Reactions to Corticosteroids: Some New Aspects Regarding Cross-Sensitivity

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GOAL

To describe contact allergy from corticosteroid sensitivity.

OBJECTIVES

1. To outline the specific agents responsible for cross-reactions to both topical and systemic corticosteroids.
2. To discuss which corticosteroids are best used as screening agents.
3. To describe factors that are critical for the sensitization and cross-sensitization potential of individual corticosteroids.

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Patch test results obtained with corticosteroid allergic patients tested with a large corticosteroid series validated the earlier classification of corticosteroid molecules in four groups of cross-reacting molecules: i.e., group A (hydrocortisone type), group B (acetonides), group C (betamethasone type-non esterified) and group D (esters). The latter group can now be subclassified into 2 groups, i.e., group D1 (halogenated and with C16 substitution) and group D2 (the "labile" prodrug esters without the latter characterisitics).

Contact allergy to corticosteroids is now a well-established phenomenon, and cases from all over the world have been reported in the literature. The incidence of the reactions observed, however, varies. It depends on several factors, such as the nature and amount of the corticosteroids used, the patient's prescription habits, the awareness among the medical profession of the importance of corticosteroid sensitivity, the selection of the patients and their referral to test centers, the routine testing of screening agents for corticosteroid sensitivity including all of the corticosteroids used by the patient, and the testing and reading methods used.[1-4]

Patients with contact allergy to corticosteroids generally present with a chronic dermatitis that is not exacerbated by, but fails to respond to, corticosteroid therapy. The allergenic and simultaneous anti-inflammatory effects of topical corticosteroids cause a nonspecific, self-supporting, eczematous condition (Figures 1 and 2), which is rarely recognized as a potentially iatrogenic sensitivity.[5]

Although relatively infrequent compared to their large scale use, allergic reactions may also arise in response to inhalant corticosteroids used in the treatment of rhinitis or bronchial asthma.[6] Generalized reactions may also occur after systemic corticosteroid administration (oral, intravenous, or intra-articular). The lesions may appear as eczema, exanthema, purpura, urticaria, and so on.[7,8]

Most contact allergies go undiagnosed if corticosteroids are not routinely tested. Therefore, in many countries, two or three screening corticosteroids have been added to the standard series: tixocortol pivalate (0.1% petrolatum), budesonide (0.1% petrolatum), and, sometimes, hydrocortisone-17-butyrate (1% ethanol).

Cross-Sensitivity

In general, corticosteroid-sensitive patients react to several corticosteroids. This may partly be because

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most of these patients have used large numbers of corticosteroids and would thus be vulnerable to concomitant sensitization. However, the existence of cross-reactions is irrefutably proven by reactions to substances to which the patient had never previously been exposed. Studies about such reactions can help to identify screening agents and provide information about the topical and systemic corticosteroids that corticosteroid-sensitive patients can safely use. Our earlier studies have led us to suggest the following four groups of cross-reacting molecules:[9]

- Group A: hydrocortisone type: no substitution on the D ring except a short chain ester on C21 or a thioester on C21, i.e., tixocortol pivalate
- Group B: triamcinolone acetonide type: C16, C17-*cis*-ketal or -diol structure
- Group C: betamethasone type: C16-methyl substitution
- Group D: hydrocortisone-17-butyrate type: long-chain ester at C17 or C17 and C21, with or without C16-methyl substitution.

Clinical observations identified tixocortol pivalate as a good screening agent for Group A. This finding has also been confirmed by other authors.[10,11] Budesonide was found to be a marker for different groups of corticosteroids, not only for other acetonides (Group B, to which it theoretically belongs), but also for certain esters (Group D), such as hydrocortisone-17-butyrate, and prednicarbate. This has to do with the peculiar molecular structure of budesonide.[12]

Membership in a certain group, however, does not indicate the sensitizing potential of a given molecule. Certain molecules are extremely rare sensitizers, such as betamethasone and its esters (e.g., valerate and dipropionate), diflucortolone valerate, diflorasone diacetate, clobetasone proprionate, clobetasone butyrate, and the newer mometasone furoate and fluticasone propionate. They can be classified as the less-sensitizing D1 corticosteroid esters. The precise reasons why this is the case are still unclear.[13]

Contact-allergic reactions are much more frequently observed with esters, such as hydrocortisone-17-butyrate, hydrocortisone aceponate, and hydrocortisone butyrate, as well as methylprednisolone aceponate and prednicarbate. They can be classified as the more sensitizing D2 corticosteroid molecules.[13] These are the "pro-drug" corticosteroids that, because of their high lipophilicity, easily penetrate the skin where they break down into the corresponding structures with the hydroxyl groups at the C21 and/or C17 positions. For example, prednicarbate[14] is hydrolyzed to form prednisolone-17-ethylcarbonate and then slowly to prednisolone, while methylprednisolone aceponate[15] is metabolized to form methylprednisolone-17-propionate, which, in turn, is rapidly converted to methylprednisolone.

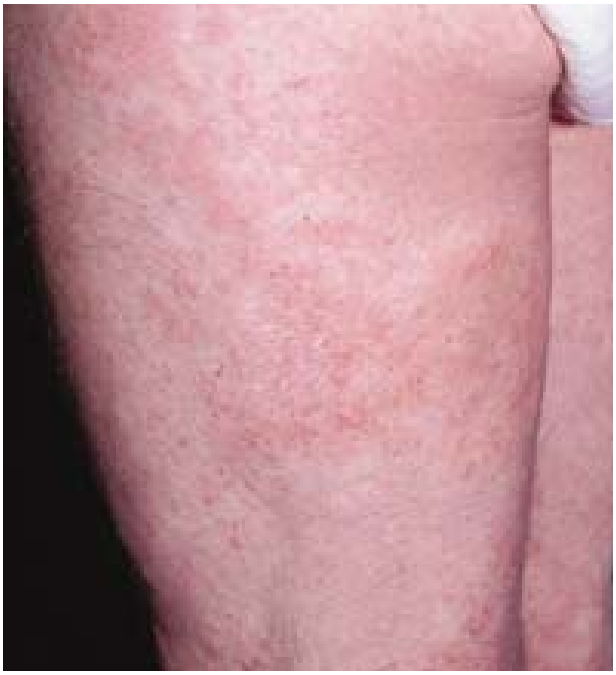

FIGURE 1. "Chronic" dermatitis as a result of a contact allergy to topical corticosteroids, in this case, betamethasone valerate, a rare sensitizer.

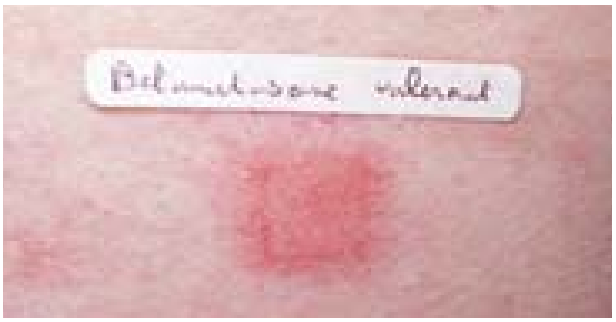

FIGURE 2. Positive patch test to betamethasone valerate in the same patient.

In regard to the influence of the skin metabolization of corticosteroids, recent patch-test results (data to be published elsewhere in detail) have shown that positive reactions to several of the recently developed molecules (e.g., prednicarbate and methylprednisolone aceponate) correlate significantly with reactions obtained with Group A corticosteroids ($p<0.01$). Skin metabolism might also account for cross-reactions that have been observed between hydrocortisone and hydrocortisone-17-butyrate (our own data),[16] the latter being able to be converted to hydrocortisone-21-butyrate, which is rapidly hydrolyzed to form hydrocortisone.[17] However, individ-

ual skin metabolization characteristics certainly influence the cross-sensitivity patterns observed. This suggests that these "labile" esters are able to sensitize both in their ester form and in their metabolized form.

Conclusion

The sensitization and cross-sensitization potential of individual corticosteroids depend on their molecular configuration, the presence of certain substituents, their solubility in the vehicle used, and their penetration and metabolization in the skin. These observations prompted us to divide the ester group D corticosteroids into two groups, namely, the less sensitizing D1 and the more frequently sensitizing D2 ester corticosteroids.

In practice, when a patient does not respond properly to corticosteroids, all topical treatment should be stopped. If corticosteroid therapy is absolutely necessary, one of the "safer" (Group D1) corticosteroids (e.g., mometasone furoate, fluticasone propionate, betamethasone esters, or diflucortolone esters) could be used, and then only in a paraffin base to avoid other pharmaceutical allergens. For systemic use, betamethasone or dexamethasone derivatives may be appropriate.[18]

All patients should be patch tested to screen for corticosteroid allergy. If a corticosteroid sensitivity is detected, a more extensive corticosteroid series should be tested, if possible, to determine cross-reactivity patterns. This measure will ensure that appropriate advice can be given for future local and systemic corticosteroid therapy.[19]

Acknowledgment—If one has ambitions in science, choose a great teacher. One of the authors (A.G.) had the rare privilege of having found Dr. Alexander A. Fisher. She is delighted to have this opportunity to express her gratitude and appreciation for his inspiration and guidance.

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Dr. Goossens reports no conflict of interest.