

Corticosteroids

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CORTICOSTEROIDS still constitute the main armamentarium for the symptomatic treatment of inflammatory skin diseases. One drawback that has been recognized during the last 10 to 15 years is hypersensitivity to these substances; delayed-type hypersensitivity is by far the most common, but type I allergy has also been observed. Routine patch testing with one or two corticosteroids in consecutively tested dermatitis patients has detected a fairly high frequency of hypersensitivity to corticosteroids after topical as well as systemic administration; figures of up to 5% have been presented.¹⁻⁵ The three aspects of corticosteroid contact allergy that we wish to focus on here must be considered; otherwise, the risk of missing such allergy may be significantly increased.

Clinical Picture

The first issue is the clinical picture. Corticosteroid contact allergy is rarely suspected from the history of the patient or from the appearance of the dermatitis, which may be modified by the antiinflammatory action of the corticosteroid itself.⁶ Any patient with a long-standing nonhealing dermatitis (such as stasis dermatitis,⁷ atopic eczema, or chronic hand eczema) that has been treated with corticosteroids should at some time be investigated for corticosteroid allergy. A topically treated eczema may evolve into a chronic inflammatory skin lesion that may heal by itself if administration of the incriminating corticosteroid is stopped. Deterioration of a previous dermatitis, sometimes with spreading, may also be seen.⁸⁻¹³ However, reactions that are more acute (such as a genital edema with erythema and vesicles,¹⁴ erythema multiforme-like contact dermatitis,¹⁵ generalized rashes,^{16,17} angioedema of the face, and an acute oozing eczematous reaction after local corticosteroid treatment¹⁰) have also been reported.

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Patch Testing

The second issue deals with patch testing. Corticosteroid markers should be present in any standard series in order to detect corticosteroid contact allergy because the clinical picture is not obviously one of a contact eczema. Unfortunately, more than one marker for corticosteroid contact allergy must be used because studies have shown that four groups of simultaneously reacting or cross-reacting corticosteroids exist.¹⁸ Three screening markers for corticosteroid contact allergy are tixocortol pivalate (a marker for group A),^{1,2,18,19} budesonide (marker for group B),^{18,20,21} and hydrocortisone-17-butyrate (Hc-17-B),^{1,2,6,22,23} which together seem to detect the majority of patients who are allergic to corticosteroids.

Concerning the optimal patch-test preparation, both the vehicle and the concentration of the allergen are involved.

The optimal vehicle for most corticosteroids is yet to be found. Either ethanol or petrolatum is recommended for tixocortol pivalate and budesonide since studies have shown equivalent patch-test results with either vehicle.^{3,21} For Hc-17-B, however, only ethanol is recommended because Hc-17-B in petrolatum penetrates to a lesser degree¹⁸ and because fewer positive reactions have been seen when parallel testing has been undertaken. The ethanol preparation must be freshly made every 6 to 8 weeks because Hc-17-B degrades spontaneously to hydrocortisone-21-butyrate when stored in ethanol. Ethanol is considered the vehicle of choice for most corticosteroids because penetration is enhanced when ethanol is used instead of petrolatum.^{3,21,24-26}

Another concern is the optimal patch-test concentration, which has not been worked out scientifically for most corticosteroids (ie, by patch-testing consecutive dermatitis patients with specific corticosteroids in serial dilutions). A high patch-test concentration of a potent

corticosteroid may yield a negative test result on an early reading occasion whereas a low concentration may yield a positive test result.²⁷ This can be explained by the anti-inflammatory action of the corticosteroid itself, which influences patch-test results at early readings (when the antiinflammatory effect prevails), leading to a false-negative test result if the antiinflammatory action predominates over the elicitation of the allergy test eczema.²⁷ This paradox is a unique feature when patch testing is done with some potent corticosteroids. Actually, this phenomenon has been demonstrated in European comparative studies, in which lower concentrations detected more allergic patients than did higher concentrations; therefore, budesonide 0.01% in petrolatum and tixocortol pivalate 0.1% in petrolatum are included in the European Standard series.²⁸⁻³⁰ In certain cases, however, higher concentrations may be needed if the standard concentration yields a negative result and there is a strong suspicion of contact allergy to these corticosteroids.²⁷ Most other corticosteroids have been tested at 1.0%, and this concentration is still used when testing with Hc-17-B and the majority of corticosteroids.

Another phenomenon that is related to the paradox concerns the "edge effect,"²⁷ which is a positive test reaction in the shape of a ring just outside the patch-test site and a negative reaction where the patch chamber has been placed. The edge effect can be seen at early readings, when high concentrations of potent corticosteroids such as budesonide are tested. This must be interpreted as a negative test result^{27,31,32} because an eczematous reaction confined to the periphery just outside the test area does not meet the minimal criterion of an allergic patch-test reaction. However, if one also reads the test on a later occasion (day 6 or 7), the test result usually will be positive. Testing with a substantially lower concentration than the one giving the edge effect may yield a positive test result on the early reading occasion. These seemingly contradictory features can also be explained by the interaction of the factors of significance for the patch-test reaction, namely, the degree of individual patch-test reactivity, the temporal dose-response for the antiinflammatory action of the corticosteroid, and the spreading of the test substance.²⁷

A dermatitis patient should be patch-tested also with the different corticosteroids used by that patient (ie, the pure corticosteroid in an appropriate vehicle and concentration). For example, in the United Kingdom, betamethasone valerate and clobetasol propionate are widely used, and patients sensitized to them are not identified with the markers for groups A and B.³³ Once a patient has reacted to a screening marker or to a separate cortico-

steroid, he or she should be tested with an extended corticosteroid series³⁴ containing at least the corticosteroids that are available in that country³⁵ (so as not to miss other contact allergies and to detect cross-reactions), so that further treatment and appropriate information regarding local and systemic therapy may be given. Again, however, the concentrations and vehicles for many of these other corticosteroids have not been extensively investigated, and because there are differences in reactivity among patients, patients will occasionally test negatively to these additional corticosteroids albeit they are allergic to them. For example, patients who are allergic to tixocortol pivalate should refrain from using hydrocortisone even if the test result from hydrocortisone is negative, and patients who are sensitized to budesonide should refrain from using Hc-17-B even if the test result for Hc-17-B is negative. The above-mentioned kind of testing also pertains to patients with corticosteroid-treated asthma/rhinitis and to patients who have taken systemic corticosteroids, in case a corticosteroid type IV allergy is suspected.^{36,37}

Late Readings

The third issue is the importance of performing late readings, mainly because of intrinsic antiinflammatory properties that may influence the patch-test result. The allergic reaction may be suppressed at early readings, and negative patch-test reactions may be seen despite the patient's being allergic to the particular corticosteroid.²⁷ Therefore, an additional reading on day 6 or 7 has been recommended,^{20,22,25,38} and the following description of one of our recent patients illustrates this very important point. A 50-year-old woman who worked on a restaurant staff had been suffering from what she strongly suspected was a work-related hand dermatitis for a year. She had used a cream containing Hc-17-B daily during the previous year. Patch tests with a standard series containing the three aforementioned corticosteroid markers and with a corticosteroid series were performed. She reacted only to budesonide and only on day 7 (not on day 3). Budesonide cross-reacts with Hc-17-B and seems to be a better marker for Hc-17-B allergy than is Hc-17-B itself, tested at 1.0% in ethanol. After she stopped using the cream containing Hc-17-B and after treatment with another corticosteroid that did not cross-react with budesonide or Hc-17-B, her condition cleared within a month, and she has not had any lesions since.

A Swedish study was the first to investigate the importance of consistent late readings in consecutive dermatitis

patients being routinely patch-tested with corticosteroids. Thirty percent of the cases of contact allergy to corticosteroids would have been missed had not readings on day 7 (late readings) been performed. Since then, this phenomenon has been shown in other studies.^{28,29}

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