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Contact Allergy to Topical Corticosteroids and Systemic Contact Dermatitis from Prednisolone with Tolerance of Triamcinolone

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We report the case of a 27-year-old female who had an allergic contact dermatitis to topical corticosteroids belonging to the corticosteroid groups A and D. Upon oral treatment with prednisolone a disseminated exanthema began within 24 h. Patch tests revealed sensitization to corticosteroids of group A, C and D, including prednisolone-21-acetate and betamethasone valerate, but not of group B corticosteroids such as triamcinolone. After intradermal testing of corticosteroids the exanthema flared again and the patient was treated with oral triamcinolone, with rapid improvement of her symptoms. A literature review revealed that exanthematous reactions after systemic treatment with corticosteroids have been rarely reported. Since corticosteroids are essential emergency drugs, a safe corticosteroid should be identified for such patients. Patch and intradermal tests may be used for that purpose. ***Key words: patch test; lymphocyte transformation test; cross-reactivity.***

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In the last decade contact hypersensitivity to corticosteroids has been found to be a problem of considerable clinical relevance. Reported prevalences of positive patch tests to corticosteroids range from 0.2 to 5% (1–4). Particularly patients suffering from allergic contact dermatitis after topical use have been observed. In addition, a few patients with exacerbation of local dermatitis or systemic immediate type or generalized delayed type hypersensitivity after systemic application of corticosteroids have been reported (3, 5, 6). For the diagnosis of delayed type hypersensitivity reactions, patch and intradermal tests have been used.

Based on patch test results cross-reactivity between different corticosteroids has been supposed, and based on the substitution of the D ring four groups (A–D) of structurally related corticosteroids have been suggested (7). Statistical analysis of patch test results and conformational analysis of the electronic shape of the molecules have confirmed correlations in between the members of groups A, B and D (8). We report on a patient who suffered initially from an allergic contact dermatitis to topical corticosteroids and then from a generalized exanthema to oral prednisolone. Skin tests made it possible to identify a safe corticosteroid. Similar cases from the literature are reviewed.

CASE REPORT

A 27-year-old woman developed a facial dermatitis after application of a cosmetic cream. Despite a 3-day treatment with topical prednisolone-21-acetate (Hexacorton® cream), the symptoms increased. The treatment was changed to betamethasone valerate (Betnovate® cream) but her dermatitis further deteriorated. Finally she was given oral prednisolone 40 mg/day. Twenty-four hours later she felt generally sick and developed oral enanthema, angioedema of the face, erythematous patches of the great folds, and maculopapular exanthema of the trunk. Oral antihistamines (terfenadine and clemastine) and intramuscular tetracosactid (Synacthen® = synthetic ACTH) were given, and symptoms improved markedly within a week.

She had a history of asthma, flexural eczema and contact allergy to jewellery. Earlier treatments with inhaled budesonide and several topical corticosteroids, including betamethasone valerate, prednisolone acetate and trimacinolone acetonide, had been tolerated. Skin prick tests were positive to grass and rye pollens. Two months after the incidence patch tests were performed with a standard series, a preservative series including the preservatives benzyl alcohol, butylhydroxyanisol, chlorhexidine, chlorocresol and triclosan, contained in the respective corticosteroids, and a corticosteroid series (Table I). She had positive results to nickel, palladium chloride and colophony. The results of the corticosteroid series are shown in Table I. In order to exclude an immediate hypersensitivity reaction intradermal tests with hydrocortisone succinate (Solu-Cortef®, 10 mg /ml), prednisolone hemisuccinate (Solu-Dacortin®, 2.5 mg/ml), methylprednisolone succinate (Solu-Medrol®, 4 mg/ml) and triamcinolone acetonide (Kenakort A®, 1 mg/ml) were performed. As positive control histamine hydrochloride 0.1 mg/ml and as negative control the diluent 0.9% NaCl were employed. The tests with the corticosteroids were negative in 2 controls who had been treated with systemic corticosteroids. A wheal and flare reaction was present at 20 min to the three former substances. Eight hours later generalized pruritus and a flare-up of the facial and flexural dermatitis began. After 24 h a generalized maculopapular exanthema was present and the three earlier positive skin test sites were infiltrated. A biopsy of the skin tests was denied. Based on the skin test results oral triamcinolone (12 mg per day) was given, which resulted in a rapid improvement of symptoms. A lymphocyte transformation test (9) with methylprednisolone acetate, methylprednisolone succinate and triamcinolone acetonide was negative.

DISCUSSION

Contact allergy to topical corticosteroids is now a frequent problem, whereas immediate type hypersensitivity and generalized delayed type hypersensitivity reactions upon local (10, 11) or systemic application of corticosteroids are rare (3, 5, 6). We found more than 25 patients reported in the literature who had delayed, generalized exanthematous reactions to oral or parenteral corticosteroids. The clinical signs most often observed were maculopapular exanthemas, generalized erythema or widespread eczema. In cases of oral administration, most often prednisolone and its derivatives (12–25) or prednisone (26–29) were involved. Only rarely were oral betamethasone and its derivatives (24, 30), dexamethasone (30), triamcinolone (19), and hydrocortisone (24, 25) the causing agents. Five patients reacted to both oral and parenteral administration (22, 24, 26, 29), and several patients with exanthematous reactions to parenteral corticosteroids such as prednisolone and its derivatives (14, 29, 31–35), and dexamethasone (11) have been reported. With some exceptions (13, 28) these patients have been diagnosed by patch or intradermal tests with the respective corticosteroids. More

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Table I. *Patch test results with corticosteroids*

No	Group	Corticosteroid	Concentration (%)	Vehicle	D2/D3/D4
1	A	Hydrocortisone	1.5	ethanol	+/+/+
2	A	Prednisolone	5	pet	−/+/++
3	A	Tixocortol pivalate	1	pet	−/++/++
4	B	Amcinonide	1	pet	−/−/−
5	B	Fluocinolone acetonide	1	pet	−/−/−
6	B	Halcinonide	1	pet	−/−/−
7	B	Triamcinolone acetonide	1	pet	−/−/−
8	B/D	Budesonide	1	pet	−/−/−
9	C	Desoximetasone	1	pet	+/+/+
16	C	Diflucortolone-21-valerate	1	pet	−/+/+
10	C	Flumetasone-21-pivalate	1	pet	−/−/−
11	C	Halometasone	1	pet	−/−/−
12	D	Betamethasone-17,21-dipropionate	5	pet	−/−/+
13	D	Betamethasone-17-valerate	5	pet	+/+/+
14	D	Clobetasol-17-propionate	0.5	pet	−/−/−
15	D	Hydrocortisone-17-butyrate	1	ethanol	+/+/+
17	A	Hexacorton® cream	as is	−	+/++/++
18	D	Betnovate® cream	as is	−	−/−/++

than a dozen patients were orally challenged or treated with an alternative corticosteroid without experiencing an adverse reaction (Table II) (11–13, 16, 17, 26–30).

The question whether patients with contact sensitization to hydrocortisone react also to oral hydrocortisone or stimulation of cortisol secretion by ACTH has been addressed in an interesting experiment (36). Upon oral challenge with 100 to 250 mg hydrocortisone erythematous flare-up of previous sites of contact dermatitis or of recently positive patch test reactions to hydrocortisone was observed. In one patient stimulation of endogenous cortisol by intravenous tetracosactid (synthetic ACTH) also resulted in a positive reaction. Flare-up of generalized exanthema after provocation with oral hydrocortisone and intramusucular ACTH has also been observed in another patient (25). These cases indicate that in patients sensitized to hydrocortisone endogenous cortisol may also elicit a flare-up of skin reactions.

According to cross-reactivity patterns between different corticosteroids, four groups of structurally related corticosteroids have been suggested according to the substitution of the D ring (7). These include group A (hydrocortisone type), group B (triamcinolone acetonide type), group C (betamethasone type) and group D (hydrocortisone-17-butyrate type) (Fig. 1). Statistical analysis of patch test results and conformational analysis of the electronic shape of the molecules have confirmed strong correlations in between the members of groups A, B and D (8). Moreover, the value of marker corticosteroids such as tixocortol pivalate for group A, and budesonide as a marker for group B and D corticosteroids, has been confirmed by these studies (8). The corticosteroid molecules belonging to group C are more difficult to classify, as no significant group specific characteristics of volume and shape were found. Typically, they have no substitution on C 17 or C 21 but an alkyl group on C 16. Some corticosteroids, such as flumetasone pivalate and diflucortolone valerate, with an ester substitution on C 21 undergo rapid deesterification in vivo and therefore classify for group C and not for group D.

Initially, our patient presented with a severe exacerbation of the facial dermatitis to a topical corticosteroid of group A (prednisolone acetate), and then to one of group D (betamethasone valerate). Upon oral prednisolone a maculopapular exanthema and a systemic contact dermatitis occurred. The short interval suggests that the patient has been previously sensitized by topical use of corticosteroids. Intramuscular tetracosactid was well tolerated despite the positive patch test to hydrocortisone. Patch tests revealed sensitization to all group A, to most group D and to some group C corticosteroids tested, including the two corticosteroids that had been used topically (Table I). Upon the intradermal tests which gave positive immediate and late reactions the generalized dermatitis flared. Oral triamcinolone, a group B corticosteroid, which was selected because of negative intradermal and patch tests, was then given, with rapid improvement of symptoms.

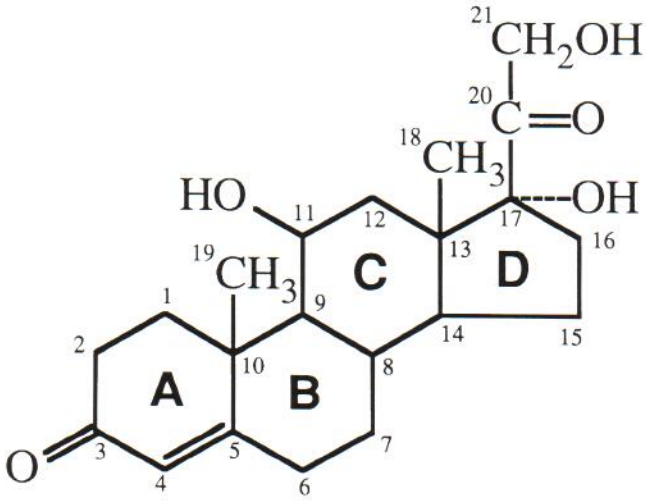

Fig. 1. Chemical structure of hydrocortisone. Corticosteroid groups include: Group A (hydrocortisone type: no substitution on D ring except short chain ester on C17 or C21 or thioester on C21); Group B (triamcinolone acetonide type: C16 C17-cis-ketal or -diol structure); Group C (betamethasone type: C16 -methyl substitution); Group D (hydrocortisone butyrate type: long chain ester at C17 and/or C21 with or without C16 -methyl substitution).

The lymphocyte transformation test has been rarely used to investigate an exanthematous reaction to a corticosteroid. As

Table II. *Corticosteroid-allergic patients with tolerance of other systemically applied corticosteroids*
i/a = intraarticular, id = intradermal, i/v = intravenous, nd = not done, nm = not mentioned.

No	Age/Sex/Indication	Eliciting steroid	Group	Administration	Symptoms	Positive skin tests	Negative skin tests	Tolerated steroid	Group	Ref
1	54/f/contact dermatitis	prednisone	A	oral, i/a	rash	prednisone (id) hydrocortisone	betamethasone	betamethasone	C	26
2	50/m/SLE	prednisone	A	oral	angioedema, pruritus	prednisone (id) hydrocortisone	dexamethasone	dexamethasone	C	27
3	55/m/Waldenström	prednisone	A	oral	papular rash	nd	nd	dexamethasone (at low doses)	C	28
4	29/f/contact dermatitis	prednisolone	A	oral	macular exanthema	prednisolone	betamethasone hydrocortisone triamcinolone	betamethasone hydrocortisone	C A	12
5	33/f/rheumatoid arthritis	prednisolone	A	oral	angioedema erythematous rash	nd	nd	betamethasone	C	13
6	36/f/contact dermatitis	prednisolone	A	oral	generalized rash	prednisolone	nd	triamcinolone	B	16
7	50/f/contact dermatitis	dexamethasone betamethasone	C	oral	maculopapular exanthema	dexamethasone betamethasone	fluocortolone methylprednisolone hydrocortisone triamcinolone	fluocortolone methylprednisolone	C A	30
8	59/m/contact dermatitis	prednisolone	A	oral	maculopapular exanthema	prednisolone	dexamethasone hydrocortisone triamcinolone	dexamethasone	C	17
9	nm/nm/drug rash	prednisolone	A	oral	maculopapular exanthema	prednisolone	dexamethasone hydrocortisone triamcinolone	dexamethasone	C	
10	nm/nm/contact dermatitis	prednisolone	A	oral	maculopapular exanthema	prednisolone	dexamethasone hydrocortisone triamcinolone	dexamethasone	C	
11	55/f/splenic lymphoma	prednisone	A	i/v, oral	rash	prednisone hydrocortisone tixocortol pivalate	paramethasone fluocortolone betamethasone triamcinolone acetonide	paramethasone fluocortolone	C C	29
12	40/m/Henoch Schönlein syndrome	methylprednisolone	A	oral	maculopapular exanthema	methylprednisolone	nd	betamethasone	C	21
13	71/f/foot spur	dexamethasone	C	local injection	generalized erythema, scaling	dexamethasone	hydrocortisone hydrocortisone butyrate triamcinolone acetonide	prednisone	A	11
14	27/f/contact dermatitis	prednisolone	A	oral	maculopapular exanthema	cf Table I	cf Table I	triamcinolone	B	present case

in our case it was usually negative or even showed a decreased reactivity as compared to unstimulated control cultures when peripheral blood monocytes were used (27, 31, 34). It has been shown that epidermal Langerhans' cells, but not peripheral blood monocytes, could act as antigen-presenting cells in *in vitro* corticosteroid hypersensitivity tests (37). This explains negative lymphocyte transformation test results with corticosteroids when no specially prepared antigen-presenting cells are used. It also suggests that delayed hypersensitivity to corticosteroids is more likely induced through epidermal contact than by systemic application.

The published data on delayed allergic reactions to systemically administered corticosteroids suggest that in most cases the cross-reactivity patterns are the same as in contact allergic reactions. It was often possible to diagnose a delayed hypersensitivity reaction to corticosteroids and to identify corticosteroids safe for systemic application by patch testing (Table II). In some cases, however, intradermal tests were necessary to improve the diagnostic certainty (24, 38). In 2 patients (12, 30), however, a skin test negative corticosteroid belonging to the same group as the eliciting agent was given orally without adverse effects (Table II). Therefore, it appears that if patch and probably intradermal tests (24) to a corticosteroid or several members of a corticosteroid group are negative, this corticosteroid or a member of this group, respectively, may still be given by the oral or parenteral route. However, caution is required, since patch and intradermal tests may give false negative results in delayed hypersensitivity to corticosteroids.

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