	Triamcinolone benetonide	0.1% eth	31002-79-6	42
57	Fluticasone propionate	0.1% eth	80474-14-2	14
58	Hydrocortisone aceponate	1% eth	74050-20-7	86
59	Mazipredone	0.1% eth	13085-08-0	67
60	Alclomethasone dipropionate	0.5% eth	66734-13-2	57
61	Triamcinolone acetonide	0.1% eth	76-25-5	51
62	Prednicarbate	1% eth	73771-04-7	111
63	Methylprednisolone aceponate	0.1% eth	86401-95-8	105
64	Glutaraldehyde	1% aq	111-30-8	17
65	Glyoxal	2% aq	107-22-2	11
66	Prednisolone pivalate	0.1% eth	1107-99-9	46
67	Ethanol DMSO		64-17-5/67-68-5	38
68	Diffuprednate	0.1% eth	23674-86-4	15
69	Tixocortol pivalate	0.1% pet	55560-96-8	135
70	Budesonide	0.01% pet 0.002% eth	51333-22-3	191
71	Hydrocortisone-17-butyrate	0.1% eth	13609-67-1	96
72	Prednisolone caproate	0.1% eth	69164-69-8	70



Fig. 1. Airborne contact dermatitis on the face with flare-up reactions of previously affected sites that had been treated with a budesonide-containing topical product.

GlaxoSmithKline, Brentford, UK) (nos 2 and 9) and association of ipratropium bromide and salbutamol (Combivent[®], Boehringer Ingelheim BV, Ingelheim am Rhein, The Netherlands) (patient no. 9) tested negatively as well. Some of the patients (nos 8, 11, 14 and 15) also tested positively to other potentially



Fig. 2. Affected sites on the hands treated with budesonide-containing topical product.

responsible allergens such as methyldibromogluta-nitrile and fragrance-mix, but avoidance of these allergens did not relieve the symptoms, which only improved when exposure to the budesonide-containing aerosol was stopped. For most patients, 'by proxy' airborne exposure was also probably the sensitization route. This was certainly the case for two women (nos 1 and 8), who reacted exclusively to budesonide and who were exposed to aerosols regularly used by family members. Besides eyelid and facial eczema, respectively, the second one also presented with stomatitis.

One woman (no. 2, Table 2) was occupation-ally involved in child care and had experienced improvement of her facial and eyelid eruption during weekend and holidays. She tested positively to budesonide as well as to hydrocortisone aceponate

Table 2. List of patients with airborne sensitization and/or contact dermatitis to corticosteroids

Sex	Age	Occupation	Lesion location	Date cons.	Positive tests to corticosteroids	Other positive tests	Budesonide aerosol exposure	Relevance
1	F 44	Office work	Eyelids	May 2006	Budesonide++		Daughter	Contact dermatitis
2	F 51	Children day-care	Face and eyelids	October 2007	Budesonide+, hydrocortisone aceponate++, alclomethasone dipropionate+, prednicarbate++	Nickel sulphate, cobalt chloride	Son and children day-care ^a	Contact dermatitis
3	F 59	Office work	Eyelids	September 2007	Budesonide+, hydrocortisone aceponate+, prednicarbate+		Father and grand-son	Contact dermatitis
4	F 58	Unknown	Scalp	November 2001	Budesonide+	Methylidibromoglutaronitrile	Grand-daughter	Sensitization
5	M 27	Prison guard	Feet	November 2005	Budesonide++, amcinonide++++, beclomethasone dipropionate++, betamethasone++, desonide++, desoxymethasone+, dexamethasone+, flunisolide++ –fluocinolone acetoneide++, fluocortin butyl ester+, procinonide+, triamcinolone+, triamcinolone hexacetoneide+, fluocinonide++, triamcinolone benetonide+, triamcinolone acetoneide++, prednicarbate+, glyoxal++	Fragrance mix I, myroxylon pereirae	Girlfriend ^a	Sensitization
6	F 36	Teacher	Eyelids	January 2005	Budesonide++, amcinonide+, hydrocortisone aceponate+ –prednicarbate+	Nickel sulphate	Daughter	Contact dermatitis
7	F 40	Housewife	Hands	February 2004	Budesonide++, triamcinolone benetonide+	Nickel sulphate, cobalt chloride, fragrance mix I	Mother	Sensitization
8	F 51	Unknown	Face and oral cavity	April 2004	Budesonide++	Myroxylon pereirae, colophonium, fragrance mix I	Daughter	Contact dermatitis
9	F 42	Office work	Eyelids	June 2002	Budesonide++, amcinonide++, betamethasone++, desonide++, dexamethasone++, flumoxonide+, flunisolide+, fluocinolone acetoneide+, fluocortin butyl ester+, progesterone+, triamcinolone+, triamcinolone hexacetoneide++, fluocinonide+, triamcinolone benetonide+, hydrocortisone aceponate+, triamcinolone acetoneide+, prednisolone pivalate+, ethanol++	Neomycin	Daughter ^a	Contact dermatitis
10	F 58	Unknown	Legs	May 2003	Budesonide++	Myroxylon pereirae, colophonium, wool alcohols, parabens	Husband ^b	Sensitization

Table 2. (Continued)

	Sex	Age	Occupation	Lesion location	Date cons.	Positive tests to corticosteroids	Other positive tests	Budesonide aerosol exposure	Relevance
11	F	41	Dentist	Face and hands	March 2003	Budesonide++++, amcinonide++++, beclomethasone dipropionate+, betamethasone++++, clobetasone butyrate++, desonide++, desoxymethasone++, dexamethasone++, fluchloronide+, flumoxonide++, flunisolide++++, fluocinolone acetone++++, fluocortin butyl+, halcinonide++++, procinonide++, triamcinolone++, triamcinolone hexacetone++, fluocinonide++, triamcinolone benetonide++++, hydrocortisone aceponate++, alclomethasone dipropionate++, triamcinolone acetone, prednicarbate+, methylprednisolone aceponate++	Neomycin, wool alcohols, thiuram mix, Euxyl K400 TM , epoxy resin, 2-bromo-2-nitropropane-1,3-diol	Son ^a	Contact dermatitis
12	F	39	Farmer	Feet	December 1998	Budesonide+++, amcinonide++	Nickel sulphate, cobalt chloride, fragrance mix I, Euxyl K400 TM	Son	Sensitization
13	F	25	Nurse	Armpits	January 1998	Budesonide+	Nickel sulphate fragrance mix I	Father and patients	Sensitization
14	F	29	Office work	Face and Eyelids	January 2000	Budesonide+, hydrocortisone aceponate+, prednicarbate++, methylprednisolone aceponate+, prednisolone pivalate+, hydrocortisone 17-butyrate++, testosterone propionate+, ethanol/DMSO+	Potassium dichromate, cobalt chloride, colophonium, paraphenylenediamine, myroxylon pereirae, methyl/dibromo glutaronitrile	Son	Contact dermatitis
15	F	44	Housewife	Face	March 2008	Budesonide++, amcinonide++, flunisolide+, fluocortin butyl+++, fluocortolone pivalate+, fluorometholone+, fluprednisolone acetate+, hydrocortisone acetate+, hydrocortisone 21-butyrate+, hydrocortisone hemisuccinate++, prednisolone metasulfo-benzoate+, triamcinolone++++, dichlorisone acetate+, triamcinolone benetonide+, hydrocortisone aceponate+, mazipredone+, alclomethasone dipropionate+, prednicarbate++, methylprednisolone aceponate+, prednisolone pivalate+, hydrocortisone 17-butyrate++, progesterone+, testosterone propionate+, ethanol/DMSO+	Fragrance mix I, sorbitan sesquileate	Daughter and son ^b	Contact dermatitis

^aAlso fluticasone propionate.^bAlso beclomethasone dipropionate, both reacting negative on patch testing.

and prednicarbate (both labile esters from Group D2). Other potentially responsible allergens such as preservatives, cosmetics or fragrance components tested negatively. She had never used topical corticosteroid herself, but was treating, on a daily basis, children in the day-care centre and recently also her son, with inhalation corticosteroids containing budesonide and fluticasone propionate, the latter remaining negative on patch testing.

Six more patients (nos 3, 6, 9, 11, 14 and 15, Table 2) had asthmatic children and presented with facial and/or eyelid eczema that had developed a few times after having been exposed to inhalation corticosteroid. None of them had used budesonide nor corticosteroids from Group B previously, but did react to different corticosteroids including budesonide; One of them (no. 11) also reacted to beclomethasone dipropionate that had never been used by family members. One patient (no. 15) had used hydrocortisone 17-butyrate in the past and reacted to its metabolite, the 21-ester.

Cross/concomitant reactions patterns

Five out of 15 patients (33%) (nos 1, 4, 8, 10 and 13, Table 2) tested positively to budesonide only and two additional patients (nos 7 and 12) to budesonide and other B group corticosteroid molecules. Four patients (27%) (nos 5, 6, 9 and 14) who had never used corticosteroids from the D2 group in the past, i.e. hydrocortisone 17-butyrate and/or methylprednisolone aceponate, presented positive reactions to budesonide and corticosteroid from D2. The remaining four (27%) patients (nos 5, 9, 11 and 15) tested positively to multiple corticosteroid molecules from the B–C–D1 and D2 groups, and one of them to corticosteroids from all five classes.

Follow-up

All 15 patients were contacted again by letter (February 2009) in order to obtain information on the evolution of their clinical symptoms, whether they were still exposed to aerosols, and on the outcome of avoidance. Ten out of 15 patients (66%) replied to our questionnaire, i.e. seven (nos 2, 3, 6, 8, 9, 11 and 15, Table 2) with a history of airborne contact dermatitis and three (nos 5, 7 and 10, Table 2) with airborne sensitization. Among the seven patients with clinical symptoms earlier, four were still exposed to aerosols used by relatives, but definitely tried to avoid contact with them. Their clinical symptoms clearly got better on avoidance. The other three patients had no symptoms anymore but had no patients near-by who used aerosols regularly.

Three patients with airborne sensitization were still, but to a lesser extent and only occasionally,

exposed to subjects using corticosteroid aerosols, but did not present any dermatitis.

Discussion

This study reports on a series of 15 budesonide-allergic patients exposed to aerosols containing this corticosteroid after taking care or living together with patients who used them regularly because of a chronic respiratory affection. Some of them were also exposed to fluticasone propionate and/or beclomethasone dipropionate-containing aerosols, which remained negative on patch testing. Most of them seemed to have been sensitized by 'by proxy' aerosol exposure and nine of them also presented with typical symptoms of an airborne contact dermatitis, which only improved when budesonide-containing-aerosol exposure was avoided.

For two patients, the exposure was occupationally related, i.e. for a nurse and a woman who was working in a day-care centre for children, respectively.

corticosteroids, and in particular budesonide, are not classically described as airborne allergens. The airborne nature in these cases was judged on the basis of: the exposure route of the allergen, i.e. aerosols, the particular distribution pattern of the dermatitis, the nature of the lesions, the history and follow-up of the patients, and the results of epicutaneous testing.

Connubial, consort or 'by proxy' dermatitis are dermatitis in which lesions are due to substances not used by the patient themselves but by the partner or other persons who live near-by. Reported cases are produced after exposure to different allergens, particularly cosmetics and perfumes (30).

With regard to corticosteroids, this type of dermatitis has also previously been described (19–21), mainly through occupational exposure (20–21). In this study, however, most patients were exposed in a familial (not professional) context, a sensitization source frequently overlooked.

The higher rate of sensitization in individuals exposed to corticosteroid aerosols used by patients near-by compared with patients effectively treated themselves with such products is possibly due to induction of oral tolerance: systemic absorption during the first contacts with the allergens through the oral mucosa may facilitate tolerance or non-sensitization, instead of active sensitization. Systemic immunological unresponsiveness or 'oral tolerance' has indeed been described by several authors (31–34), such as, for example, with nickel and chromium (35).

One-third of the patients tested positively to budesonide only. Two-thirds reacted positively to budesonide and/or other B group molecules and/or also to corticosteroids from the D2 group, which is

due 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 CSs (27–28, 36–37).

Conclusion

Air exposure to inhalation corticosteroids and to budesonide, in particular, needs to be taken into account as a potential cause of primary sensitization and/or airborne allergic contact dermatitis. However, patients who use nasal or oral inhalation corticosteroids personally seem to be less apt to become sensitized than those who are taking care of or living together with patients who use them regularly, which may be attributed to 'oral tolerance induction'. All patients described here were exposed through members of their families and two of them also from occupational exposure.

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