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Skin Reactions to Inhaled Corticosteroids

Incidence, Avoidance and Management

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Abstract

Corticosteroids intended for inhalation into the lungs or into the nose have been used since the 1970s. Only 2 attempts to assess contact allergy attributable to inhaled corticosteroids in patients with asthma and/or rhinitis have been made, and only 1 single case of contact allergy attributable to budesonide and tixocortol pivalate was found. However, several case reports of allergic mucosal and skin symptoms caused by corticosteroids applied locally to the mucosa have been published. Local adverse effects from nasal corticosteroids have ranged from nasal congestion, pruritus, burning, and soreness to perforation of the nasal septum. Inhalation of corticosteroids into the lungs has been reported to cause pruritus, dryness, erythema and oedema of the mouth, a dry cough and odynophagia. Systemic signs reported from the use of nasal corticosteroids and inhalation of corticosteroids into the lungs have been eczematous lesions, particularly on the face, sometimes with spreading to the trunk and flexures. Urticaria has also been noted.

1. Method of Literature Evaluation

The material in this article has been obtained through Medline search from 1966 to May 2000, using the following key words: contact allergy, corticosteroids, rhinitis, asthma, inhalation, flare-up. Reference lists of papers were scanned for further references.

2. Incidence

Corticosteroids have been used since the beginning of the 1950s to symptomatically treat inflammatory skin diseases. By 1959, the first case reports of corticosteroid-induced contact allergy were published. Sporadic cases were published in the years to follow, but it was not until the late 1980s that the fairly high frequency, with figures ranging from 2.9 to 5%, was disclosed.[1,2] Such high figures were obtained when consecutive patients with dermatitis who were being patch tested because of suspected contact allergy were tested with corticosteroid marker molecules such as tixocortol pivalate and budesonide. Because corticosteroids retain their anti-inflammatory potential even if they act as sensitisers, the clinical signs of a corticosteroid allergy are not always obvious.[1] Upon local application of the incriminating corticosteroid to a skin lesion, the dermatitis is likely to be modified by the anti-inflammatory action of the corticosteroid itself,[3] and the locally treated eczema may evolve into a chronic dermatitis or there may be deterioration of a previous dermatitis.[4-9] A genital oedema with erythema and vesicles has been reported.[10] Erythema-multiform-like contact dermatitis from budesonide has been reported in 2 patients.[11] Angioedema of the face and an acute, oozing eczematous reaction after local corticosteroid treatment may also be seen.[6] Injectable corticosteroids may give eczematous lesions at the injection site.

Corticosteroids intended for inhalation have been used in the treatment of respiratory diseases such as asthma and chronic obstructive lung disorders since the 1970s as well as in several forms of inflammatory diseases of the nose such as allergic rhinitis. However, few attempts to assess allergy attributable to inhaled corticosteroids have been made. In 1 study 65 patients with asthma were patch tested with several corticosteroids, but no patients with such an allergy were found.[12] A pilot study encompassing 34 patients (10 with asthma, 13 with rhinitis, 11 with both) revealed only 1 patient hypersensitive to tixocortol pivalate and budesonide.[13] On the other hand, several case reports exist of allergic mucosal and skin symptoms caused by corticosteroids applied locally to the mucosa in patients with asthma and/or rhinitis.

3. Confirmed Contact Hypersensitivity

In cases where contact hypersensitivity to inhalation corticosteroids, intended for the nose or the lungs, has been confirmed by patch testing, both local adverse effects as well as systemic adverse signs and symptoms have been reported.

3.1 Local Adverse Effects

Local adverse effects attributable to nasal corticosteroids containing budesonide or tixocortol pivalate have ranged from nasal congestion,[14-16] pruritus,[17-19] nasal burning,[19,20] soreness of the nasal cavity,[21] and worsening of rhinitis[20,22,23] to perforation of the nasal septum.[24] In addition, inhalational corticosteroids intended for pulmonary use have given rise to pruritus, dryness, erythema and oedema of the mouth,[20] a dry cough[25] and odynophagia.[20,26] Contact stomatitis from tixocortol pivalate lozenges has also been reported.[27]

3.2 Systemic Signs and Symptoms

Systemic signs and symptoms reported from the use of tixocortol pivalate and budesonide in nasal corticosteroids have been eczematous lesions of the face,[15,16,18,21,23,25,28,29] sometimes spreading to the trunk[30] and flexures.[18,28]Inhalation of budesonide by patients with asthma resulted in eczematous and erythematous lesions of the face and body,[31] and urticaria.[32]

4. Adverse Effects without Confirmed Contact Hypersensitivity

There have also been reports of adverse effects involving the skin after use of inhalation corticosteroids where patch testing either was not performed or resulted in a negative reaction. A spongiotic dermatitis occurred after inhalation of budesonide,[33] but budesonide was not tested, so the precise nature of the reaction remains obscure. There have been 2 case reports of facial flushing after administration of intranasal fluticasone propionate, accompanied by chest tightness and hypotension.[34] No patch testing was performed.

5. Experimental Studies

No experimental, controlled studies on contact allergy to inhaled corticosteroids have been published as yet. In an unpublished, placebo-controlled, double-blind, randomised study, 15 patients without asthma, but who were hypersensitive to budesonide, inhaled either budesonide (7 of 15) or placebo (8 of 15), were studied. Four of the 7 individuals inhaling budesonide experienced flares at the sites on their backs where budesonide and its 2 diastereomers[35] had been tested 6 weeks earlier. In these 4 patients, toxicoderma-like eruptions with maculopapular exanthema on other parts of the body were also seen. The doses the 4 patients had inhaled ranged from 900 to 1700μg. No flare-up reactions were noted in the other 11 patients. A statistically significant difference ($p = 0.026$; Fisher's exact test) was found between the proportion of flare-ups in those inhaling budesonide and those inhaling placebo (unpublished observations). It is likely that the same phenomenon could occur with other inhaled corticosteroids if the individual is allergic to the particular corticosteroid.

6. Are Patients with Asthma Less Prone to Develop Corticosteroid Allergy?

In relation to the large scale of inhaled corticosteroid use, only a few reports on contact allergy to inhaled corticosteroids in patients with asthma have been published.[36] This could be because of under-reporting, but other explanations are possible. The rate of sensitisation may be lower in patients with asthma. One explanation could be the development of tolerance. Atopic dermatitis develops early in life but corticosteroid allergy is rarely reported in children. Asthma in children has usually started by the age of 2 and 85% of childhood asthma has developed by the age of 5. However, figures from our department do not substantiate this: 1.8% of patients with asthma and/or rhinitis were found to be allergic to budesonide, as compared with 1.0% of patients without asthma and/or rhinitis.

Table I. Classification of commonly used corticosteroids intended for the skin (S) or mucosa (M) according to their stereochemistry

Group A	Group B	Group C	Group D
Cortisone acetate (S)	Amcinonide (S)	Betamethasone (S)	Alclomethasone dipropionate (S)
Hydrocortisone (S)	Budesonide (M, S)	Desoximethasone (S)	Beclomethasone dipropionate (S, M)
Hydrocortisone acetate (S)	Desonide (S)	Dexamethasone (S, M)	Betamethasone benzoate (S)
Methylprednisolone acetate (S)	Flunisolide (M)	Dexamethasone valerate (S)	Betamethasone dipropionate (S)
Prednisolone (S, M)	Fluocinolone acetonide (S)	Diflorasone diacetate (S)	Betamethasone-17-valerate (S)
Prednisolone acetate (S)	Fluocinonide (S)	Fluocortolone (S)	Clobetasone butyrate (S)
Tixocortol pivalate (M)	Halcinonide (S)		Clobetasol propionate (S)
	Triamcinolone (S)		Diflucortolone valerate (S)
	Triamcinolone acetonide (S, M)		Fluticasone propionate (S, M)
			Hydrocortisone-17-butyrate (S)
			Methylprednisolone aceponate (S)
			Mometasone furoate (S, M)
			Prednicarbate (S)

7. Avoidance

A patient already hypersensitive to budesonide should not be given this corticosteroid as an inhalant (unpublished observation). It is likely that exposure to other inhaled corticosteroids in patients known to be allergic to that particular corticosteroid would produce similar results and therefore should be avoided. If a patient with asthma already using inhaled corticosteroids develops a skin reaction for the first time, corticosteroid-induced contact allergy should be considered and possibly ruled out.

8. Management

Corticosteroids can be divided into 4 groups, A to D, depending on the cross-reactivity pattern.[37,38] A patient allergic to a corticosteroid from 1 group should therefore be given a corticosteroid from another group that does not cross-react with the group to which the incriminating corticosteroid belongs (table I). For example, if a patient is allergic to budesonide, which belongs to group B, a corticosteroid from another group that does not cross-react with budesonide and which is available for inhaled use should be administered,[39] e.g. beclomethasone dipropionate, fluticasone propionate or mometasone furoate. Triamcinolone acetonide also belongs to group B and should therefore not be administered to the patients who are sensitive to budesonide. If a patient experiences a reaction to an inhaled corticosteroid that he or she is known to be allergic to and needs prompt treatment with a corticosteroid, a corticosteroid from another group can be administered systemically or topically.

9. Conclusions

In relation to the large scale use of inhaled corticosteroids, the number of reports of skin reactions is low. Local as well as systemic adverse effects have been observed in selected patients with contact hypersensitivity to the inhaled corticosteroid. An as yet unpublished study (in 15 patients who did not have asthma), has shown that subsequent inhalation of budesonide can reactivate previous patch test sites in individuals who had shown hypersensitivity to the drug and its diastereomers. This substantiates the clinical relevance of this corticosteroid allergy.

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