



Effective prescribing in steroid allergy: Controversies and cross-reactions

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Abstract Contact allergy to topical corticosteroids should be considered in all patients who do not respond to, or are made worse by, the use of topical steroids. The incidence of steroid allergy in such patients is reported as 9% to 22% in adult patients and in 25% of children. It can often go undiagnosed for a long time in patients with a long history of dermatologic conditions and steroid use. Although rare, both immediate and delayed-type hypersensitivity reactions have been reported to systemic corticosteroids with an incidence of 0.3%. Reported reactions range from localized eczematous eruptions to systemic reactions, anaphylaxis, and even death. Delayed type reactions to systemically administered steroids may present as a generalized dermatitis, an exanthematous eruption, or occasionally, with blistering or purpura. In this contribution, we clarify the issues surrounding the pathogenesis of steroid allergy, cover the importance of cross-reactions, and describe strategies for the investigation and management for patients with suspected steroid allergy.

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Introduction

Topical corticosteroids have been used since 1957. Within only a few years of introduction, the initial reports of contact dermatitis to hydrocortisone emerged. To date, allergic reactions have been reported with topical, intramuscular, intraarticular, intralesional, oral, inhaled, transdermal, and intravenous glucocorticoids. Type IV delayed hypersensitivity reactions are the most commonly reported, although type I and III reactions have also been observed.¹

Studies initially suggested that it was the precursor, hydrocortisone aldehyde hydrate, that was responsible, because it produced a stronger patch test reaction than hydrocortisone itself.² In the late 1980s, it became apparent that tixocortol pivalate was a good marker for topical

corticosteroid allergy.³ A classification system was introduced that consists of four groups based on steroid cross-reactivity.⁴ Further studies on cross-reactivity in the 1990s suggested that tixocortol pivalate was a better marker for topical hydrocortisone allergy than hydrocortisone itself.⁵ It is reported that testing to tixocortol pivalate and budesonide should identify approximately 90% of patients with corticosteroid sensitivity,⁶ and these are now included in many baseline series.

Epidemiology

The prevalence of corticosteroid allergy in the literature is between 0.2% and 5%,^{7–9} with 85% of these patients having multiple steroid allergies.⁷ The variability between centers may be due to regional differences in patch test methodology, in vehicle, concentration, and timing of the readings. Regional prescribing habits and awareness of potential reactions are also thought to influence the prevalence observed.

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In a 6-year retrospective study performed in the United States, of 1188 patients patch tested with corticosteroids, 127 patients (10.7%) had a positive reaction to at least one steroid, and 56 reacted to multiple steroids.¹⁰ The most recent report from the European Surveillance System on Contact Allergies showed a wide variation in incidence of tixocortol-pivalate positive patch tests, ranging from 0.1% to 1.7% of patients tested.¹¹ Contact allergy to budesonide tends to be seen less frequently and results are more consistent, with positive reactions in 0.6% to 0.7% of patients tested. One large study, however, recently reported positive reactions to budesonide as high as 1.6%, higher than the rate of tixocortol positives seen.⁷

The incidence of corticosteroid allergy is highest in patients with leg ulcers and stasis dermatitis, followed by patients with anogenital, foot, and less frequently, hand and face dermatitis.¹² Patients with multiple medicament sensitivities are also more likely to have corticosteroid allergies.¹³ A series in 1996 showed 72.6% of patients had positive reactions to at least one of five corticosteroids tested.⁸ In this group, hand dermatitis cases outnumbered stasis/leg dermatitis. Hydrocortisone is reported to be the third most common allergen in patients with stasis dermatitis and the eighth most common allergen in patients with hand dermatitis.¹⁴

A recent study on sensitization routes confirmed that 75% of patients that become sensitized to corticosteroids do so through a topical route. Inhaled steroids were thought to be responsible in 7% of patients and ophthalmic preparations in 6%.⁷

Pathogenesis and pathology

T lymphocytes are the immune response effector cells implicated in allergic contact dermatitis. The mechanisms triggering T-lymphocyte recruitment in corticosteroid

allergy have been explained by the hapten theory. The low molecular weight of the corticosteroid makes it insufficiently immunogenic, unless it is covalently bound to a protein, producing a complete antigen. The C17 side chain on the corticosteroid is thought to be the site of protein binding responsible for allergen production. Degradation of the side chain results in the formation of a glyoxal that then binds covalently with amino acid to form an allergenic molecule.

The ability of steroid molecules to cause allergy may be directly related to the ability to bind to arginine (Figure 1). A correlation has been demonstrated between steroid usage, number of reactions, and the degree of arginine binding, with the more allergenic steroids binding more readily to arginine.¹⁶ Halogenated steroids, such as betamethasone, have a reduced ability to bind arginine and are less allergenic. After haptenization through binding to skin proteins, the hapten is internalized into the antigen-presenting cell and presented to the lymphocyte T-cell receptor in association with the major histocompatibility complex) antigens. This results in the release of T lymphocytes, and it triggers the inflammatory response. In vitro lymphocyte transformation tests have demonstrated that the epidermal Langerhans cells, rather than peripheral blood monocytes, present corticosteroid haptens to T lymphocytes.¹⁷

Pathologically, allergic contact dermatitis resulting from corticosteroids does not appear to be different from any other contact allergy. Histology studies of skin taken from the site of positive patch test reaction to hydrocortisone show histologic features typical of allergic contact dermatitis.¹⁸ Immunohistochemical analysis has shown no difference between reactions induced by tixocortol pivalate and those caused by nickel sulfate, providing evidence for the immunologic basis of the hypersensitivity reaction.¹⁹ Biopsy specimens from positive test reactions to tixocortol pivalate show increased expression of interleukin (IL)-1a and tumor

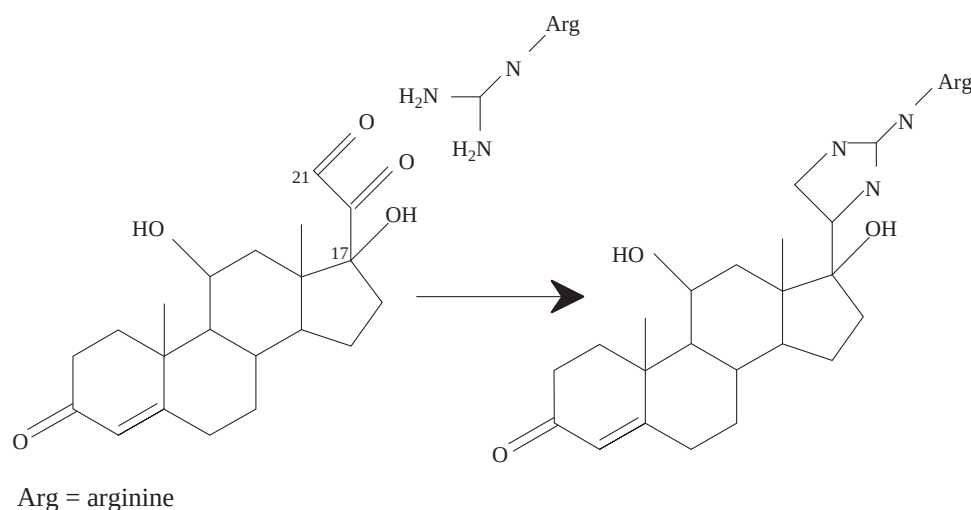


Fig. 1 Formation of the corticosteroid allergen by binding to arginine.¹⁵

necrosis factor (TNF)- α receptors in the dermis, as well an upregulation of adhesion molecules on keratinocytes and endothelial cells (Figure 2).

Cross reactions

Positive reactions to tixocortol were reported in patients not exposed to the allergen.²⁰ These patients also had positive reactions to hydrocortisone. The tixocortol reaction was, therefore, assumed to be a cross-reaction to hydrocortisone.²⁰ These findings led to steroids being classified according to their cross-reaction patterns into four classes⁴; class A: hydrocortisone type; class B: triamcinolone acetonide type; class C, betamethasone type; and class D: hydrocortisone-17-butyrate type (Table 1, Figure 3). Later class D was divided into two subgroups, D1 (stable esters) and D2 (labile esters).²¹ A later conformational analysis was done of the observed cross-reactions and supported this classification and the role of constituents of the D ring.²²

There have subsequently been reports, however, of reactions between the groups, particularly A, B, and D. This led to an alternative theory that proposes that in addition to a protein-binding site at the C21 position, there are two further sites of immune recognition on the corticosteroid molecule: one influenced by C16/17 substitution and one by C6/9 substitution.¹⁵ This results in charge differences, with hydrogen carrying a positive charge while fluorine carries a negative charge. This may explain cross-reactions when no structural similarities among degradation products are observed (eg, between members of group A and group B). Despite this classification system, it is not always easy to

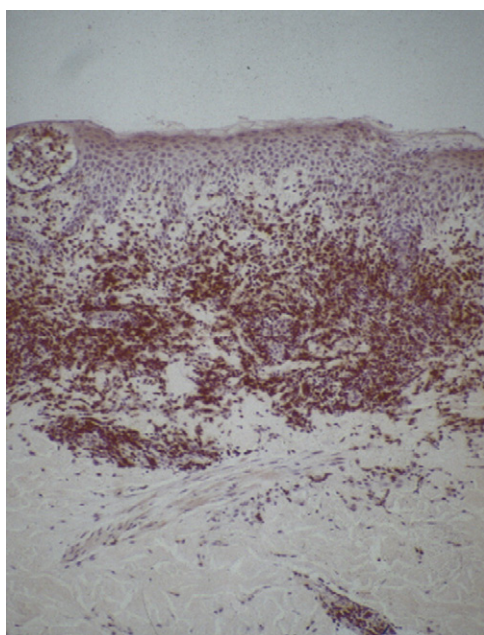


Fig. 2 Histopathology of a positive patch test reaction shows perivascular lymphocytic infiltrate in the upper portion of the dermis.

Table 1 Classes of allergenic cross-reactivity among topical corticosteroids^{4,21}

Class and structural characteristics	Examples
Class A Hydrocortisone types with no modification of the D ring or C20-C21 or short-chain esters on C20-C21	Hydrocortisone, prednisolone, and methylprednisolone and their ester acetate, sodium phosphate and succinate, cortisone, prednisone, tixocortol pivalate
Class B Triamcinolone acetonide types with cis/ketolic or diolic modifications on C16-C17	Triamcinolone acetonide, flucinolone acetonide, amcinonide, desonide, fluocinonide, halcinonide, budesonide, flunisolide
Class C Betamethasone types with a -CH ₃ methylation on C16, but no esterification on C17-C21	Betamethasone, dexamethasone, desoximetasone, fluocortolone, halomethasone
Class D1 (stable esters) Fluorination on C9, methylation on C16, and an esterified side chain on C17	Clobetasone butyrate, clobetasol propionate, beclomethasone dipropionate, betamethasone-17-valerate, betamethasone dipropionate
Class D2 (labile esters) No halogenation on the carbon rings, neither methyl group on C16 nor ester on C17	Hydrocortisone-17-aceponate, hydrocortisone-17-butyrate, methylprednisolone aceponate, prednicarbate

predict accurately reaction patterns in individual patients. Some patients will react to one or a small number of steroids, whereas others may react to multiple steroids tested.

Clinical features

Topical steroids

Contact allergy to topical corticosteroids should be considered in all patients who do not respond to, or are made worse by, the use of topical steroids. The incidence of steroid allergy in such patients is reported as 9% to 22% in adult patients²³ and in 25% of children²⁴ and can often go undiagnosed for a long time in patients with a long history of dermatologic conditions and steroid use. A recent review found a prevalence topical steroid allergy of 2.7%, with most patients having allergies to multiple topical preparations.⁶ The variation in incidence seen is largely due to the clinician's awareness of the problem and emphasizes the need to have a low threshold to patch test any patient who appears unresponsive to topical steroid treatment.

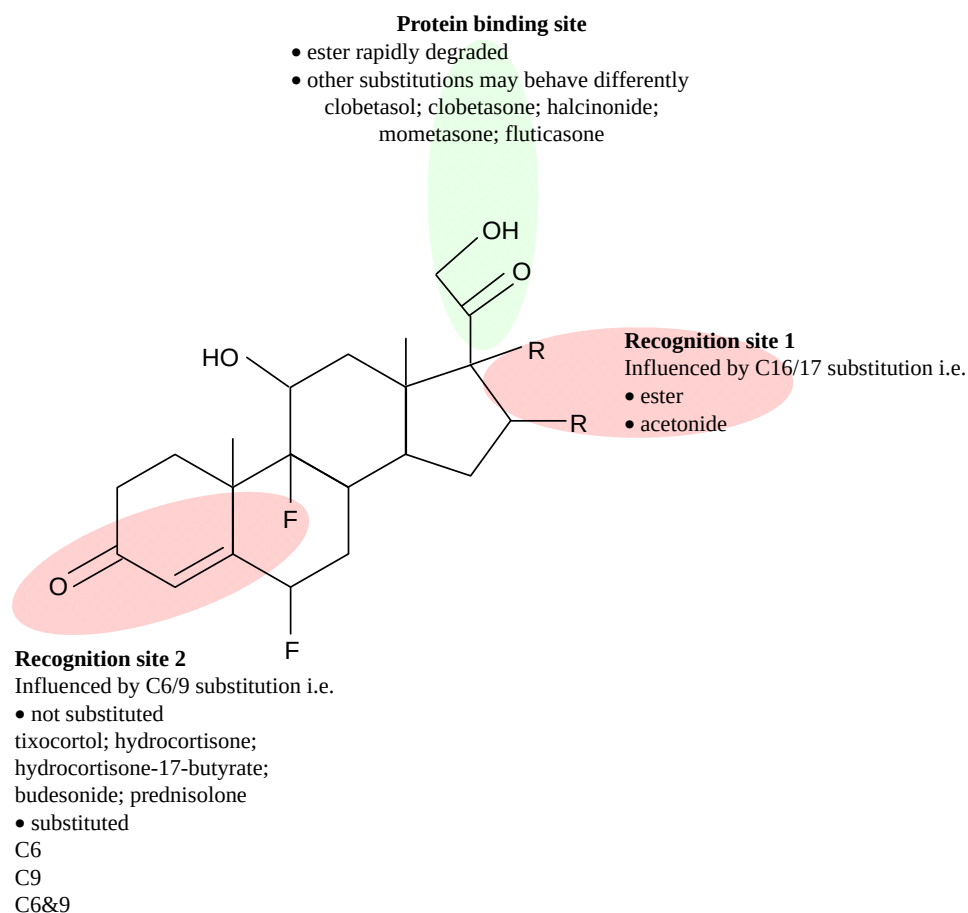


Fig. 3 Representation of factors influencing corticosteroid cross reactions.¹⁵

Patients may develop a flare of dermatitis locally, prolonged healing, or indeed, a distant flare of disease with corticosteroid allergy. The clinical relevance of budesonide contact allergy has been clearly demonstrated.²⁵ Experimental dermatitis was induced by nickel in patients with sensitivity to both nickel and budesonide. The affected area was then treated with topical budesonide. Patients developed a marked deterioration of their dermatitis and, in some cases, ipsilateral distant flares when treated with topical budesonide, demonstrating not only the relevance of the corticosteroid allergy but also that dermatitis recurring shortly after terminating treatment with a corticosteroid could well reflect a contact allergy to steroid.

Systemic including intraarticular reactions

Although rare, both immediate and delayed-type hypersensitivity reactions have been reported to systemic corticosteroids, with an incidence of 0.3%. Reported reactions range from localized eczematous dermatitis to systemic reactions, anaphylaxis, and even death.²⁶

Delayed-type reactions to systemically administered steroids may present as a generalized dermatitis, an exanthematous dermatitis, or occasionally, with blistering or purpura.²¹ Reactions may occur within a few hours of

exposure, or days or even months after chronic exposure. There have also been reports of acute generalized exanthematous pustulosis developing after oral administration of prednisolone. Sensitization to corticosteroids of group A was later confirmed by epicutaneous testing and positive lymphocyte transformation tests.²⁷

Reactions to parenteral methylprednisolone are rare but include two cases of conjunctival inflammation after retrobulbar injection for iridocyclitis,²⁸ generalized nonpruritic rash after intraarticular injection,²⁹ and widespread urticaria after intraarticular injections.³⁰

Hypersensitivity to corticosteroids is more commonly seen in patients with asthma and aspirin allergy, with or without nasal polyps.^{31,32} In this group, bronchospasm is generally observed within 5 minutes of steroid administration. It is most frequently observed with succinate esters (hydrocortisone sodium succinate and methylprednisolone sodium succinate)³¹ and is thought to occur through a nonimmune mechanism similar to aspirin. Phosphate-containing corticosteroid preparations are not considered to be associated with these hypersensitivity reactions.³

Problems have also been reported with intramuscular and intraarticular steroid injections and include delayed-type eczematous reactions at the injection site,³³ widespread dermatitis, and immediate type anaphylactoid reactions.³⁴

Inhaled and mucosal steroids

There are increasing reports of both delayed contact allergy and immediate hypersensitivity to inhaled steroids used in the management of allergic rhinitis and asthma. Rates of type IV hypersensitivity to corticosteroids of 3.9% and 2.9%, respectively, were reported in 2 series of patients who reported side effects from inhaled steroids.^{35,36} Symptoms may include pruritus, dryness, mucosal irritation and edema, dry cough, and odynophagia. Eczematous lesions, particularly on the face and sometimes affecting the trunk and flexures, have also been reported.³⁵ Results of one study³⁷ suggested that most patients with inhaled steroid allergy appear to be allergic to a single corticosteroid molecule, unlike patients with skin contact allergy, who often show multiple sensitizations. Cases of cross-reactivity between budesonide and corticosteroids of group D2^{35,38} and group A³⁸ in asthma patients have also been reported.

The mucosal surfaces of the nose, oral cavity, bronchial tree, genital organs, and the rectum, are all potential sites of contact with topically applied corticosteroids. Most examples of mucosal contact allergy occur with nasal sprays,³⁹⁻⁴² usually with the steroids tixocortol pivalate and budesonide. Clinical manifestations include exacerbation of rhinitis, periorbital edema, dermatitis at both local and distal sites, vesicular eruptions, and angioedema. Inhaled budesonide can reactivate previous positive patch test sites in budesonide allergic patients.⁴³ Despite the effect of the skin, inhalation does not appear to have any effect on lung function tests.

Irritation from a steroid enema was reported in a 57-year-old patient who tested positive to budesonide on patch testing.⁴⁴ A subsequent study found positive patch reactions to corticosteroids in 9% of patients with inflammatory bowel disease who were tested.⁴⁵ Not all of these patients had used steroid enemas, so in some cases, sensitization must have been by an alternative route.

Sensitivity to corticosteroids applied to the oral mucosa is seen less frequently. There are, however, a number of reports of stomatitis, mucosal erythema and edema, and facial angioedema developing in patients through contact with tixocortol pivalate in oral lozenges.^{37,46} Oral budesonide spray has been associated with dry cough and a widespread facial dermatitis.⁴⁷

Sex steroids, including autoimmune progesterone/estrogen dermatitis

About 20% of patients using transdermal estradiol patches complain of adverse local side effects. Largely, the causative agent is something other than the active steroid. Although still rare, however, there are increasing reports of positive patch test reactions to the steroid component of these devices. Patch testing to 17-hydroxyprogesterone hexanoate 1% in ethanol is positive in 19.4% of corticosteroid-sensitive patients. This

is felt to be a cross-reaction and is more often seen in patients with multiple steroids allergies. One report documented a patient with hand and foot dermatitis who also had a history of allergic contact dermatitis to a hormone replacement patch containing both estrogen and progesterone.⁴⁸ Patch testing showed positive reactions to hydroxyprogesterone, progesterone, and estradiol, in addition to multiple corticosteroid allergies. The authors of the report suggested that evaluation for sex steroid allergy should include patch testing with hydroxyprogesterone 1% in ethanol, medroxyprogesterone 1% in acetone, progesterone 1% in ethanol, estradiol 1% in ethanol, and testosterone 1% in ethanol.

There is an increasing awareness that more severe systemic problems may develop in patients sensitized to topical estradiols, if oral agents are used. There have been reports of positive patch test reactions to estradiol in patients who developed local cutaneous reactions at the site of application of transdermal estradiol devices and estradiol-containing gels, with subsequent generalized dermatitis, when patients were switched to oral alternatives.^{49,50} The possibility of such widespread reactions should be kept in mind, when commencing patients on oral hormone replacement.

Sensitivity to topical androgens is rare but has been reported in association with transdermal testosterone patches.^{51,52} One report documented development of localized erythema and vesiculation at the site of the patch. Patch testing was positive for testosterone propionate, testosterone undecanoate, and progesterone.⁵¹

Hypersensitivity reactions may also result from endogenous steroids. Autoimmune progesterone dermatitis is a rare condition with about 50 documented cases. The disease represents an autoimmune hypersensitivity to endogenous progesterone. It is characterized by recurrent skin manifestations starting 5 to 8 days before menses and resolving at the start of menses. Diagnosis is made, if there is a premenstrual flare, reproducibility of the eruption with intramuscular progesterone, and prevention of dermatitis with inhibition of ovulation.⁵³ The exact pathogenesis is unknown. In cases with prolonged progesterone therapy, such as oral contraceptive use, uptake by antigen-presenting cells and presentation to T-helper cells could result in IgE synthesis.⁵⁴ Another theory is that patients may be able to tolerate low levels of progesterone, but as the levels rise during the premenstrual period or pregnancy, it may reach levels that trigger a hypersensitivity reaction.⁵⁵

Reports of hypersensitivity to endogenous estrogens are very few, with less than 10 in the literature. Symptoms are similar to those seen in autoimmune progesterone dermatitis. Although two estrogen peaks occur in the menstrual cycle, only one patient has been reported as having symptoms coinciding with both peaks.⁵⁶ All other cases report symptoms associated with only the premenstrual estrogen peak and not with the peak seen at ovulation.

Testing for sensitivity to endogenous steroids should include intradermal testing, because results of patch testing are often negative.⁵⁷

Diagnosis

Much debate continues about the optimum method of screening patients for corticosteroid allergies. Patch testing can result in false-negative results, and optimum conditions for testing are still being clarified.

Tixocortol pivalate and budesonide are widely accepted to be the optimum steroids to patch test to and will detect approximately 88% of corticosteroid allergic patients.^{6,7} The addition of hydrocortisone-17-butyrate has been shown to detect another 4%.⁷ One-third of patients allergic to hydrocortisone will also be allergic to hydrocortisone-17-butyrate and possibly other corticosteroids.⁸ The current recommendation is that patients should be tested to tixocortol pivalate and budesonide, in addition to their own steroid preparations. Patients found to have positive reactions should then have a more extensive steroid series applied to detect possible cross-reactions and other sensitivities.⁸ It has been shown in patients who have undergone patch testing and intradermal testing that patch testing to a corticosteroid series successfully identifies all patients with corticosteroid allergies, but intradermal testing detects additional steroid hypersensitivities in patch test-positive patients.⁵⁸ The risk of possible sensitization and localized atrophy should, however, be kept in mind when undertaking intradermal testing.

The appropriate concentration of corticosteroid to use in patch testing is difficult to establish. It is possible that high concentrations can suppress the allergic reaction, whereas

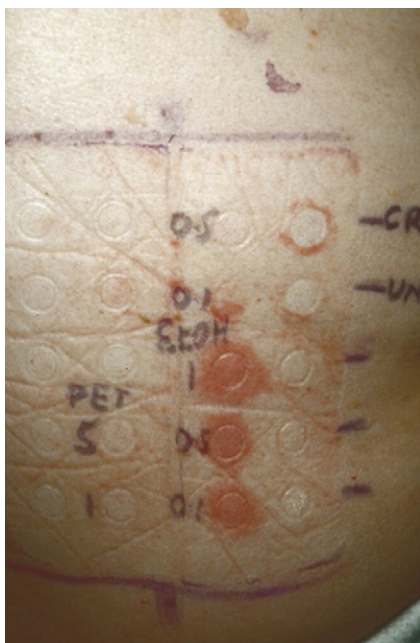


Fig. 4 Patch test reactions to hydrocortisone 17 butyrate show negative reactions when petrolatum is used as a vehicle but positive reactions with ethanol and an annular reaction to the cream formulation.



Fig. 5 Positive patch test reaction to budesonide presents as an annular reaction.

concentrations too low may not be sufficient to trigger a positive response. This was first demonstrated in a 1986 study in which a 2% solution in ethanol gave a positive reaction, whereas a 25% solution in petrolatum was negative.²⁰ This result was supported by later work that showed a stronger patch test reaction to 5% fluocinonide than to 10%.⁵⁹ There had also been suggestions that a weaker concentration should be used to minimize the risk of sensitization.⁶⁰ A review of 7168 patients, however, showed that there was no significant difference in the number of positive reactions when testing to budesonide 0.1% compared with 0.01%. There was, however, a significantly higher number of positive reactions to tixocortol pivalate 1% compared with 0.1%.⁶¹ These findings have been supported in other studies,⁶² and the British Contact Dermatitis Society currently recommends the use of 1% tixocortol-21-pivalate instead of 0.1%.

The vehicle within which the steroid is suspended is also of importance. It needs to be a suitable suspension for the steroid being tested while also being nonsensitizing and nonirritating. Petrolatum is a suitable vehicle for tixocortol pivalate and budesonide but not for hydrocortisone 17 butyrate and other steroids, for which ethyl alcohol is most suitable (Figure 4). The use of cream formulations may result in false-positive reactions due to an excipient within the creams.⁶³

There is then the question of when reactions should be read. Corticosteroid allergies tend to be late in developing. A reading on day 3 and 5 may miss a significant number of positive reactions.⁶⁴ It is thought to be best to read at day 7, but this may be difficult in practice. When reading patch test reactions to topical steroids, the possibility of an annular reaction or "edge effect" should be remembered. This occurs when there is a positive test reaction at the periphery of the patch-test site and a negative reaction centrally (Figure 5). The edge effect can be seen at early readings, when high concentrations of corticosteroids are tested. At later readings, however, the test may be positive throughout. This phenomenon can be explained by the high concentration of steroid in the center of the patch having a predominantly antiinflammatory effect that suppresses the immune response, whereas at the peripheries where, due to diffusion of the steroid, the concentration of steroid is less and the allergic response predominates.

The use of the lymphocyte transformation test measures proliferation of T lymphocytes in vitro when cultured cells are exposed to haptens. It has proven to be of varying success and historically has only successfully been used to confirm nickel allergy, a diagnosis that rarely causes diagnostic difficulty. There are reports of positive lymphocyte transformation tests in topical corticosteroid allergy,^{17,65} and although this may be of value where there is diagnostic difficulty, in practice it is not used, especially because corticosteroids may suppress the T-cell proliferative response.

Treatment

In patients with isolated positive patch test reactions, a suitable topical steroid alternative can usually be suggested from another steroid group based on cross-reactivity patterns. In those that have multiple positive steroid patch test reactions, intradermal testing is thought to be the best method of determining which topical steroid is safe to use.¹² As an alternative, nonsteroid macrolide drugs may be used.

Because corticosteroids are important emergency drugs, it is important to try to establish a safe option to use if needed. There is strong possibility of cross-reactivity between hydrocortisone, methylprednisolone, and prednisone, and it has therefore been recommended to avoid all three in patients sensitized to hydrocortisone and budesonide.^{66,67} Patients with a history of immediate reactions to systemic hydrocortisone that had positive results on intradermal testing to hydrocortisone and methylprednisolone were negative when tested to alternative fluorinated steroids. The results of subsequent systemic challenge with fluorinated preparations, such as betamethasone and dexamethasone, were also negative. The authors suggested that these steroids be used in an emergency situation in patients with adverse reactions to hydrocortisone and prednisolone.⁶⁸

Conclusions

Contact allergy to topical steroids has been reported since their first use in the 1950s. The prevalence is increasing and is currently reported as being between 0.2% and 5% of corticosteroid users. The increasing prevalence is largely due to an increased awareness among clinicians of the possibility of such reactions in patients who are not responding appropriately to topical preparations. In recent years there have also been reports of not only type 4 reactions, but also type 1 immediate hypersensitivity to steroids administered by other routes; inhaled, intramuscular, intra-articular, intralesional, oral, transdermal, and intravenous steroids in addition to patients' own endogenous steroids in the form of autoimmune progesterone and autoimmune estrogen dermatitis.

Steroids are an invaluable tool in the treatment of many dermatologic and medical conditions and are essential emergency drugs. A clear understanding of the pathogenesis of steroid allergy and an awareness of cross-reaction patterns should allow us to accurately predict reactions and safely prescribe alternative steroids for use in patients with corticosteroid allergy.

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