

Allergic Contact Dermatitis from Corticosteroids: Reproducibility of Patch Testing and Correlation with Intradermal Testing

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Background: Corticosteroid contact allergy is not uncommon. The diagnosis can be made with either patch testing or intradermal (ID) testing. In view of a few problems that have been encountered with patch testing, patch testing is considered inferior to ID testing. The reported reproducibility of positive patch-test results in the literature ranges from 47 to 98%.

Objectives: This study was conducted to (1) determine the reproducibility of patch testing with topical steroid preparations and their clinical relevance, (2) correlate positive results with ID testing, (3) address the issue of cross-reactivity between different steroid groups, and (4) identify the percentage of positive reactions to preservatives and vehicles used in commercial topical steroids.

Methods: A total of 19 patients with positive patch-test reactions to steroids from 1995 to 2004 were identified. Atopic patients and patients with type I hypersensitivity were excluded. The patients were patch-tested with a steroid series, select commercial steroid products, and vehicles and preservatives used in these preparations. The same patients were subjected to ID testing with select steroids. Readings were done on days 2, 5, and 7. ID testing was also performed on 9 control patients.

Results: Tixocortol-21-pivalate is the most common steroid allergen (68%). The reproducibility of patch testing with topical steroid preparations ranged from 66 to 100%. Reactions to both ID testing and patch testing occurred in 16 patients (89%); 1 patient reacted to patch testing and 1 other reacted to ID testing. Formaldehyde and formaldehyde releasers accounted for the majority of reactions in the vehicles and preservatives group.

Conclusion: Patch testing is sufficient in diagnosing allergic contact dermatitis from topical steroids. Testing with commercial products is not a good screen for steroid allergy. The most common cross-reactions were between group A (hydrocortisone-type) corticosteroids and group D2 corticosteroids (composed of labile esters, with a long-chain ester at C17 and possibly C21).

ALLERGIC CONTACT DERMATITIS (ACD) from steroids is a problem that has been recognized only recently. Although the first case to be reported in the literature was described in 1959 by Burckhardt,¹ it was not until the late 1980s, when tixocortol-21-pivalate was introduced as a steroid marker, that ACD from steroids became a well-recognized problem.² Tixocortol-21-pivalate was incorporated into the North American Contact Dermatitis Group (NACDG) standard series in the early 1990s, followed by budesonide 0.1% in 1995.³ The 2003–2004 NACDG standard series was expanded to include budesonide 0.01% petrolatum (pet), triamcinolone acetonide 1% pet, clobetasol-17-propionate 1% pet, and hydrocortisone-17-butyrate 1% pet.

ACD to steroids should be suspected when with its use the dermatitis worsens, does not improve, or the clinical pattern of disease is changed as in atopic dermatitis. It commonly occurs in patients who have an impaired barrier function,⁴ such as patients with stasis dermatitis, leg ulcers, and atopic dermatitis.

Corticosteroids' antiinflammatory actions lead to difficulty in interpreting their patch-test results. Some problems encountered may result from initial vasoconstriction and delayed vasodilatation,⁵ reactions developing as late as 5 to 7 days, the concentration used,⁵ or the vehicle used.⁶ False-negative patch-test readings may result from using a weak or strong concentration, owing to the inherent antiinflammatory nature of steroids.^{5,7} Reproducibility as reported in the literature ranges between 42% and 98%.^{8–10}

A study was designed with the following objectives:

1. Determine the reproducibility of patch-testing to topical steroid preparations and their clinical relevance.
2. Correlate positive results with intradermal testing.

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Table 1. Corticosteroids Used in Patch Tests

Budesonide 0.01% pet
Betamethasone-17-valerate 1% pet
Triamcinolone acetonide 1% pet
Tixocortol-21-pivalate 0.1% pet
Alcomethasone-17,21-dipropionate 1% pet
Clobetasol-17-propionate 1% pet
Dexamethasone-21-phosphate disodium 1% pet
Prednisolone 1% pet
Dexamethasone 1% abs alc
Betamethasone 1% abs alc
Hydrocortisone 1% pet
Prednisone 1% abs alc
Hydrocortisone acetate 1% DMSO/abs alc
DMSO/alc abs 50/50
Budesonide 0.1% pet
Hydrocortisone-17-butyrate 1% alc

abs = absolute; alc = alcohol; DMSO = dimethyl sulfoxide; pet = petrolatum.

3. Address the issue of cross-reactivity between different steroid groups.
4. Identify the percentage of positive reactions to preservatives and vehicles used in commercial topical steroids.

Materials and Methods

In December 2004, charts dating from 1995 to 2004 were reviewed. Fifty patients with positive patch-test results for corticosteroids were identified and contacted; 19 patients (11 males and 8 females) were willing to participate. After informed consent was obtained, the patients were patch-tested with a steroid series (Table 1), select commercial products (Table 2), and vehicles and preservatives used

Table 3. Vehicles and Preservatives Used in Patch Tests

<i>Vehicle and Preservative</i>	<i>No. of Patients</i>	<i>% of Patients</i>
Formaldehyde 1% aq	6	32
Ethylenediamine dihydrochloride 1% pet	3	16
Quaternium-15 2% pet	8	42
Diazolidinylurea 1% pet	4	21
DMDM hydantoin 1% pet	2	10
Imidazolidinylurea 2% pet	5	26
5-Chloro-2-methyl-4-isothiazolin-3-one (Kathon CG), 100 ppm, aq	1	5
Paraben mix 12% pet	0	0
Propylene glycol 30% aq	4	21
(MDGN)/phenoxyethanol 2% pet	4	21
Polysorbate 80 (Tween 80)	0	0
Stearyl alcohol 30% pet	1	5
Benzyl alcohol 1% pet	0	0

Adapted from Fisher AA.¹¹

aq = aqueous; MDGN = methyldibromoglutaronitrile; pet = petrolatum; ppm = parts per million.

in these products (Table 3¹¹). Patch tests were performed with Finn Chambers (Epitest Ltd Oy, Tuusula, Finland) mounted on Scanpor tape (Norgesplaster A/S, Vennesla, Norway) left in place for 48 hours. Readings were done on days 2, 5, and 7. A positive allergic reaction was interpreted as +, ++, or +++, manifested by erythematous papules, vesicles, and/or a spreading reaction, sometimes with crusting and ulceration.

Intradermal (ID) testing was performed on the volar surface of both forearms, with 0.1 mL of 0.025% budesonide, 0.4% dexamethasone, 10% hydrocortisone, 4% methylprednisolone, 4% triamcinolone acetonide, ethanol, and

Table 2. Commercial Products Used in Patch Tests

<i>Commercial Product (Generic Name)</i>	<i>Manufacturer</i>	<i>No. of Reactors</i>
Prevox HC (hydrocortisone)	Trans CanaDerm Inc. (Quebec City, Quebec, Canada)	0
Prevox B (betamethasone valerate)	Trans CanaDerm Inc.	1
Dermovate Ointment (clobetasol propionate)	Taro Pharmaceuticals Inc. (Brampton, Ontario, Canada)	1
Dermatop Cream (prednicarbate)	Dermik Laboratories Canada Inc. (Laval, Quebec, Canada)	7
Cyclocort Cream (amcinonide)	Stiefel Canada Inc. (Saint Laurent, Quebec, Canada)	4
Cyclocort Ointment (amcinonide)	Stiefel Canada Inc.	4
Halog ointment (halcinonide)	Bristol-Myers Squibb Canada Inc. (Montreal, Quebec, Canada)	1
Tiamol Cream (fluocinonide)	Taro Pharmaceuticals	3
Lyderm Cream (fluocinonide)	Taro Pharmaceuticals	2
HydroVal Cream (hydrocortisone valerate)	TaroPharma	8
Nerisalic Cream (diflucortolone valerate)	Stiefel Canada Inc.	1
Neo-HC 2% (hydrocortisone 2%)	Neolab Inc. (Montreal, Quebec, Canada)	4
Topactin Cream 0.05% (fluocinonide)	Neolab Inc.	1



Figure 1. Intradermal test reactions at day 7.

benzyl alcohol (Figs 1 and 2). Alcohol was used to prepare the ID products, and tests were therefore done with ethanol and benzyl alcohol. All patients were observed for 30 minutes following the injections. Readings were done along with the patch tests on days 2, 5 and 7. A total of 18 patients were tested (one patient refused). ID testing was also performed on a control group of 9 patients with no history of ACD from steroids.

Results

Figure 3 and Table 4 show initial and repeat patch-test results for steroids. Table 5 shows the frequency of steroid

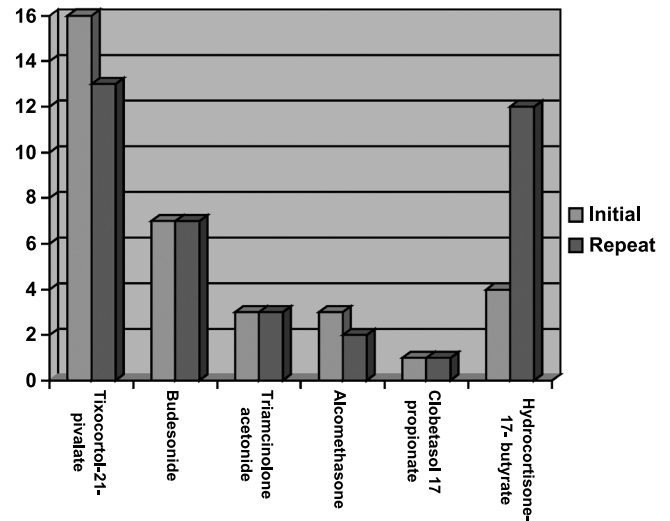


Figure 3. Comparison of initial and repeat patch-test results.

allergies. Figures 4–6 and Table 6 show a comparison between ID testing and patch-test results. No ID reactions to benzyl alcohol were detected, and all control patients had negative results on day 7. Sixty-eight percent of the patients were broad reactors (ie, reacted to more than one steroid group), 26% were narrow reactors, and 6% had nonreproducible results.

The most common cross-reactions were between steroid groups A and D2 (8 patients). Six patients reacted to steroid groups B and D2, 3 patients reacted to steroid groups A and B, and 2 patients reacted to steroid groups B and D1 (see “Discussion,” below, for steroid classifications). Forty-two percent of patients reacted to quaternium-15, 32% to formaldehyde, and 26% to imidazolidinylurea (see Table 3). The number of reactors to each of the commercial products tested are shown in Table 2.

Discussion

The apparent advantage of ID testing is the introduction of the allergen directly into the dermis via a needle whereas



Figure 2. Intradermal test reaction to 4% methylprednisolone at day 7.

Table 4. Reproducibility of Patch Testing with Different Corticosteroids

Corticosteroid	Reproducibility (%)
Tixocortol-21-pivalate	81.0
Budesonide	100
Triamcinolone acetate	100
Alcomethasone-17,21-dipropionate	66.6
Clobetasol-17-propionate	100

Table 5. Patients with Positive Reactions to Various Corticosteroids Tested

Corticosteroid	No. of Patients	% of Patients
Tixocortol-21-pivalate	13	68
Hydrocortisone acetate	12	63
Hydrocortisone butyrate	12	63
Budesonide	7	37
Triamcinolone acetonide	3	15
Betamethasone	3	15
Alcomethasone-17,21-dipropionate	2	10
Hydrocortisone	2	10
Betamethasone valerate	1	5
Clobetasol propionate	1	5

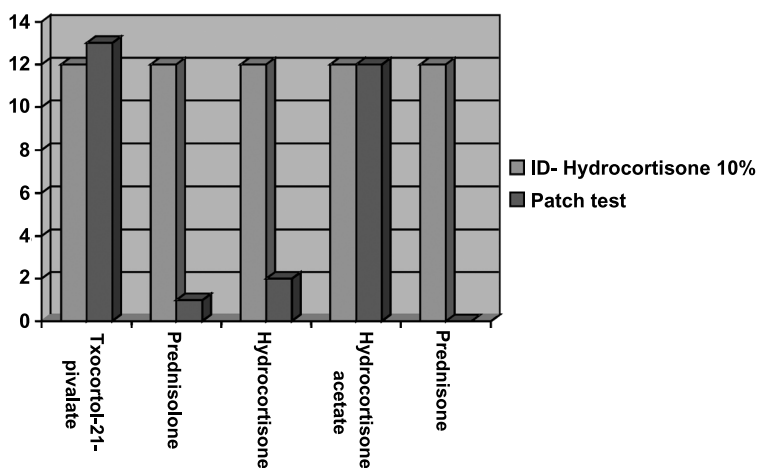
with patch testing, inadequate percutaneous absorption through intact skin may limit sensitivity, added to which are difficulties in interpreting results.¹² Risks associated with ID testing include pain at the site of injection, local dermal atrophy that fades in 6 to 12 months, generalized skin reactions, active sensitization, and anaphylactic or anaphylactoid reactions.¹³ In our study, only one patient developed a generalized urticarial reaction in the 10 minutes following the intradermal injection; this completely subsided with the administration of 25 mg of Benadryl (Pfizer Global Pharmaceuticals, Kirkland, Quebec, Canada).

Two studies of contact allergy to corticosteroids, one by Wilkinson and English and the other by Wilkinson and colleagues, have shown that patch testing is not a sensitive method for determining allergy to corticosteroids.^{14,15} Their conclusion was that ID testing is necessary to absolutely exclude the possibility of corticosteroid sensitivity. Positive patch-test reactions with negative ID test reactions were interpreted as possibly irritant. Our data showed that

of the 18 patients who had ID tests and patch tests, 16 reacted to both, 1 reacted to patch testing alone, and 1 reacted to ID testing alone. Twelve of the 13 reactions to tixocortol-21-pivalate were positive with ID hydrocortisone (the patient who refused ID testing was a tixocortol-21-pivalate reactor). Therefore, tixocortol-21-pivalate is an excellent marker for hydrocortisone. All reactions to budesonide were detected by patch tests and ID testing. ID dexamethasone correlated best with dexamethasone-21-phosphate disodium. No reactions were detected in the control group. We believe that patch testing is an adequate screen for ACD from corticosteroids, and ID testing is indicated if patch-test results are negative despite a strong clinical history.

Benzyl alcohol is an aromatic preservative used in injectable and topical steroid preparations. It is considered to be a rare sensitizer.^{16,17} (A case of sensitization to benzyl alcohol was reported by Verecken and colleagues.)¹⁸ We tested all our patients as well as our control group to exclude false-positive reactions to corticosteroids. No reactions were detected among any of the tested patients.

After retesting 19 patients, our reproducibility ranged between 66.6 and 100%. Devos and Van Der Valk⁹ found an overall reproducibility of 47.2% whereas Bircher and colleagues¹⁰ found a concordance of 70 to 98% on retesting, depending on the corticosteroid and the score of positive reaction. In a study by Ferguson and colleagues,⁸ only 5 of 12 patients who previously had positive patch-test reactions to budesonide had positive results on retesting. Repeat testing with hydrocortisone butyrate identified three times as many patients (12 patients) with positive results as did the initial testing (4 patients). The vehicle used for repeat testing was alcohol (available in steroid series) as opposed to the petrolatum used in the standard series. On reviewing the initial positive results, we noticed that 3

**Figure 4.** Intradermal test results for hydrocortisone 10% versus patch-test results for group A corticosteroids.

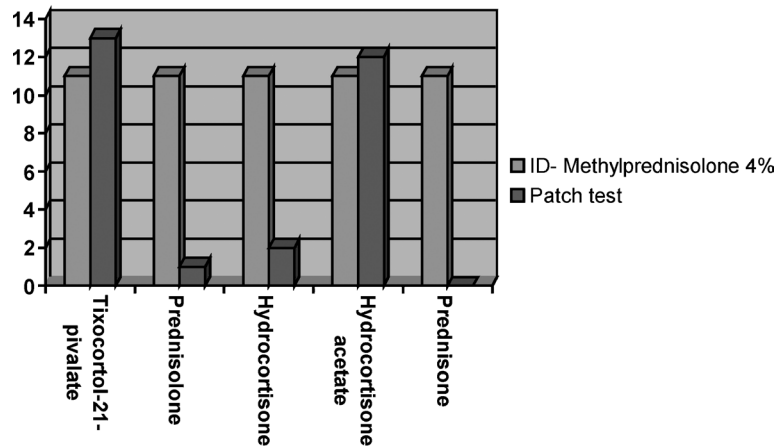


Figure 5. Intradermal test results for methylprednisolone 4% versus patch-test results for group A corticosteroids.

of the initial 4 patients reacted only to the hydrocortisone butyrate in the steroid series (1% alcohol) and not to the hydrocortisone butyrate in the standard series (1% pet). We believe that these reactions are true positives and that one should consider replacing the vehicle used in the standard series.

All budesonide reactions were detected at both concentrations (0.01% and 0.1%) and were of equal intensity. The same findings were reported in a multicenter study in the United Kingdom by Chowdhury and colleagues¹⁹ and in the NACDG 2003–2004 patch-test study (M. Pratt, personal communication, November 2004).

The available evidence suggests that with corticosteroids, the allergen is not the steroid itself but a degradation product.²⁰ The corticosteroids degrade to the reactive corticosteroid glyoxal, which then reacts with arginine to form an antigen. The corticosteroid glyoxal is formed on the C17 side chain. The corticosteroids are divided into four

groups on the basis of structure and cross-reactivity patterns.²¹ Group A, the hydrocortisone type, consists of corticosteroids without methyl substitution on C16 and without a lateral chain on C17 but possibly with a short chain on C21. Group B, the acetonide steroids, includes those with C16 or C17 cis-ketal or -diol additions and possibly a lateral chain on C21. Group C steroids, the betamethasone type, have a methyl substitution at the C16 position and no lateral chain on C17 but possibly a lateral chain on C21. Group D corticosteroids have a long-chain ester at C17 and possibly on C21 as well. Group D is subdivided into groups D1 and D2.⁶ Group D1 steroid molecules contain a methyl group at C16 and halogenations of the B steroid ring. D2 steroids, on the other hand, are composed of labile esters, which lack C16 methyl and beta-ring halogen substitutions.

In our study, the most common cross-reactions were between steroids in groups A and D2 (8 patients), followed by

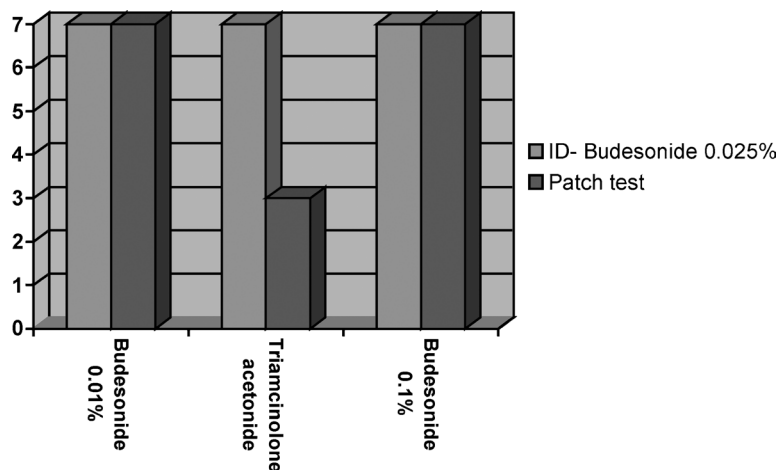


Figure 6. Intradermal test results for budesonide versus patch-test results for group B corticosteroids.

Table 6. Intradermal Reactions to Dexamethasone 0.4% versus Patch-Test Reactions to Group C Corticosteroids

Intradermal Test Result		Patch-Test Results	
Dexamethasone	Betamethasone	Dexamethasone- 21-phosphate disodium	Dexamethasone
+	—	—	—
+	+	+	—
+	+	—	—
—	+	—	—

groups B and D2 (6 patients) and groups A and B (3 patients). Sixty-eight percent of our patients were broad reactors.

The majority of reactions to vehicles and preservatives were to formaldehyde and to formaldehyde releasers (65%), neither of which were present in the commercial products tested. Propylene glycol accounted for 10% of the reactions. All reactors who were positive for commercial products containing propylene glycol also reacted to the steroid screening agent for the respective commercial products. It is our feeling that propylene glycol and corticosteroids are co-reactors in some cases.

The only relevant reaction to a preservative was to stearyl alcohol present in HydroVal cream (TaroPharma, Brampton, Ontario, Canada); this patient also reacted to hydrocortisone-17-butyrate. There were no reactions to parabens.

We found few reactions to commercial products containing steroids in groups A and D1. The majority of reactions to commercial products were to Cyclocort Cream and Cyclocort Ointment (Stiefel Canada Inc., Saint Laurent, Quebec, Canada) (group B, 4 patients) and to HydroVal cream (group D2, 8 patients).

Conclusion

Patch testing remains the “gold standard” for diagnosing allergic contact dermatitis from corticosteroids. Intradermal testing can aid in confirming positive reactions or in diagnosing negative or equivocal results and multiple allergies. Screening for corticosteroid allergy should not be performed with commercial products. Further studies need to address whether hydrocortisone-17-butyrate 1% alcohol should replace hydrocortisone-17-butyrate 1% pet in the standard series and whether betamethasone is a better screen for group C corticosteroids than is dexamethasone-21-phosphate disodium in the steroid series.

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