

Original article

Corticosteroid allergy in asthma

Background: Glucocorticosteroids form the basis of therapy for asthma and other allergic diseases. However, they frequently cause delayed contact allergy and occasionally immediate allergy. The purpose of this study was to investigate the occurrence of corticosteroid allergy among patients with asthma and with some complaints caused by inhaled corticosteroids.

Methods: Patch tests with corticosteroids were performed in 51 asthma patients with side-effects from inhalant corticosteroids and in 50 symptom-free asthma patients using the Finn Chamber[®] system. The corticosteroids and their vehicles were: betamethasone-17-valerate 1% in petrolatum, hydrocortisone-17-butyrate (Hc-17-B) 1% in ethanol, tixocortol-21-pivalate 1% in petrolatum, budesonide 0.1% in petrolatum, beclomethasone dipropionate 0.1 and 0.5% in petrolatum and as inhalant powder 200 µg, and fluticasone propionate 0.1 and 0.5% in petrolatum and as inhalant powder 250 µg. The results were read twice, on D4–5 and again on D10.

Results: Two patients in the symptomatic group reacted to corticosteroids in patch tests, one to betamethasone-17-valerate, Hc-17-B and budesonide, and the other to budesonide and Hc-17-B. The first patient suffered from widespread eczematous dermatitis when using beclomethasone. Fluticasone caused oropharyngeal irritation, hoarseness and shortness of breath. The second patient experienced a severe rash after the fourth budesonide inhalation. She had used various topical corticosteroids for her atopic dermatitis without any side-effects. None of the symptom-free patients showed positive results.

Conclusions: Delayed allergy to corticosteroids occurs occasionally in asthma, perhaps in the same frequency as in dermatitis. A positive patch test reaction usually means clinical allergy, i.e. the patient cannot use that particular steroid. Cross allergy between corticosteroids is common. However, such patients usually tolerate some other common corticosteroids.

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Glucocorticosteroids cause both immediate and delayed allergies. Immediate reactions to systemic corticosteroids have been described as case reports (1) and no comprehensive investigation on the occurrence or incidence has been published, so far. The most commonly implicated corticosteroids in systemic use are methylprednisolone and hydrocortisone. Immediate allergic reactions are reported to occur more frequently in asthmatic and renal transplant patients than in other patient populations. Delayed contact allergy to corticosteroids used in dermatological preparations has been known for decades. The frequency of positive patch test reactions to corticosteroids, most often to tixocortol pivalate and budesonide, among dermatitis patients varies from one country to the other within a wide range, usually between 0.5 and 5% (2).

Allergic reactions caused by inhaled corticosteroids are either immediate or delayed in nature. To our knowledge, only two cases of immediate, probably allergic, reaction

to inhaled corticosteroids have been published (3, 4). In both cases, the exact mechanism of the reaction remained somewhat obscure. It is probable that both immediate and delayed allergic mechanisms were involved.

Reports on delayed allergic reactions in patients with asthma or allergic rhinitis are also few as reviewed by Isaksson (5). Other side-effects such as irritation in the mouth and pharynx, hoarseness, dysphonia and oral candidiasis are encountered in over half of children inhaling corticosteroids (6). In another study, oropharyngeal side-effects were reported occasionally in 48% and frequently in 3% of paediatric and adult practices (7). Local allergic side-effects from nasal corticosteroids include nasal congestion, pruritus, burning, soreness and septum perforation. Inhaled corticosteroids have given rise to pruritus, dryness, erythema and oedema of the mouth, dry cough and odynophagia as reviewed recently by Isaksson (5). Delayed allergic systemic reactions from intranasal and inhaled corticosteroids appear

as dermatitis on the face spreading to the trunk and flexures, perinasal pruritus, rhinorrhoea, swelling of the eyelids and worsening of previous dermatitis (5, 8).

The aim of the present study was to investigate the occurrence of corticosteroid allergy in adult asthmatic patients treated with inhaled corticosteroids and who had also some oropharyngeal or other side-effects attributed to the use of corticosteroids.

Subjects and methods

The study population consisted of 51 asthmatic patients with some local oropharyngeal or other side-effects attributed to inhaled corticosteroids, diagnosed at the Pulmonary Department of South Karelia Central Hospital, Lappeenranta, Finland, in 1998–2001. Fifty age- and sex-matched asthmatic patients with inhalant corticosteroid therapy from the same department served as a comparison group (controls). The demographic data of both groups are presented in Table 1. Asthma diagnosis was made on an average of 11 years prior to this investigation (range 0.5–47 years). All patients except one had used inhaled corticosteroids (beclomethasone, budesonide or fluticasone) for at least 6 months. That particular patient got allergic symptoms from inhaled budesonide already within 2 days after starting the therapy. The use of corticosteroids was rather similar in both groups. All patients had been instructed to rinse their mouth after corticosteroid inhalation to reduce oropharyngeal irritation. Patients in the symptomatic group had changed their medication slightly more often than those in the comparison group. As a whole, hypersensitivity to drugs was more common in the symptomatic group but untoward reactions from acetylsalicylic acid were of the same frequency.

A patient was considered atopic if skin-prick tests or specific IgE antibodies in the serum revealed immediate allergy to at least one of the eight common inhalant allergens tested (house dust mite, cat, dog, horse, birch pollen, timothy pollen, mugwort pollen and natural rubber latex). The term hypersensitivity rhinitis included both allergic and nonallergic/noninfectious nasal symptoms. Skin

Table 2. Patch test series

	Percentage	Vehicle
Betamethasone-17-valerate	1	Pet.*
Hydrocortisone-17-butyrate	1	Alc.*
Tixocortol-21-pivalate	1	Pet.*
Budesonide	0.1	Pet.*
Beclomethasone dipropionate	0.1	Pet.†
Beclomethasone dipropionate	0.5	Pet.†
Beclomet (200 µg)		Powder‡
Flixotide (250 µg)		Powder‡
Fluticasone propionate	0.1	Pet.†
Fluticasone propionate	0.5	Pet.†

* From Chemotechnique (Malmö, Sweden).

† Made by the hospital pharmacy.

‡ Commercial drug as such.

diseases such as atopic dermatitis, eczematous dermatitis and dermatoses treated with topical corticosteroids were also recorded.

All patients had mild to severe asthma, 73 of whom had also hypersensitivity rhinitis treated usually with intranasal beclomethasone, budesonide, fluticasone, mometasone or triamcinolone. Half of the asthma patients (52) had used oral prednisolone or methylprednisolone during asthma attacks. Intravenous hydrocortisone and methylprednisolone were used as the rescue medications. Thirty-two patients with dermatoses had been treated with corticosteroid creams, ointments or lotions/liniments.

The patients of both groups were patch tested with the corticosteroid series seen in Table 2. We used the Finn Chamber® method (Epitest Ltd Oy, Tuusula, Finland). The test site was the upper back skin and the occlusion time was 48 h. The readings were performed on days 4–5 and 10 according to the criteria of the International Contact Dermatitis Research Group.

The patients took part in the investigation voluntarily. Informed consent was obtained in every case and the study protocol was approved by the Ethics Committee of the hospital.

Results

In the symptomatic group, local oropharyngeal irritation and hoarseness were the most common complaints caused by inhaled corticosteroids followed by skin symptoms, cough and dyspnoea (Table 3). Three patients had suffered from itching, hand dermatitis or widespread exanthema when using oral prednisolone. Nasal corticosteroid therapy caused eczematous lesions of the face in two patients, nasal symptoms in two and swelling of the eyelids in one patient.

In the patch tests, two patients in the symptomatic group showed positive reactions, one from budesonide, betamethasone-17-valerate and hydrocortisone-17-butyrate (Hc-17-B), the other from budesonide and Hc-17-B. The first patient was a 60-year-old woman who had used topical steroids for her hand eczema since 1976 and inhaled beclomethasone since 1990. She had experienced a widespread eczematous rash apparently from her asthma medication already in 1996. In 1996, patch tests revealed delayed allergy to budesonide, betamethasone-17-valerate and Hc-17-B. Beclomethasone was not tested.

Table 1. Clinical characteristics of 101 asthmatic patients

	Symptomatic	Controls
Number	51	50
Female (n)	32	29
Mean age (years)	54	52
Duration of asthma (years)	10.9	11.5
Rhinitis (n)	39	34
Skin disease (n)	18	14
Atopy	22	24
Inhaled/nasal corticosteroids	51	50
Beclomethasone	31	24
Budesonide	37	37
Fluticasone	33	28
Mometasone	4	2
Triamcinolone		3
Oral/intravenous corticosteroids	28	24
History of other drug hypersensitivity	25	16
Acetylsalicylic acid	7	8
Penicillin	8	5
Sulpha compounds	11	2
Other antibiotics	10	3
Paracetamol	1	

Table 3. Symptoms caused by or associated with inhaled corticosteroids in 51 patients

	Number	Percentage
Oropharyngeal irritation	20	39
Hoarseness	17	33
Skin symptoms	12	24
Itching	3	
Urticaria	3	
Bruising	2	
Burning sensation	1	
Dryness of skin	1	
Erythema multiforme	1	
Folliculitis	1	
Cough and dyspnoea	8	16
Nausea	3	6
Gastric symptoms	2	4
Headache	2	4
Dizziness	1	2

Beclomethasone was then replaced by fluticasone powder. However, fluticasone treatment caused oropharyngeal irritation, hoarseness and dyspnoea. Therefore patch testing was repeated in 2000, and budesonide and Hc-17-B were positive again, but betamethasone-17-valerate was negative. Since 2000 her asthma has been successfully treated with leucotriene antagonists, fluticasone being used in exacerbation phases only.

The second patient with corticosteroid allergy was a 50-year-old woman who had used topical corticosteroids without any known side-effects for atopic dermatitis in childhood and for psoriasis in adult age. Asthma was diagnosed in 1998 and inhaled budesonide was started. After four inhalations eczematous, very itchy dermatitis appeared all over the trunk and thighs. Her palms turned red. In the patch tests, budesonide and Hc-17-B elicited positive reactions. Budesonide inhalations were replaced by fluticasone powder and she experienced dryness of the mouth and dyspnoea. Patch testing with corticosteroids was repeated in 2000 with the same result. Since then the patient has been treated successfully with fluticasone and spacer.

All patch tests in the comparison group were negative.

Discussion

In most countries with high quality medical facilities, the occurrence of contact allergy to corticosteroids among people suffering from dermatoses treated with topical corticosteroids has been reported to vary between 0.5 and 5%, (usually between 1 and 4%) (2, 9–11). The skin symptoms in contact allergy vary from delayed healing of the dermatitis to widespread dermatitis. Allergic reactions from inhaled or nasal corticosteroids are rare and published usually as case reports. In such cases, both local adverse effects and systemic adverse signs and symptoms such as eczematous lesions and urticaria have

been reported (5). On the other hand, local irritant side-effects from inhaled corticosteroids occur in half of the patients (6, 7, 12). Lower doses of inhaled corticosteroids, use of the spacers and rinsing of the mouth may resolve some of the local side-effects such as oral candidiasis (12).

In the present study, two of the 51 asthma patients with some side-effect from inhaled corticosteroids reacted to budesonide and Hc-17-B in patch tests. Both patients were sensitized by topical corticosteroid preparations used for their skin problems. One of these two patients got systemic contact dermatitis for inhaled budesonide while the other patient experienced an exanthematous rash during inhaled beclomethasone therapy but in the other case the relationship between the drug and rash remained vague.

In the present study, only two of the six corticosteroids gave positive results in patch testing. They were 0.1% budesonide in petrolatum and 1% Hc-17-B in ethanol. In addition to budesonide and Hc-17-B, tixocortol pivalate is another corticosteroid producing positive results frequently in dermatological patients. Tixocortol also produces positive patch test reactions in countries where tixocortol pivalate has never been on the market, such as USA (13). It is generally assumed that tixocortol pivalate patch test identifies patients allergic to hydrocortisone more easily than hydrocortisone patch itself. Nine of the 11 patients with positive tixocortol patch test reacted also to intradermal hydrocortisone (14). In another patch test study, all 11 patients positive to tixocortol pivalate were also positive to hydrocortisone (15). Cross reactivity between tixocortol and hydrocortisone has also been demonstrated in guinea pig maximization test (16). Isaksson et al. (17) tested 3951 dermatitis patients with tixocortol pivalate 1% in petrolatum, with allergic reactions being 1.4% of 1018 patients with asthma or rhinitis and 0.9% of 2933 patients without airway symptoms. The difference was not statistically significant.

Patch testing with corticosteroids has some pitfalls. The concentrations and vehicles have not yet been standardized. The reactivity to various concentrations of corticosteroids vary from one patient to the other. Testing with 1.0 and 0.1% tixocortol pivalate and with 0.1 and 0.002% budesonide identified 105 of 110 patients reacting to any of the two concentrations of three corticosteroids (tixocortol pivalate, budesonide and Hc-17-B) and their mixes tested, all in petrolatum (15). Budesonide 0.1% identified 54 of 110 (49%) and budesonide 0.002% 48 of the 110 (44%) patients.

In another recent study, 16 of 1562 (1%) dermatitis patients reacted to either betamethasone valerate or clobetasol propionate pointing out the importance of including unusual corticosteroid allergens also in the patch test series (18). It is also noteworthy that in that particular study, positive reactions were seen variably both from allergens mixed with petrolatum and those solved in ethanol, ethanol being superior to petrolatum. While the patch test concentrations and vehicles of most

common topically used corticosteroids have been established by several contact dermatitis research groups, the concentrations and vehicles of inhaled corticosteroids are more ambiguous. Therefore, we used two concentrations of beclomethasone dipropionate and fluticasone in petrolatum and the commercial powders for inhalant therapy.

Patch test results are usually read 72 (D3) or 96 h (D4) after applying the test strips onto the skin. However, up to 30% of positive patch test results to corticosteroids are missed if the tests are read on D3–4 but not on D7–10 (15). That is why we read the result on D4–5 and again on D10.

All patients with a positive patch test reaction to any contact allergen do not react to them when applied to the skin or given internally. In an experimental study, 15 nonasthmatic budesonide allergic persons were divided into two groups, seven persons inhaling budesonide and eight persons placebo. Four of the seven persons in the former group experienced flare-ups of 6-week-old patch test reactions and widespread maculopapular exanthema while no reactions were seen in the other 11 cases (19). In the repeated open application test (ROAT), application of 0.1% Hc-17-B cream on healthy skin was positive in two of the three dermatitis patients with + or ++ patch test reaction to 1% Hc-17-B in petrolatum (20). In the ROAT on inflamed skin, 0.025% (w/w) budesonide fatty cream worsened dermatitis in five of the seven patients with positive patch test result to budesonide while the other two patch test positive patients were unaffected (21). Thus, for unknown reasons, a minority of the patients with positive patch test reaction to externally used corticosteroids are able to continue their external or internal use.

Intradermal testing with corticosteroids is performed occasionally. Wilkinson et al. (22) subjected 65 patients with moderate/severe asthma to intradermal testing with 1 mg budesonide, 1 mg beclomethasone dipropionate and 1 mg methylprednisolone suspended in 0.1 ml saline and 1 mg hydrocortisone sodium succinate in saline. Readings were made at 30 min and 48 h. Two patients showed a positive reaction at 30 min, one to

hydrocortisone and the other to hydrocortisone and budesonide, but none were positive at 48 h. In neither of the two positive patients was allergy attributed to asthma medication.

As to patch testing with inhalant corticosteroids, proper concentrations and vehicles are not yet established. It is probable, that we miss positive results when testing with corticosteroids which cause allergy only rarely. Using several concentrations and ethanol, in addition to petrolatum, as the vehicle more cases could be detected.

Corticosteroids are classified into four groups according to their stereochemical structure: (a) hydrocortisone type (e.g. hydrocortisone, tixocortol pivalate, prednisolone and methylprednisolone acetate), (b) triamcinolone acetonide type (e.g. triamcinolone, desonide and budesonide), (c) betamethasone type (e.g. betamethasone, desoximethasone and dexamethasone) and (d) Hc-17-B type (2). Group D has been subclassified into stable esters D₁, which do not cause contact allergy often (e.g. betamethasone-17-valerate, clobetasol propionate, beclomethasone dipropionate, fluticasone propionate and mometasone furoate) and labile esters D₂ (e.g. Hc-17-B), which may cross-react with other corticosteroids. However, cross allergy between the substances within each group is rarer than formerly expected. As mentioned before, tixocortol pivalate and budesonide are the two corticosteroids usually used for screening purposes (23).

In conclusion, delayed allergy to corticosteroids occurs occasionally in asthma patients. Despite the large scale use of inhaled corticosteroids, the number of reports of allergic reactions is low. If contact allergy to inhaled corticosteroids is suspected, patch tests should be carried out to identify the agent responsible for the symptoms. Cross allergy between corticosteroids is common. However, such patients usually tolerate some other common corticosteroids. Patient already hypersensitive to budesonide or other inhaled corticosteroid should not be given that steroid as an inhalant therapy. It is also evident, that corticosteroid contact allergy does not explain a significant number of adverse skin and mucosal symptoms in asthma and rhinitis patients.

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