

Patch, prick or intradermal tests to detect delayed hypersensitivity to corticosteroids?

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Summary

Background. Contact allergy to topical corticosteroids is usually detected by patch testing.

Objectives. This study compares the test results obtained with patch, prick and intradermal testing, to assess the most sensitive method for diagnosing corticosteroid hypersensitivity.

Patients/Methods. Nineteen corticosteroid-allergic subjects and three control subjects were included. Patch, prick and intradermal tests were performed with five commercial corticosteroid preparations, as well as with the respective active principles diluted in ethanol. The test readings were performed at different time points, i.e. at 8, 24, 48 and 96 hr, and at 7 days.

Results. Patch tests with ethanolic preparations produced more positive reactions than the commercial ones. The intradermal tests became positive earlier than the patch tests, a concordance between patch and intradermal tests being found in 11/15 (two positive intradermal test results with negative patch test results and vice versa). However, several subjects developed skin atrophy (14/22) at intradermal injection sites.

Conclusion. Patch testing with the active principles diluted in ethanol remains the diagnostic method of choice for the detection of delayed hypersensitivity to corticosteroids. Intradermal tests with late readings, despite detecting additional contact allergy cases, should not be routinely performed, because of an important risk of atrophy, particularly with corticosteroid suspensions.

Key words: corticosteroids; delayed hypersensitivity; diagnosis; intradermal tests; patch tests; prick.

Corticosteroids, which are potent anti-inflammatory and immunomodulatory agents used in the treatment of

various inflammatory diseases, are capable of inducing immediate or delayed hypersensitivity reactions.

The prevalence of allergy to corticosteroids is extremely variable: allergic contact reactions occur in 0.2–5% of patients attending patch test clinics (1–4), whereas immediate hypersensitivity is uncommon, representing 0.1–0.3% (5, 6).

The prevalence of allergic reactions following systemic administration of corticosteroids is not known, and neither is the frequency of such reactions in subjects with known contact allergy to them.

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Delayed hypersensitivity reactions are usually detected by skin tests, mainly patch tests. Tixocortol pivalate, budesonide and, in some departments, also hydrocortisone 17-butyrate are included in the baseline series, the two former detecting nearly 90% of corticosteroid-allergic patients (7). Whereas petrolatum is an appropriate vehicle for tixocortol pivalate and budesonide, ethanol is the vehicle of choice for most other corticosteroids (8, 9). As a result of the anti-inflammatory activity of corticosteroids, there is often an inverse relationship between the concentration of the test solution and the rate of positive responses; if the concentration is too low, false-negative results may occur, and if the concentration is too high, the anti-inflammatory effect dominates, and again a false-negative reaction can result. However, higher concentrations are sometimes necessary when there are negative test results (at the usual concentrations) and a strong clinical suspicion of allergy. Numerous publications have debated the optimal test concentration of corticosteroids in patch test preparations; however, most corticosteroids have been tested at a concentration of 1% (10).

The anti-inflammatory effect of a corticosteroid also influences the reading time, especially when its concentration is high; the reaction may be false-negative at early readings, so late readings at day 6 or day 7, or even later, have been proposed (11). Sometimes, so-called 'edge effects' (a ring of induration, erythema and/or papulovesicles around the patch test site, with no reaction in the centre) may appear at early readings (12). Another problem that is frequently encountered in skin testing is an initial period of vasoconstriction, resulting in whitening of the skin (and the attendant risk of a false-negative reading), so-called 'skin blanching', followed by massive vasodilatation with marked erythema (and the attendant risk of a false-positive reaction) (12).

However, the frequency of false-negative reactions in cases of delayed hypersensitivity to corticosteroids is not known, and some authors (13–17) have proposed that, in suspected cases, negative patch test results should be followed by intradermal tests with late readings.

The principal objective of this study was to compare patch, prick and intradermal tests, with the aim of assessing the most sensitive method for detection of delayed hypersensitivity to corticosteroids.

Subjects, Materials, and Methods

Subjects

Nineteen subjects with positive patch test reactions to corticosteroids (11 women, mean age 55 years; and 8 men, mean age 49 years) and 3 control subjects (2

women, 54 and 64 years old; and 1 man, 66 years old) were included in this study. The Institutional Ethical Committee, Commission d'Ethique Biomédicale Hospitalo-Facultaire de l'Université Catholique de Louvain (NCT B340320084407) approved the study, and informed consent for the diagnostic procedures was obtained from all subjects.

Patch tests

All subjects were clinically examined and patch tested with five commercial corticosteroid preparations ('as is', diluted 30% and 10% in 0.9% saline): three suspensions – Pulmicort® (budesonide, 0.25 mg/ml, 2 ml; AstraZeneca NV/SA, Brussels, Belgium), Kenacort-A10® (triamcinolone acetonide, 10 mg/ml, 5 ml; Bristol-Myers Squibb Belgium SA, Braine-l'Alleud, Belgium), and Diprophos®, (betamethasone dipropionate/betamethasone sodium phosphate, 10 mg + 4 mg/2 ml; Schering-Plough NV/SA, Uccle, Belgium); and two solutions – Celestone® (betamethasone disodium phosphate, 4 mg/1 ml; Schering-Plough, Heist-op-den-Berg, Belgium), and Solu-Cortef® (hydrocortisone sodium succinate, 100 mg/2 ml; Pfizer SA, Brussels, Belgium), or Solu-Medrol®, (methylprednisolone sodium succinate, 40 mg/1 ml; Pfizer SA). In contrast to solutions, which contain water-soluble forms of corticosteroids (18), in corticosteroid suspensions the molecules are not completely dissolved in the solvent.

Additional patch tests with the same active principles, diluted 0.1% in ethanol (96%; Belgalco NV/SA, Gent, Belgium), were also performed. Ethanol is the first choice of vehicle but, owing to its weak transepidermal penetration, even under occlusion, hydrocortisone was diluted in an equal mixture of ethanol and dimethyl sulphoxide (DMSO). Ethanol and ethanol/DMSO were also tested as controls. Because of the anti-inflammatory properties of corticosteroids, 0.1% was the test concentration used instead of 1%, as classically described in the literature (10). Budesonide was tested at 0.01% in pet. (8), but weaker ethanol solutions (between 0.02% and 0.002%) are sometimes necessary to diagnose patients with budesonide allergy; for this reason, budesonide was also systematically tested at 0.002% in ethanol (9).

All corticosteroids were compounded by our hospital pharmacy; the substances used for these preparations had been obtained from the pharmaceutical companies marketing them, and the test solutions with the commercial corticosteroid preparations were freshly prepared (4). The patch test materials used were Haye's® chambers (Destaing, Grasse, France) covered on the upper back with Fixomull stretch® (Smith and Nephew, Auckland, New Zealand).

The patches were applied in quadruplicate, and every series was removed after 8, 24, 48 and 96 hr; the patch test reactions were evaluated at 8, 24, 48 and 96 hr, and at 7 days, according to the International Contact Dermatitis Research Group criteria (11). All clearly positive test results (+, ++, or +++) were taken into account.

Prick and intradermal tests

Prick and intradermal tests were performed with 0.04 ml solution of the same five commercial preparations 'as is', diluted 30, 10, and 1% in 0.9% sterile serum saline. Skin prick tests were performed on the forearm with a negative (saline) and positive control (histamine chlorhydrate 10 mg/ml, Stallergene, Antony, France), and intradermal tests were carried out on the back, with saline as negative control, together with the patch tests. Prick and intradermal tests were read after 30 min, after 8 hr, 1, 2, 4, and also 7 days. Positivity of the prick/intradermal tests was determined by measuring the greatest diameter of the wheal reaction at the injection site:

- between 5 and 10 mm, +
- between 10 and 15 mm, ++
- above 15 mm, +++

However, reactions were only considered to be positive if they were 5 mm greater than the negative control.

Skin atrophy at the prick and intradermal injection site was evaluated by clinical examination during the first week, and also up to 4 months after completion of the tests.

Results

Patch tests (Fig. 1a)

Fifteen of nineteen subjects presented with positive patch test reactions, 9/19 to molecules belonging to one group of corticosteroids, and 6/19 to molecules belonging to at least two different groups of corticosteroids, according to the classifications of Coopman and Matura, and the recent classification of Baeck (19–21).

Patch tests were most often positive when removed after 48 hrs and read on day 4 and/or day 7 (Table 1).

Patch tests prepared with corticosteroid molecules diluted in ethanol became positive earlier and more frequently than those with the commercial preparations, which, tested 'as is' and diluted 30% in serum saline, gave similar results; the 10% dilution seemed to be less efficient. Seven subjects, including the 3 controls, tested negatively; two subjects presented with severe skin reactions (++++) that faded in approximately 15 days.

Prick and intradermal tests (Fig. 1b and c)

None of the subjects developed immediate (30 min) positive prick or intradermal test reactions. Seven of nineteen prick tests and 15/19 intradermal tests gave positive results, with the earliest reactions being seen between 8 and 48 hrs (Table 1), the latter apparently being the optimal reading time.

Intradermal tests with corticosteroid preparations 'as is', and diluted 30% and 10%, despite individual variations, more often gave positive results than those with the 1% dilutions.

The Pulmicort® intradermal injections (the commercial preparation is intended for inhalation only), tested 'as is', 30% and 10%, were painful for all subjects.

No side effects were observed with the prick tests. With intradermal tests, in one subject, skin atrophy was observed during the first week with Diprophos® 'as is', and diluted 30% and 10%. Most subjects (14/22), however, presented with atrophy when clinically examined 4 months later, particularly with Diprophos® (numbers 2, 3, 4, 7, 9, 10, 11, 13, 14 and 17, and two controls), owing to its potent anti-inflammatory effect, but also with Kenacort® (numbers 4, 8, 9, and 17) and Pulmicort® (numbers 6 and 9), independently of the concentrations used, except for the 1% solution (Fig. 2). No atrophy was noted for Solu-Cortef®, Solu-Medrol®, or Celestone®.

Two patients reacted positively to corticosteroid molecules (hydrocortisone and other group A corticosteroids) for which they tested negatively before the patch, prick and intradermal test procedure (numbers 7 and 8).

Comparison of patch, prick and intradermal tests (Fig. 3)

Patch and intradermal test results were concordant in 11 of 15 positive subjects. Two subjects presented with negative patch test results and positive intradermal test results with the same molecule: number 2 and number 19 had negative patch test results with Solu-Medrol® and Solu-Cortef®, respectively, whereas the intradermal tests were positive after 1 day. Two had negative intradermal test results, but positive patch test results (Table 1): number 3 only reacted positively to Solu-Cortef® tested 'as is', and number 4 had positive patch test reactions to Celestone® and Pulmicort® tested 'as is' and diluted 30%, whereas prick and intradermal test results were negative in both cases.

Moreover, 3 patients (numbers 11, 13, and 15) had positive reactions to intradermal tests and ethanolic patch tests, but negative patch test results with the corresponding commercial preparations. This shows the superiority of ethanol as test vehicle in the exploration of delayed hypersensitivity reactions to corticosteroids (see Discussion) (8, 9).

Table 1. Comparison of patch, prick and intradermal tests (time, score, vehicle, concentration and corticosteroid molecule, and/or commercial preparation)

Subject number	Type*	Sex/age (years)/time period between first corticosteroid-allergy detection and study	Clinical presentation	(T) Topical/ (S) systemic corticosteroid exposure	Patch tests		Prick tests		Intradermal tests	
					Time [†] and score	Molecule or commercial preparation/ vehicle/ concentrations	Time [†] and score	Commercial preparation/ concentrations (NaCl)	Time [†] and score	Molecule or commercial preparation/ concentrations (NaCl)
1	A	F/86/1 month	Generalized eruption	S	48 hr/++	Hydrocortisone/ ethanol–DMSO 0.5%	—	—	24 hr/++/++	Solu-Cortef®/ 100/30/ 10%
					96 hr/++	Hydrocortisone acetate/ethanol 0.1%			24 hr/++	Solu-Medrol®/ 100/10%
					96 hr/++	Budesonide/NaCl 100%/NaCl 30%				
					96 hr/++	Solu-Cortef®/ ethanol 0.002%/ ethanol 0.01%				
					7 days/+	Solu-Medrol®/NaCl 30%				
2	B	F/55/1 year	Generalized eruption	S	48 hr/++/++	Pulmicort®/NaCl 100%/NaCl 30%	48 hr/+ /++	Pulmicort®/ 100/30/10% Diprophos®/ 100%	24 hr/++	Solu-Medrol®/ 100%
					48 hr/++	Diprophos®/NaCl 100%/NaCl 30%	48 hr/+		24 hr/++/++	Diprophos®/ 100/30/10/ 1%
					48 hr/++/++	Budesonide/ethanol 0.002%/ethanol 0.01%			24 hr/++/++	Celestone®/ 100/30/10%
					48 hr/++	Betamethasone dipropionate/ ethanol 0.1%			24 hr/++/++	Pulmicort®/ 100/30/10/ 1%
					48 hr/++	Triamcinolone acetate/ ethanol 0.1%				
3	A	F/52/10 years	Generalized eruption	S	7 days/++	Celestone®/NaCl 100%/NaCl 30%				
					48 hr/++	Hydrocortisone acetate/ethanol 0.1%	48 hr/+	Solu-Medrol®/ 1%	24 hr/++/++	Solu-Medrol®/ 100/30/10%

Table 1. Continued

Subject number	Type*	Sex/age (years)/time period between first corticosteroid-allergy detection and study	Clinical presentation	(T) Topical/ (S) systemic corticosteroid exposure	Patch tests		Prick tests		Intradermal tests	
					Time [†] and score	Molecule or commercial preparation/ vehicle/ concentrations	Time [†] and score	Commercial preparation/ concentrations (NaCl)	Time [†] and score	Molecule or commercial preparation/ concentrations (NaCl)
4	B	F/64/1 year	Generalized eruption	S	7 days/+	Solu-Cortef®/NaCl 100%				
					7 days/+	Solu-Medrol®/NaCl 100%/NaCl 30%				
					48 hr/+	Pulmicort®/NaCl 100%	24 hr/+	Diprophos®/ 100%	48 hr/+	Diprophos®/ 30/10% Kenacort®/ 100/30%
					48 hr/+	Diprophos®/NaCl 100%				
					48 hr/+	100%/NaCl 30%				
					48 hr/+	Celestone®/NaCl 100%				
					48 hr/+	Hydrocortisone/ ethanol-DMSO 0.5%				
					96 hr/+	Kenacort®/NaCl 100%				
					96 hr/+	Celestone®/ NaCl 30%				
					96 hr/+	Pulmicort®/NaCl 30%				
5	C	M/47/ 4 months	Atopic dermatitis	T	96 hr/+	Budesonide/ethanol ++				
					96 hr/+	0.002%/ethanol 0.01%				
					96 hr/+	Triamcinolone acetone/ ethanol 0.1%				
					48 hr/+	Diprophos®/NaCl 100%/NaCl 30%	—	—	24 hr/+	Diprophos®/ 100/30/10% Celestone®/ 100/30/10%
					96 hr/	Celestone®/NaCl 100%/NaCl 30%			24 hr/+	
					96 hr/+	Betamethasone dipropionate/ ethanol 0.1%			++	
					96 hr/+				++	

Table 1. Continued

Subject number	Type*	Sex/age (years)/time period between first corticosteroid-allergy detection and study	Clinical presentation	(T) Topical/ (S) systemic corticosteroid exposure	Patch tests		Prick tests		Intradermal tests	
					Time [†] and score	Molecule or commercial preparation/ vehicle/ concentrations	Time [†] and score	Commercial preparation/ concentrations (NaCl)	Time [†] and score	Molecule or commercial preparation/ concentrations (NaCl)
6	B	F/40/ 9 months	Facial eczema	T/S	48 hr/++ 96 hr/ +++/ +++ 96 hr/ +++	Budesonide/ ethanol 0.01% Pulmicort®/NaCl 100%/NaCl 30% Budesonide/ethanol 0.002%	48 hr/+	Pulmicort®/ 100%	48 hr/++/ ++/++/+	Pulmicort®/ 100/30/ 10/1%
7	B	M/58/2 years	Generalized eruption	S	48 hr/++/ ++ 48 hr/++	Pulmicort®/NaCl 100%/NaCl 30% Budesonide/ ethanol 0.01%	48 hr/+/ +/-	Pulmicort®/ 100/30/10%	8 hr/+/+/+	Pulmicort®/ 100/30/10/ 1%
8	B	M/31/4 years	Facial eczema	T (i.e. by proxy aerosols)	48 hr/ +++/ +++/ ++ 48 hr/++	Pulmicort®/NaCl 100%/NaCl 30%/NaCl 10% Kenacort®/NaCl 30%/NaCl 10% Budesonide/ethanol 0.002%/ethanol 0.01%	24 hr/++/ ++/++	Pulmicort®/ 100/30/10%	8 hr/++ 24 hr/++/+	Kenacort®/ 100% Kenacort®/ 30/10%
9	B	M/64/ 13 years	Foot eczema	T	96 hr/++/ ++ 96 hr/++	Triamcinolone acetanide/ethanol 0.1% Pulmicort®/NaCl 100%/NaCl 30%/NaCl 10% Budesonide/ethanol 0.002%/ethanol 0.01%	—	—	7 days/++	Pulmicort®/ 100/30%

Table 1. Continued

Subject number	Type*	Sex/age (years)/time period between first corticosteroid allergy detection and study	Clinical presentation	(T) Topical/ (S) systemic corticosteroid exposure	Patch tests		Prick tests		Intradermal tests	
					Time [†] and score	Molecule or commercial preparation/ vehicle/ concentrations	Time [†] and score	Commercial preparation/ concentrations (NaCl)	Time [†] and score	Molecule or commercial preparation/ concentrations (NaCl)
10	B	F/5/7 years	Hand and foot eczema	T	—	—	—	—	—	—
11	A	M/51/1 year	Hand eczema	T	48 hr/++	Hydrocortisone/ ethanol–DMSO 0.5%	—	—	24 hr/++	Solu-Cortef®/ 100/30%
12	A	F/51/9 years	Leg eczema	T	—	—	—	—	—	—
13	A	M/77/1 year	Generalized eczema	T/S	96 hr/+	Hydrocortisone/ ethanol–DMSO 0.5%	—	—	24 hr/+	Solu-Cortef®/ 100%
14	A	F/60/ 6 months	Generalized eczema	T	48 hr/++	Solu-Cortef®/NaCl 100%/NaCl 30%	—	—	8 hr/++	Solu-Cortef®/ 100%
					48 hr/++	Solu-Medrol®/NaCl 30%	—	—	24 hr/++	Solu-Cortef®/ 30%
					48 hr/++	Betamethasone/ ethanol 0.1%	—	—	24 hr/++	Solu-Medrol®/ 100/30/10%
					96 hr/+	Solu-Cortef®/NaCl 10%	—	—	48 hr/+	Solu-Cortef®/ 10%
15	A	F/49/ 6 months	Generalized eruption	T	96 hr/ ++/++	Solu-Medrol®/NaCl 100%/NaCl 10%	—	—	96 hr/++	Solu-Medrol®/ 100/30%
					7 days/+	Betamethasone sodium phosphate/ethanol 0.1%	—	—	—	—

Table 1. Continued

Subject number	Type*	Sex/age (years)/time period between first corticosteroid-allergy detection and study	Clinical presentation	(T) Topical/ (S) systemic corticosteroid exposure	Patch tests		Prick tests		Intradermal tests	
					Time [†] and score	Molecule or commercial preparation/ vehicle/ concentrations	Time [†] and score	Commercial preparation/ concentrations (NaCl)	Time [†] and score	Molecule or commercial preparation/ concentrations (NaCl)
16	C	M/59/14 months	Atopic dermatitis	T	—	—	—	—	—	—
17	B	M/75/8 years	Generalized eczema	T	—	—	—	—	—	—
18	A	F/27/4 months	Generalized eruption	T	24 hr/++	Hydrocortisone/ ethanol–DMSO 0.5%	24 hr/+/+	Solu-Cortef®/ 100/30%	24 hr/+	Solu-Cortef®/ 30%
					48 hr/+/+/+	Solu-Cortef®/NaCl 100%/NaCl 30%/NaCl 10%	48 hr/+/+/+	Solu-Cortef®/ 100%	48 hr/++	Solu-Cortef®/ 100%
							96 hr/+/+/+/+	Solu-Medrol®/ 100/30%	96 hr/+/+/+/+	Solu-Medrol®/ 100/30%
19	B	F/69/1 month	Facial eczema	T	96 hr/++	Hydrocortisone/ ethanol–DMSO 0.5%	—	—	24 hr/++	Solu-Cortef®/ 100%
					7 days/++/++/++	Pulmicort®/NaCl 100%/NaCl 30%/NaCl 10%			24 hr/++	Solu-Medrol®/ 100%
					7 days/++/++	Budesonide/ethanol 0.002%/ethanol 0.01%			96 hr/+	Pulmicort®/ 100%
									7 days/+/+	Solu-Medrol®/ 30/10%
									7 days/+/+/++	Pulmicort®/ 30/10/1%

DMSO, dimethyl sulphoxide; F, female; M, male.

*Positive corticosteroid marker(s): A, tixocortol pivalate; B, budesonide; C, number 5, hydrocortisone-17-butyrate; number 16, betamethasone-17-valerate.

†Time of first positive reaction.

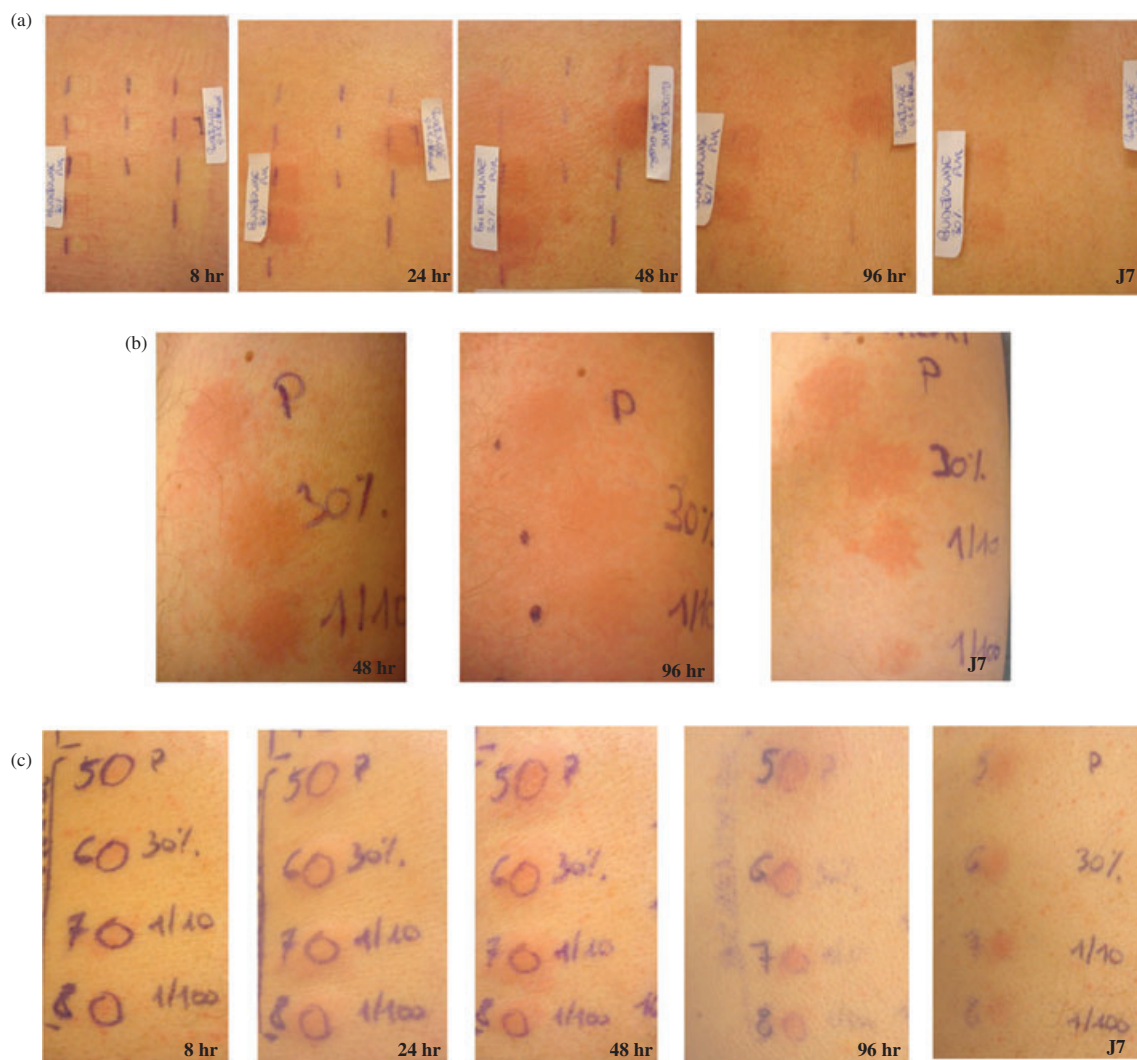


Fig. 1. Skin test results. Comparison of the test results obtained at different reading times (8, 24, 48 and 96 hrs, and at 7 days) with patch tests (a) with Pulmicort® 'as is', and 30% and 10% in 0.9% NaCl, and with budesonide 0.002% in ethanol and 0.01% petrolatum, as well as with prick (b), and intradermal tests (c) with Pulmicort® 'as is', and 30% and 10% in 0.9% NaCl.

The intradermal tests gave positive results earlier than patch tests in 11 of 15 subjects, at the same time point in 2 subjects, and later than the patch tests in 1 subject. They were less intense and more transitory (short-lasting) than the patch tests, and also more comfortable for the patients, as no occlusion is needed.

Two subjects developed local eczema induced by the skin tests.

Discussion

As early as 1992, Wilkinson and English (13, 14) had compared patch and intradermal tests with different

corticosteroid molecules: triamcinolone acetonide, hydrocortisone butyrate, and betamethasone valerate in 16 subjects (13); and hydrocortisone sodium phosphate, hydrocortisone butyrate, betamethasone valerate, clobetasol propionate and budesonide diluted 1% in normal saline in 11 subjects (14). Patch tests failed to detect all patients with positive intradermal reactions, and intradermal tests seemed to be necessary to absolutely exclude the possibility of corticosteroid sensitivity.

In 1993, Räsänen and Hasan (15) suggested a combination of intradermal and patch tests if allergy to systemic or intralesional corticosteroids was suspected,



Fig. 2. Side effects of intradermal tests. Skin atrophy 4 months following injection of Diprophos® 'as is', and 30% and 10%.

with, for intradermal tests, reading points starting from 3 to 6 hrs.

In 1997, Seukeran et al. (16) studied 37 corticosteroid-allergic patients in order to compare patch and intradermal tests. They noticed that 30% of the allergic reactions to hydrocortisone butyrate were missed by patch testing, and that intradermal tests produced additional positive reactions to methylprednisolone, fluocortolone, halcinonide, clobetasol propionate, flurandrenolone, and triamcinolone acetonide. However, 2 patients had positive patch test reactions to clobetasone butyrate, whereas intradermal tests gave negative results; this may have been because of the lack of solubility of the corticosteroids in the saline suspension (22). These studies thus suggested that hypersensitivity to corticosteroids might be missed by the current patch test method as the sole investigative tool, and that intradermal tests could complete the investigation.

Whereas their test concentration for intradermal testing was 1%, that is, 1 mg of corticosteroid diluted in 0.1 ml of saline (13–17), in our study, intradermal tests were prepared with commercial corticosteroid preparations, 'as is' and diluted, the former corresponding,

respectively, to 5% for Solu-Cortel®, 4% for Solu-Medrol®, 1% for Kenacort®, 0.7% for Diprophos®, 0.4% for Celestone®, and 0.025% for Pulmicort® (Table 2).

In the present study, despite some discrepancies, the concordance between patch test and intradermal test results was generally good.

Intradermal tests seemed to be easier to read than the patch tests, and became positive earlier (at least day 1 or day 2) (however, later readings, such as day 7 were, in most cases, not useful). Local intradermal reactions were less intense and lasted for less time. Moreover, intradermal tests detected a few (2/19 or 10%) additional allergic cases.

A number of subjects (4/19) who previously tested positive with corticosteroids did not react during the study, and several explanations can be proposed for this:

- two of them were taking immunomodulatory drugs (number 12, leflunomide and Medrol® 5 mg/day; number 16, Medrol® 10 mg/day along with an antihistamine medication, i.e. cetirizine);
- possible loss of sensitization, or skin hyporeactivity, or anergy (4, 23);
- false-positive results during previous patch tests (vasodilatation);
- false-negative results during the current study (insufficient quantity of allergens in the patch test chamber, inadequate occlusion, etc.);
- patch tests prepared too far in advance (evaporation of the product, especially for the ethanol dilutions).

Regarding the 2 patients who reacted positively to hydrocortisone and other group A corticosteroids, with which they had tested negatively before the testing procedure, several explanations seem possible: amplification of previously weak responses, cross-sensitivity (although molecules such as hydrocortisone and methylprednisolone, in general, do not cross-react with group B corticosteroids), or sensitization by the procedure; the last of these could have been promoted by the intradermal injection of the hapten and the large number of patch tests applied (in quadruplicate, sometimes with late removal after 4 days).

Regarding the patch tests, removal of the patch tests at day 2 with later readings, between 3 and 7 days, gave optimal detection of delayed hypersensitivity to corticosteroids. Keeping the tests on for more than 2 days gave comparable results, but, as suggested previously (24–26), may carry a (rare) risk of sensitization. Ethanol was confirmed to be the vehicle of choice; however, tests with the commercial preparations, diluted 'as is' and 30% in 0.9% serum saline (corresponding to concentrations

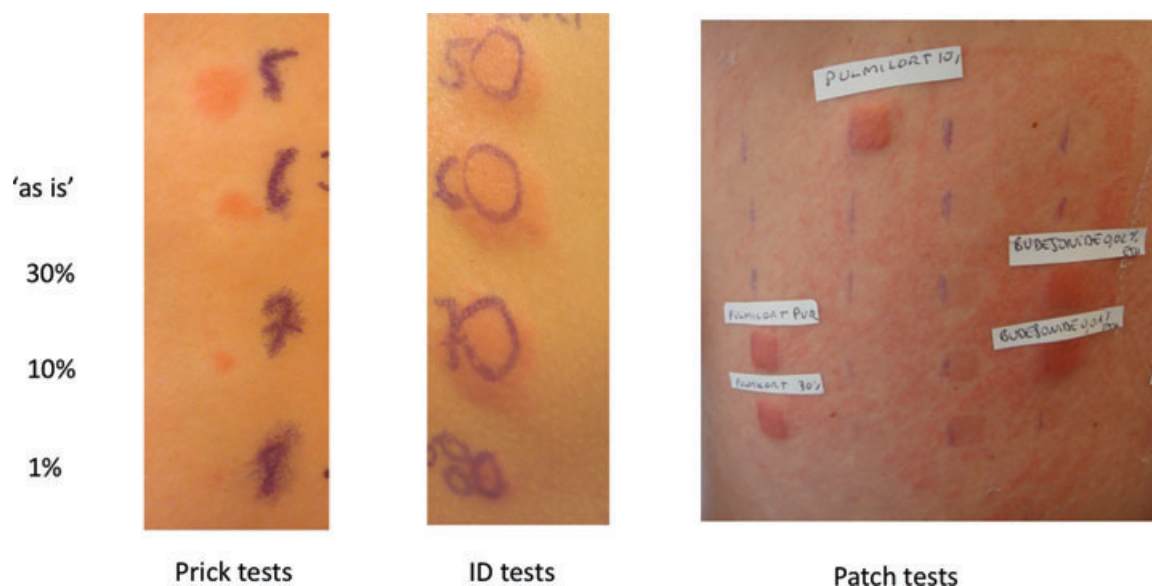


Fig. 3. Comparison of prick/intradermal (ID) and patch tests. Comparison of the different skin test results (prick, ID, and patch tests) obtained with Pulmicort® 'as is', and 30%, 10% and 1% in 0.9% NaCl and/or budesonide 0.01% pet. or 0.002% in ethanol read at 48 hr.

Table 2. The final corticosteroid concentrations of the commercial preparations tested

Commercial corticosteroids	Concentrations			
	'as is'	30%	10%	1%
Solu-Medrol® 40 mg/ml	4%	1.2%	0.4%	0.04%
Solu-Cortef® 100 mg/2 ml	5%	1.5%	0.5%	0.05%
Pulmicort® 0.25 mg/ml, 2 ml	0.025%	0.0075%	0.0025%	0.00025%
Kenacort-A10® 10 mg/ml, 5 ml	1%	0.3%	0.1%	0.01%
Celestone® 4 mg/1 ml	0.4%	0.12%	0.04%	0.004%
Diprophos® 10 mg + 4 mg/2 ml	0.7%	0.21%	0.07%	0.007%

between 0.0025% and 5%, depending on the molecule type; Table 2), gave, in most cases, comparable results.

Prick tests showed a minor diagnostic value for diagnosing delayed-type corticosteroid hypersensitivity, although no side effects were noted.

The principal side effects observed with intradermal testing were: pain caused by the injection (especially with Pulmicort®), and skin atrophy (17) with suspensions, especially Diprophos® (Schering–Plough NV/SA, Uccle, Belgium), Kenacort-A10® (Bristol–Myers Squibb Belgium SA), and Pulmicort® (AstraZeneca NV/SA), which

are also the most potent corticosteroid molecules; the corticosteroids probably remain longer in the skin than when they are completely dissolved. This risk is mentioned in the information/instructions for use of Diprophos® and Kenacort®, and was previously also observed with triamcinolone acetonide by Snyder and Greenberg (27). Skin atrophy was encountered with all of these corticosteroid dilutions, except with the 1% dilution, and was not influenced by skin test positivity, that is, cutaneous inflammation. However, the latter dilution gave false-negative results in most cases, because of a too low concentration of the active principle.

Despite the contribution of intradermal tests in diagnosing delayed hypersensitivity to corticosteroids, the risk of atrophy limits the usefulness of this test method, as previously suggested by Mimesh and Pratt (28). Therefore, these tests should only be performed in particular cases, that is, in patients with negative patch test results notwithstanding a very suggestive history, and only with commercial corticosteroid solutions for which no atrophy has been found.

Conclusion

Patch tests with 0.1% ethanolic dilution showed to be the most adequate and effective way of detecting delayed corticosteroid hypersensitivity. Removing the patch tests at day 2 (or day 4), with later readings between 3 and 7 days, provided optimal detection of delayed hypersensitivity to corticosteroids.

The use of intradermal tests allows the detection of additional contact allergy cases, thereby avoiding false-negative patch test results. However, there is an important risk of atrophy, particularly with potent corticosteroids and with corticosteroids in suspensions, in particular Diprophos®, and this is therefore a contraindication for routine use. Intradermal tests with corticosteroid solutions can be useful in cases of strong clinical suspicion, in order to complete patch testing.

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