

Contact Allergy to Corticosteroids

Diagnosis and Management

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Introduction

Since 1949, when Hench treated his rheumatoid arthritis patients for the first time with corticosteroids, this category of drugs has proven to be of great utility in the treatment of many disorders in the different areas of medicine (1). However, as seems to happen with all drugs after a period of great enthusiasm, side effects soon started to be reported (2): systemic effects (e.g., osteoporosis, diabetes mellitus, disturbances of lipid and steroid metabolism, iatrogenic cushing, infection proneness, gastrointestinal ulcers, cardiovascular problems, myopathy, and cataracts) and dermatological effects (e.g., skin atrophy, easy bruising, striae distensiae, acneiform eruptions, rosacea, poor wound healing, hirsutism, and diffuse alopecia). Nevertheless, corticosteroids remain one of the cornerstones in the treatment of many disorders, including dermatological ones. They are lifesaving in many conditions and are essential for organ transplantation.

There are many such molecules on the market, all with different potentials and more or less marked side effects (3), and research to find newer and better molecules continues unabated. Different ways of administration are available: parenteral, peroral, enemas, intra-articular, intralesional, as an aerosol, as collyrium, or in topical skin preparations. Even though the use of these molecules is so widespread, it is only in recent years that it became clear that these molecules are able to provoke allergic reactions, which is the topic of this article.

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Factors Determining the Frequency of Contact Allergic Reactions to Corticosteroids

In 1959, Burckhardt (4) described a contact allergy to a topical corticosteroid and warned that "in time, a larger number of such sensitizations will be seen." However, it has taken almost three decades for it to be realized that contact allergy to corticosteroids is not at all exceptional. There are a number of reasons why the extent of corticosteroid contact allergy has been underestimated in the past (5):

1. Corticosteroids remained above suspicion for a long time because of their relationship to cortisol, a substance naturally present in the body.
2. Because corticosteroids are anti-inflammatory, they also mask the reactions to them.
3. Corticosteroids are difficult to test, which may well be the most important factor at present for the failure to recognize sensitivity to corticosteroids. In this article, we describe the method that has proved, in our experience, to give the most reliable results. Indeed, because of their anti-inflammatory properties, readings have to be taken even as late as 5–7 d after application.
4. The clinical picture may be misleading.

To further complicate the picture, the reported frequencies of allergic reactions may differ from one country or center to another (6,7) for a number of reasons:

1. The number and quantity of corticosteroids used: For example, the consumption of corticosteroids is twice as high in Belgium as in The Netherlands (6).
2. The nature of corticosteroids used: The "classic," mostly fluorinated, corticosteroids give fewer reactions. The newer corticosteroids seem to have a greater allergenic potential, perhaps because of their biotransformation in the skin which makes them more "biologically" active and because of their improved cutaneous bioavailability. The former are popular in The Netherlands, the latter in Belgium (6).
3. The reason why the corticosteroid is prescribed: Patients with psoriasis are less apt to be sensitized than patients suffering from eczema. In The Netherlands, the more potent and newer corticosteroids are prescribed almost only for psoriasis.
4. The selection of patients to be tested: Sensitization to corticosteroids is expected less in a consultation for an occupational dermatitis than in a consultation oriented more toward allergic reactions to cosmetic and/or pharmaceutical products. For example, patients with chronic venous insufficiency, especially those with venous ulcers, are significantly more apt to develop a corticosteroid allergy.

Clinical Picture (8,9)

General Picture

The clinical picture of a corticosteroid contact allergy is generally neither specific nor spectacular. Most such patients suffer from a long-lasting dermatitis. With them, one commonly encounters an eczematous eruption on the legs in chronic venous insufficiency; an exacerbation of an existing eczema of the hands, the face (mainly seborrhoeic), or the anal or perianal skin; or an exacerbation of a chronic eczema, which may be allergic, irritant, dyshidrotic, or nummular.

When an eczema is complicated by a corticosteroid contact allergy, the only sign may be an insidious aggravation of the eczema. Due to the anti-inflammatory properties of the steroid, the allergic reaction to it is masked. Therefore, one has to consider corticosteroid contact allergy when a topical corticosteroid treatment does not give the therapeutic response hoped for. An acute exacerbation may be encountered, however, but this is exceptional.

Very often the patient has been using topical corticosteroids for several months and then frequently several brands in turn. Non-eczematous eruptions, such as a rosacea-like picture or skin atrophy, may even be the presenting sign of an allergic reaction to corticosteroids. Changing to another brand of corticosteroid, a common practice in the event of therapeutic failure, often does not resolve the problem, since crossreactions among different corticosteroid molecules are frequent. This is discussed in the following sections.

Most corticosteroid allergic patients have multiple positive patch-test reactions to different ingredients in their topical pharmaceutical preparations, such as neomycin, propylene glycol, wool alcohols, ethylene diamine, and even ethanol (10,11).

Special Features

Atopic Eczema

There is a good deal of controversy about the frequency of allergic contact allergy in atopic dermatitis. Sensitization attempts, with strong allergens like dinitrochlorobenzene (DNCB), do, indeed, point to higher sensitization thresholds in atopics (12), and this seems to parallel the serum IgE levels and seriousness of the eczema. Recent investigations, however, have shown that the frequency of allergic contact dermatitis in atopic-eczema patients is the same as that in other dermatitis patients (13,14).

Corticosteroids may also cause problems in children (15). The clinical picture then may be quite misleading: an eczema that does not respond to the topical corticosteroid, exacerbation in spite of intensification of the therapy, and extension to places that are usually spared

(e.g., lower arms, upper arms, and buttocks). After an initial or previous positive therapeutic response, the eczema worsens while the treatment is continued. However, acute exacerbation, mostly redness appearing a few moments after application of a greasy topical preparation (mostly an ointment), is not an allergic but rather an irritant reaction: sweating caused by the greasiness. Changing to a less fatty preparation may resolve the problem.

Contact Dermatitis Provoked by Inhalation (16)

The first reports of allergic reactions to inhaled corticosteroids came from France: acute eczematous lesions in the face owing to a new inhalation corticosteroid, tixocortol pivalate, in nose drops. Reactions sometimes extended to the eyelids and occasionally spread to other parts of the body. In some of these cases, reactions were seen on the very first days of application, which indicates the possibility of an already-existing corticosteroid allergy. Later on, budesonide, a new corticosteroid that became popular in aerosols, provoked similar problems. Reactions to other nasal or oral inhalation corticosteroids are less frequent. The symptoms may be subtle: lack of response to inhalation corticosteroids and endonasal complaints such as burning or itching, redness, and congestion of the nasal mucosa. Serious bronchial spasms and hemorrhagic nasal ulcers are rare. Sensitization through inhalation corticosteroids is probably rare, but patients with a known corticosteroid allergy are at risk for secondary reactions, when they are given an inhalation corticosteroid to which they have been sensitized.

Patch Testing with Corticosteroids

Of the pitfalls in the diagnosis of corticosteroid allergy, the testing conditions are among the most important (5,17). As with other allergens, the back is the most appropriate testing site. The patient's condition should be under control and the back completely free of eczema.

Many vehicles have been proposed: petrolatum, ethanol, a mixture of ethanol and dimethyl sulfoxide (DMSO) (5), and even xerogels (18), which are dried gel formulations containing the allergen. We were able to demonstrate the importance of the vehicle since it considerably influences the patch-test results (19,20). In our experience, a saturated solution of the corticosteroid in ethanol 94° (2%) seems to be appropriate for most corticosteroids, although one has to keep in mind possible degradation reactions. For budesonide and tixocortol pivalate, petrolatum seems satisfactory (20). Some corticosteroids, like hydrocortisone, penetrate poorly, so DMSO is sometimes added, which may irritate the skin. Xerogels (18), which are dried gel formulations containing the allergen designed to improve test conditions, work quite

well for budesonide, tixocortol pivalate, hydrocortisone-17-butyrate, amcinonide, and prednicarbate. Hydrocortisone seems to be the most difficult corticosteroid molecule to test so some authors advise testing it intradermally (21).

Besides false-negative patch-test reactions, other peculiar patch-test results, such as the edge effect, are seen at early readings, especially with strong corticosteroids. In the edge effect, the edema and erythema are confined to the outer edge of the patch where the amount of the test corticosteroid and thus also the anti-inflammatory effect are lower than in the center. At later readings, the complete patch-test area becomes eczematous. A suppression of adjacent patch-test reactions to other allergens could not be detected in a study with nickel sulphate (22). At the first readings, a vasoconstrictive effect of corticosteroids can sometimes cause blanching. At later readings, a vasodilatory effect can sometimes be observed. These signs do not indicate an allergy.

This anti-inflammatory property of the corticosteroid is also responsible for the retarded positivity, sometimes only after 5 or 6 d, of the corticosteroid patch tests. Therefore, when a corticosteroid allergy is suspected, we perform readings not only at 48 and 96 h as is usual, but also later on at 120 and even 144 h.

Since more than 30 different corticosteroids are in current use, a marker would be very valuable in identifying a corticosteroid allergy. In our opinion, budesonide and tixocortol pivalate are the best candidates (20,23), and they have recently been added into the standard series in several centers. Hydrocortisone-17-butyrate is another candidate for routine testing (24). It is also advisable to test the topical preparations the patients have used and their ingredients, in addition to the corticosteroid molecule itself (20). When, in this first screening, a corticosteroid allergy is found, a complete battery of corticosteroid molecules has to be tested because crossreactions are frequent but not always predictable, even within the crossreacting groups (*see next section*).

Frequency of Reactions and Crossreactions

The overall frequency of corticosteroid contact allergy differs from one country to another (6,7), but corticosteroids seem to be among the 10 most common contact allergens in Europe. Recent findings indicate frequencies of 4.4% in Belgium (6), 1.5% in The Netherlands (6), 4.8% in the United Kingdom (21,25), and 4.1% in Finland (24,26).

Budesonide seems to cause allergic reactions the most frequently and, unlike the other corticosteroids, has been seen as a single allergen (20). Hydrocortisone, tixocortol pivalate (not used in dermatological preparations), hydrocortisone-17-butyrate, amcinonide, and the newer steroids, such as prednicarbate and alclomethasone dipropionate, also

frequently provoke positive test reactions. The fewest reactions have been reported not only to the older products like betamethasone, dexamethasone, and flumethasone and their esters (20), but also to the newer momethasone furoate. Triamcinolone does not often produce positive patch tests but may give false-negative reactions. Cross-reactions to budesonide are observed

Irrefutable proof for the existence of crossreactions is provided by reactions to nonmarketed corticosteroids, such as budesonide and prednicarbate (in earlier results) (19,20).

A statistical analysis of the cases reported in the literature and our own cases up to 1988 led Coopman et al. (27) to hypothesize that crossreactions occur primarily within certain groups of corticosteroids. Those clinical observations were supported by a study of the conformational analysis of the electronic shape of the corticosteroid molecules with the assumption, first, that all corticosteroid molecules interact with the same corticosteroid receptor and, second, that esters at the C21 position are readily hydrolyzed (23). Based on these findings, three groups were identified (Table 1):

1. Group A: corticosteroids without a substitution on the corticosteroid D-ring or C20- or C21-carbon chain, but including C17 and/or C21-short-chain esters, such as acetate and the thio-ester, such as hydrocortisone and tixocortol pivalate.
2. Group B: corticosteroids with a C16, C17-cis-ketal or -diol structure, such as triamcinolone acetonide and amcinonide.
3. Group D: corticosteroids with a long-chain ester at C17 and/or C21 and with or without a C16-methyl substitution, such as hydrocortisone-17-butyrate and clobetasone-17-butyrate.

Crossreactions are very frequent between the molecules in these groups but unusual between molecules of different groups. A fourth group (C) was statistically isolated but did not seem to form a conformational different group, since it behaves in the same way as corticosteroids of group A:

4. Group C: corticosteroids with a C16-methyl substitution, such as betamethasone and dexamethasone.

The clinical observation that budesonide can crossreact with molecules of group B with an acetonide function like amcinonide as well as with molecules of group D with an ester group like hydrocortisone-17-butyrate was explained by the conformation of budesonide, which is virtually a 1:1 mixture of two diastereomers, one with a structure analogous to the members of group B and the other to the members of group D (23).

Table 1
Classification of the Corticosteroids^a

Group A	Group B	Group C	Group D
Cloprednol	Aminonide	Beclomethasone hydrochloride	Alclomethasone dipropionate
Cortisone acetate	Budesonide ^b	Betamethasone	Beclomethasone dipropionate
Fludrocortisone acetate	Desonide	Betamethasone sodium phosphate	Betamethasone benzoate
Fluormetholone	Flucoloronide	Dexamethasone	Betamethasone dipropionate
Fluormetholone acetate	Flunisolide	Dexamethasone acetate	Betamethasone valerate
Fluorprednisolone acetate	Fluocinolone acetonide	Dexamethasone disodium phosphate	Budesonide ^b
Hydrocortisone	Fluocinonide	Dexamethasone isonicotinate	Clobetasone butyrate
Hydrocortisone acetate	Formocortal	Dexamethasone	Clobetasolpropionate
Hydrocortisone succinate	Halcinonide	metasulfobenzoate	Diflucortolone valerate
Isoflupredone acetate	Procinonide	Dexamethasone sodium phosphate	Flumethasone pivalate
Medrysone	Triamcinolone and esters	Desoxymethasone	Fluticasone propionate
Meprednisone	Triamcinolone acetonid and esters	Diflorason diacetate	
		Fluocortin butyl	
Methylprednisolone		Fluocortolone and esters	Hydrocortisone aceponate
Methylprednisolone acetate		Halomethasone	Hydrocortisone butyrate
Methylprednisolone hemisuccinate			Hydrocortisone caproate (hexanoate)
Methylprednisolone sodium phosphate			Methylprednisolone aceponate
Prednisolone (and salts)			Momethasone furoate
Prednisone			Prednicarbate
Tixocortol pivalate			

^aCorticosteroids are classified according to their chemical and molecular structure (23) and to a statistical analysis of the cases in the literature (27).

^bBudesonide theoretically belongs to the acetonides with which it crossreacts, but it also crossreacts with some corticosteroids of the ester group.

Considering these data and taking into account the penetration characteristics of the molecules, we suggested that tixocortol and budesonide should be tested (both 1% in petrolatum) as markers to detect a corticosteroid allergy (23,27); the former to detect allergies to corticosteroid molecules of group A and the latter to those of groups B and D.

Moreover, crossreactions do not seem to be restricted to the corticosteroids. Skin tests with substances like deoxycortisol, progestagens, testosterone, and estrogens revealed a division between hydrocortisone-allergic patients, for whom the C11-OH group is essential to induce the allergic reaction and hydrocortisone-sensitive patients for whom this group does not seem to be essential (28). Some of the patients of the latter group also reacted to 17-alpha OH progesterone, which might play an etiological role in autoimmune progesterone dermatitis.

Finally, it has recently appeared that an allergy to a corticosteroid is frequently associated with an allergy to alcohols and aldehydes (10,11). The question of whether there is a relationship between contact allergy to alcohols (which are thought to be rare allergens) and/or aldehydes and corticosteroids, on the one hand, and to the potential role of aldehydes as metabolism products of corticosteroids, on the other hand, deserves further investigation.

Systemic Reactions

Flare-up reactions of earlier sites of allergic contact dermatitis, macular or papulovesicular eruptions, and purpura may be provoked when corticosteroids are administered systemically to sensitized patients (29). In patients allergic to hydrocortisone, the administration of hydrocortisone as well as tetracosactrine, an ACTH analog that stimulates the body's own cortisol secretion, resulted in flare-ups of earlier eczema areas (30), as well as in erythematous skin reactions (31) and urticaria (32). Moreover, other types of allergic reactions, such as IgE-mediated anaphylactoid reactions, are occasionally seen after the use of systemically administered corticosteroids.

Therapeutic Approach

When a contact allergy to a corticosteroid is detected with a marker molecule or those corticosteroids in one of the preparations used by the patient, an extensive panel of available corticosteroids should be tested in order to determine which molecules are still tolerated (20). Crossreactions occur most often within the classes defined earlier. Generally, however, several molecules within these classes are still tolerated. Testing the incriminated products together with their ingredients is important since the marker molecule fails to detect the contact allergy in about 20% of the cases. In the meantime, if corticosteroid therapy

must be continued, betamethasone esters and mometasone-furoate in a simple petrolatum base can be advised, since few reactions to these preparation have been detected. When systemic administration of a corticosteroid is necessary, a corticosteroid molecule other than those provoking topical reactions must be chosen.

Conclusion

Contact allergy to corticosteroids is not infrequent. The diagnosis is not easy because of the atypical clinical picture and difficulties encountered in testing these anti-inflammatory drugs. As in all cases of contact dermatitis, the therapy of choice is avoidance, but here also one has to keep in mind the frequent crossreactions between several corticosteroids. Groups of corticosteroids that behave in similar ways regarding contact allergy have been identified, but this does not relieve us from the need for testing all the other corticosteroid molecules.

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