

Pattern of Corticosteroid Allergy in Thailand

Penpun Wattanakrai, Bhakinai Temnithikul, and Suwimon Pootongkam

Background: Corticosteroid allergy is a complication of topical therapy detected by patch-testing with corticosteroid allergens.

Objective and Methods: Ten-year retrospective review to study the prevalence and patterns of corticosteroid allergy in Thai patients.

Results: Of 882 patients who were patch-tested, 29 (3.29%) had allergic reactions to corticosteroids. Of these 29 patients, 17 (58.62%) had positive reactions to one corticosteroid, and 12 (41.38%) reacted to multiple corticosteroids. Rates of reaction to corticosteroid groups ranged from 31.03 to 80.95%. Concomitant reactions between groups were noted. The prevalence of topical corticosteroid allergy (using two screening allergens, tixocortol pivalate and budesonide) was 2.27% (20 of 882). Testing with additional steroid allergens in suspected cases increased the prevalence to 3.29%. Tixocortol pivalate detected 51.72% of corticosteroid-allergic cases, and budesonide detected 24.14%. Combining both tixocortol and budesonide detected 68.97% of cases.

Conclusion: Corticosteroid allergy is found to multiple corticosteroids, and concomitant reactions occur across groups. Group D1 corticosteroid esters produced a higher positive reaction rate (61.9%) than groups D2 (52.38%) and A (51.72%). This may be due to different prescribing habits or the easy access to D1 corticosteroids sold over the counter by pharmacies in Thailand.

Allergic contact dermatitis from topically applied corticosteroids was first reported in 1959 and is now a well-recognized phenomenon.^{1,2} Allergy to corticosteroids is often unsuspected from the history or clinical picture of the dermatitis prior to patch testing. Patients with topical corticosteroid allergy often present with unresponsiveness to treatment or with exacerbation of the underlying eczema. Patch testing is needed to confirm allergy to a previously or currently used corticosteroid and also to identify potential cross-reactions to corticosteroids that might be prescribed in the future.

The prevalence of corticosteroid reactions depends on several factors, such as the corticosteroids used; the physician's prescribing habits; the pharmacist's dispensing habits; medical awareness of corticosteroid sensitivity; routine testing with screening allergens (including all corticosteroids used by the patient) to detect corticosteroid allergy; the selection of patients who are

patch-tested; and the patch-testing and reading schedules.³ In countries where hydrocortisone is available over the counter, the prevalence of positive patch-test reactions to tixocortol is high. In Thailand, all potencies of topical steroids are easily purchased from pharmacies, without a doctor's prescription, but the frequency of corticosteroid allergy is not yet known. The North American Contact Dermatitis Group (NACDG) screening patch tests from 2005 to 2006 reported a 2.7% rate of positive reaction to tixocortol pivalate and a 1.5% rate for budesonide,⁴ whereas the Mayo Clinic, which patch-tested a specific group of patients with suggested allergic contact dermatitis from corticosteroids in 1998 to 2000, reported higher rates of 5.03% for tixocortol and 3.07% for budesonide.⁵

Four groups of topical corticosteroids have been described on the basis of their chemical structure and potential cross-reaction patterns^{1,3,6,7}: group A (hydrocortisone type), group B (acetonides), group C (betamethasone type, non-esterified), and group D (esters). Group D is now subclassified into two groups, namely, the less-sensitizing group D1 (halogenated with C-16 substitution) and the more-sensitizing group D2 (the labile prodrug esters) (Table 1). Cross-reactions are seen with some group A, group B, and group D corticosteroids. Group C corticosteroids are less frequently involved in corticosteroid allergy and cross-reactions.^{8,9}

From the Section of Contact Dermatitis, Division of Dermatology, Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, 10400.

Address reprint requests to Penpun Wattanakrai, MD, Division of Dermatology, Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, 10400. E-mail: rapwn@mahidol.ac.th

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Table 1. Tested Corticosteroid Allergens* Assigned to Groups

Group A (Hydrocortisone Type)	Group B (Triamcinolone Acetonide Type)	Group C (Betamethasone Type)	Group D1 (Betamethasone Dipropionate Type)	Group D2 (Methyl Prednisolone Aceponate Type)
Tixocortol-21-pivalate 0.1% pet	Budesonide 0.01% pet Triamcinolone acetonide 1.0% pet	Dexamethasone- 21-phosphate disodium 1.0% pet	Clobetasol-17- propionate 1.0% pet Betamethasone-17- valerate 1.0% pet Alclometasone- 17,21-dipropionate 1.0% pet	Hydrocortisone-17- butyrate 1.0% alc

alc = in alcohol; pet = in petrolatum.

*From Chemotechnique Diagnostics AB, Malmö, Sweden.

Materials and Methods

The authors conducted a 10-year retrospective analysis of patch-test results of patients with suspected allergic contact dermatitis who were patch-tested at the Ramathibodi patch test clinic from 1997 to 2006. This study was approved by the Mahidol University ethics committee review board.

Patients

Patients who underwent patch testing for suspected allergic contact dermatitis from January 1, 1997, to December 31, 2006, were identified from a clinical database and medical records. Patients were not patch-tested if they had been applying topical corticosteroids to the area of the back that was being used for patch testing, took immunosuppressive drugs (including oral corticosteroids), or had medical conditions that could compromise the evaluation of skin responsiveness.

The patients were patch-tested with a standard technique with Finn Chambers (Epitest Ltd Oy, Tuusula, Finland) on Scanpor tape (Norgesplaster A/S, Vennesla, Norway). The patches were applied to the upper aspect of the backs of patients and remained in place for 48 hours. Test sites were evaluated at 48 hours and 96 hours after initial patch placement. A delayed reading on day 7 was done in selected cases if reactions were not evident at the 96-hour reading. Patch-test reactions were interpreted according to NACDG criteria^{4,10} as negative reactions, macular erythema, weak reactions (nonvesicular erythema, infiltration, and possibly papules), strong reactions (edematous or vesicular), or extreme reactions (spreading, bullous, ulcerative lesions). Reactions were included if

interpreted by the physician as relevant by a history of known or likely contact of the affected skin area with substances containing the allergen. A positive patch-test reaction to corticosteroids included weak, strong, extreme, and relevant macular erythema reactions.

Corticosteroid Allergens

Initially, from 1997 to 1999, eight corticosteroids from the steroid tray marketed by Chemotechnique Diagnostics AB (Malmö, Sweden) were included in our standard screening series (see Table 1); 327 patients were screened with these eight allergens. Later, from 2000 to 2006, only tixocortol-21-pivalate and budesonide were used in the standard screening series; 555 patients were tested with these allergens. Additional corticosteroid allergens were selected to be tested in patients with a history of exposure or suspected corticosteroid allergy. Therefore, the number of corticosteroid allergens that were tested varied. For analysis, each topical corticosteroid was assigned to one of the corticosteroid groups (see Table 1)

Results

During the 10-year retrospective review, 882 patients with suspected allergic contact dermatitis were patch-tested. The mean age of the study group was 37.51 ± 16.10 years. In all, 29 patients (3.29%) had an allergic reaction to at least one corticosteroid. Among the 29 patients with positive patch-test results, 17 (58.62%) reacted to one corticosteroid and 12 (41.38%) reacted to more than one steroid. These data are shown in Table 2, which also lists 3 patients (10.34%) with positive patch-test reactions to two corticosteroids, 3 patients (10.34%) with positive

Table 2. Patients with Positive Reactions to Corticosteroids

<i>No. of Steroid Allergens Causing Positive Reactions</i>	<i>No. of Patients with Positive Reactions</i>	<i>% of Patients with Positive Reactions</i>
1	17	58.62
2	3	10.34
3	3	10.34
4	1	3.45
5	1	3.45
6	1	3.45
8	2	6.90
10	1	3.45

reactions to three corticosteroids, 1 patient (3.45%) who reacted to four corticosteroids, and 5 patients (17.24%) who reacted to more than four corticosteroids. Only relevant patch-test reactions were included.

When only positive patch-test reactions to corticosteroids are considered, the rates of allergic reactions to different groups of topical corticosteroids varied from 31.03 to 80.95%. Table 3 summarizes the reaction rates for each corticosteroid group and also illustrates the difference in reaction rates when macular reactions are included or excluded from the calculation. Our interpretation of macular erythema reactions follows that of Davis and colleagues,^{10,11} who noted reactions to corticosteroid allergens to be often only macular erythema. In our evaluations, therefore, we considered a reaction to be a positive allergic patch-test reaction, including macular erythema if it was assessed to be of past or present relevance by the clinician.

Concomitant allergic patch-test reactions between steroid groups were observed. For example, if a patient

was allergic to tixocortol, a group A marker, he or she had a 13.33% chance of also being allergic to group B corticosteroids. However, the number of our patients was small; just two patients reacted to both tixocortol and group B steroids. If a patient was allergic to group B steroids, there was an 88.88% chance of concomitant allergy to group D2 steroids. If a patient was allergic to budesonide, the group B marker, there was an 85.71% chance of also being allergic to group D2 steroids. In addition, if a patient was allergic to group C steroids, he or she had a 62.5% chance of being allergic to group D1 steroids.

The two steroid screening allergens in our standard series since 2000 (tixocortol-21-pivalate 1% and budesonide 0.1%) detected 20 (68.97%) of the 29 patients who had positive reactions to corticosteroids. Tixocortol pivalate alone detected 51.72% of corticosteroid-allergic cases, and budesonide detected 24.14%.

Discussion

The prevalence of contact allergy to corticosteroids in Thailand is unknown. Our hospital data from a routine patch test clinic indicate a prevalence of 3.29% (29 of 882 patients). This can be compared with rates of 0.52% (Melbourne, Australia), 1.4% (Germany), 2.6% (European Environmental and Contact Dermatitis Research Group), and 5.98% (Manchester, United Kingdom), as shown in a recent summary of the literature.^{5,12} NACDG patch-test data from 1994 to 2006 show rates of positive patch-test reactions of 2.5 to 3.2% for tixocortol pivalate and 1.1 to 1.8% for budesonide.^{1,4} Our data from Thailand from 1997 to 2006 indicated a lower prevalence of 1.7% (15 of 882) and 0.79% (7 of 882) for reactions to tixocortol and budesonide, respectively. In comparison, for Davis and colleagues,¹⁰ four corticosteroid screens (tixocortol-21-pivalate, budesonide, triamcinolone acetonide, and hydrocortisone-17-butyrate) detected 74% of allergies, three screens detected 70%, and two screens detected 68%. In our study, when we used two screens (tixocortol pivalate and budesonide) in the standard series for routine patch testing, we were able to detect about the same number of patients (68.97%, 20 of 29 patients) with corticosteroid allergy, whereas some investigators were able to detect up to 90% of corticosteroid hypersensitivity when patch-testing with both tixocortol pivalate and budesonide.¹³

More than half of our patients (58.62%) had reactions to one corticosteroid, and the rest (41.38%) reacted to numerous corticosteroids. Reaction rates varied between corticosteroid groups, and concomitant reactions between groups were observed. Concomitant reactions may include

Table 3. Positive Reactions, by Corticosteroid Group

<i>Group</i>	<i>N</i>	<i>Positive Reactions</i>			
		<i>Including Macular Erythema</i>		<i>Excluding Macular Erythema</i>	
		<i>No.</i>	<i>%*</i>	<i>No.</i>	<i>%</i>
A	29	15	51.72	9	31.03
B	29	9	31.03	5	17.24
C	21	8	38.1	5	23.81
D1	21	13	61.9	7	33.33
D2	21	11	52.38	8	38.1
D1 and D2	21	17	80.95	10	47.62

N = number of corticosteroid-allergic patients tested with allergens of each group.

*Percentage positive to at least one allergen in the group.

cosensitivity and possible cross-reaction between groups of corticosteroids. Concomitant reactions were most commonly found between group B and D2 steroids, at a rate of 88.88%; this was markedly observed between budesonide and group D2 steroids.

Comparing corticosteroid reactions according to groups, Goossens and colleagues reported that the rates of reaction were highest for group A allergens and lowest for the group C allergens.^{3,5} Other reports have also found group C corticosteroids to have the lowest rate of allergenicity.^{5,14} However, our data did not show this. Surprisingly, we also found the so-called less sensitizing D1 corticosteroid esters to have a higher positive-reaction rate than the more sensitizing D2 corticosteroid molecules as well as the group A corticosteroids.^{1,3,8} We postulate that our findings are the result of different prescribing habits and the ease with which various group D1 and group D2 corticosteroids (such as clobetasol-17-propionate, betamethasone dipropionate, betamethasone valerate, and prednicarbate) can be purchased from pharmacies in Thailand without prescription, whereas only hydrocortisone (group A) is available over the counter in most countries.

Conclusion

When patch testing was done with two screening markers (tixocortol pivalate and budesonide), the prevalence of allergy to topical corticosteroids at our hospital was 2.27% (20 of 882 patients). When patients with suspected corticosteroid allergy were patch-tested with additional steroid allergens, the prevalence increased to 3.29% (29 of 882). The two screening corticosteroid allergens in our current standard series (tixocortol-21-pivalate and budesonide) identified approximately 69% of positive patch-test reactions to corticosteroids. Another 31% of corticosteroid-allergic patients were detected when they were tested with additional corticosteroids as suggested by history. A large number of patients had positive reactions to more than one corticosteroid, and reactions often occurred across corticosteroid groups. Regarding the patch-test interpretation of macular erythema, we agree with Davis and colleagues^{10,11} and also propose considering macular erythema reactions as relevant because patch tests are routinely placed onto normal skin on the upper back, whereas the patient will apply the corticosteroid directly onto dermatitis skin.

The corticosteroid groups, based on structure and cross-reactivity patterns, are useful but not precise. We conclude that eczema patients whose eczema flares or does

not respond to treatment should be patch-tested with the different corticosteroids used. If corticosteroid allergy is highly suspected by patient history or detected by positive patch-test reactions to any screening steroid allergen, patch-testing with an extended corticosteroid series (including all corticosteroids used by the patient) should also be done, not only to confirm corticosteroid allergy but also to determine cross-reactivity patterns and to enable the physician to give appropriate advice for future corticosteroid therapy.

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