

Allergic Contact Dermatitis Following Ocular Use of Corticosteroids

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Abstract

Aim: To study the clinical features and to identify the molecules responsible for contact-allergic reactions following ocular use of corticosteroid (CS) preparations.

Design: Observational case series.

Methods: We reviewed the clinical data, the patch test results, and sensitization sources in patients with a CS contact allergy, who have been patch tested in the K.U. Leuven Dermatology department during an 18-year period.

Results: Eighteen subjects (out of 315 with CS delayed-type hypersensitivity) presented with allergic manifestations (conjunctivitis, eczema of the face, periocular skin or eyelids) of delayed-type hypersensitivity reactions to the use of CS-containing ocular preparations. The most common allergen was hydrocortisone, but most patients presented with multiple positive tests, not only to other CSs, but also to other active principles, preservatives, and vehicle components.

Conclusions: Ophthalmic CSs, despite their anti-inflammatory and antiallergic properties, may produce contact-allergic reactions.

Introduction

ALLERGIC CONTACT DERMATITIS (ACD) is a delayed hypersensitive inflammatory reaction due to direct contact of the skin with environmental chemicals, for example, topical drugs.¹ The immunological reaction, in which T-lymphocytes are activated in response to specific allergens, has 2 main phases: sensitization and elicitation. During the sensitization phase, the individual acquires a specific immunological memory of the contact sensitizer at the T-cell level. Upon renewed contact with the sensitizing substance, irrespective of where on the skin this contact takes place, the often lifelong memory will mount an immune response, resulting in eczema. The immune response is a delayed-type hypersensitivity reaction as classified by Coombs and Gell,² since it usually takes more than 12 h to become manifest and peaks at about 24–72 h. The molecular mechanisms that decide whether an individual will become sensitized or not are still largely unknown.³

ACD is said to occur in 46% to 74% of the patients suffering from conjunctivitis and/or eyelid dermatitis,^{4–6} the most important allergens being topical pharmaceutical products, that is, active principles, vehicle components, and preservative agents present in ophthalmic preparations.^{4,7–12}

Topical corticosteroids (CSs), potent anti-inflammatory and immuno-modulator agents, are important pharmaceutical products for treating individuals with ACD since they reduce immunological reactions. However, in some individuals, CSs could become an antigen that triggers CS allergy. This manifests as an ACD that is unresponsive to CS or provokes a worsening of a pre-existing condition.¹³

Despite the wide ocular use of CSs, only few cases of patients experiencing allergic reactions have been reported.^{4,7–11,14–17} For example, Alani in 1976¹⁴ was the first to report 2 patients suspected of allergic dermatitis due to CSs: they were both tested with the constituents of the ointments applied and showed positive patch test reactions to betamethasone valerate and to hydrocortisone, respectively. Mathias et al.^{15,16} described 3 patients, suffering from chronic iridocyclitis, who developed severe conjunctival inflammation following retrobulbar injections with a methylprednisolone-acetate suspension. Lewis¹⁷ also reported multiple contact sensitivities to eyedrop ingredients, including the drugs prednisolone. Most authors of clinical reviews mention intraocular CSs as potential causes of ACD.^{4,7,8,10–12}

However, when problems arise on the eyes and/or eyelids, the significance of contact allergy to CSs cannot easily be

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TABLE 1. CORTICOSTEROID SERIES, ALONG WITH TEST CONCENTRATIONS AND VEHICLES

	<i>Molecules</i>	<i>Vehicle/concentration</i>	<i>CAS</i>
1	Alclometasone dipropionate	0.5% ethanol	66734-13-2
2	Amcinonide	0.1% ethanol	51022-69-6
3	Beclomethasone dipropionate	0.1% ethanol	5534-09-8
4	Betamethasone	0.1% ethanol	378-44-9
5	Betamethasone dipropionate	0.1% ethanol	5593-20-4
6	Betamethasone sodium phosphate	0.1% saline	151-73-5
7	Betamethasone 17-valerate	0.1% ethanol	2152-44-5
8	Budesonide	0.01% petrolatum/0.002% ethanol	51333-22-3
9	Clobetasol propionate	0.1% ethanol	25122-46-7
10	Clobetasone butyrate	0.1% ethanol	25122-57-0
11	Cloprednol	0.1% ethanol	5251-34-3
12	Cortisone acetate	0.5% ethanol/DMSO	50-04-4
13	Desonide	0.1% ethanol	638-94-8
14	Desoxymethasone	0.1% ethanol	382-67-2
15	Dexamethasone	0.1% ethanol	50-02-2
16	Dexamethasone acetate	0.1% ethanol	1177-87-3
17	Dexamethasone sodium phosphate	0.1% ethanol	2392-39-4
18	Dichlorisone acetate	0.1% ethanol	79-61-8
19	Diflorasone diacetate	0.1% ethanol	33564-31-7
20	Diflucortolone valerate	0.1% ethanol	59198-70-8
21	Difluprednate	0.1% ethanol	23674-86-4
22	Flucloronide	0.1% ethanol	3693-39-8
23	Fludrocortisone acetate	0.1% ethanol	514-36-3
24	Flumethasone pivalate	0.1% ethanol	2002-29-1
25	Flumoxonide	0.1% ethanol	60135-22-0
26	Flunisolide	0.1% ethanol	3385-03-3
27	Fluocinolone acetonide	0.1% ethanol	67-73-2
28	Fluocinonide	1% ethanol	356-12-7
29	Fluocortin butyl	0.1% ethanol	41767-29-7
30	Fluocortolone	0.1% ethanol	152-97-6
31	Fluocortolone caproate	0.1% ethanol	303-40-2
32	Fluocortolone pivalate	0.1% ethanol	29205-06-9
33	Fluorometholone	0.1% ethanol	426-13-1
34	Fluprednidene acetate	0.1% ethanol	1255-35-2
35	Fluprednisolone	0.1% ethanol	53-34-9
36	Fluticasone propionate	0.1% ethanol	80474-14-2
37	Halcinonide	0.1% ethanol	3093-35-4
38	Halometasone	0.1% ethanol	50629-82-8
39	Hydrocortisone	0.5% ethanol/DMSO	50-23-7
40	Hydrocortisone aceponate	1% ethanol	74050-20-7
41	Hydrocortisone acetate	0.1% ethanol	50-03-3
42	Hydrocortisone-17-butyrate	0.1% ethanol	13609-67-1
43	Hydrocortisone-21-butyrate	0.1% ethanol	6677-99-2
44	Hydrocortisone hemisuccinate	0.1% ethanol	2203-97-6
45	Isofluprednone acetate	0.1% ethanol	338-98-7
46	Mazipredone	0.1% ethanol	13085-08-0
47	Medrysone	0.1% ethanol	2668-66-8
48	Meprednisone	0.1% ethanol	1247-42-3
49	Methylprednisolone aceponate	0.1% ethanol	86401-95-8
50	Methylprednisolone acetate	0.1% ethanol	53-36-1
51	Methylprednisolone hemisuccinate	0.1% ethanol	2921-57-5
52	Mometasone furoate	0.1% ethanol	83919-23-7
53	Pivalate tixocortol	0.1% petrolatum	55560-96-8
54	Prednicarbate	1% ethanol	73771-04-7
55	Prednisolone	0.1% ethanol	50-24-8
56	Prednisolone caproate	0.1% ethanol	69164-69-8
57	Prednisolone sodium metasulphobenzoate	0.1% ethanol	630-67-1
58	Prednisolone pivalate	0.1% ethanol	1107-99-9
59	Prednisolone hemisuccinate	1% ethanol	2920-86-7
60	Prednisone	0.1% ethanol	53-03-2
61	Procinonide	0.1% ethanol	58497-00-0
62	Progesterone	2% ethanol	57-83-0
63	Testosterone propionate	2% ethanol	57-85-2

(continued)

TABLE 1. (Continued)

	<i>Molecules</i>	<i>Vehicle/concentration</i>	<i>CAS</i>
64	Triamcinolone	0.1% ethanol	124-94-7
65	Triamcinolone acetoneide	0.1% ethanol	76-25-5
66	Triamcinolone benetonide	0.1% ethanol	31002-79-6
67	Triamcinolone diacetate	0.1% ethanol	67-78-7
68	Triamcinolone hexacetoneide	1% ethanol	5611-51-8
69	Ethanol	70% water	64-17-5
70	Ethanol/DMSO	50/50% water	64-17-5/67-68-5
71	Glutaraldehyde	1% water	111-30-8
72	Glyoxal	2% water	107-22-2

DMSO, dimethyl sulfoxide.

assessed, since ocular preparations are not often suspected as potential causes and, hence, have rarely been patch tested.

We wanted to study the clinical features and to identify the molecules responsible for contact-allergic reactions following ocular use of CS preparations.

Methods

We reviewed the clinical data and the results of patch testing of an extended CS series in the Dermatology Department at the K.U. Leuven University Hospital during an 18-year study period, that is, from January 1, 1990, to June 30, 2008.¹⁸ All patients attending the Contact Allergy Unit were examined clinically, and routinely patch tested with a baseline (standard) series containing (1) tixocortol pivalate 0.1% pet., a marker that detects allergic reactions to CS molecules such as hydrocortisone, methylprednisolone, and prednisolone; (2) budesonide 0.01% pet., a marker for CS such as triamcinolone acetoneide and amcinonide (19) and (3) hydrocortisone 17-butyrate and prednisolone caproate both diluted in 0.1% ethanol. Moreover, those patients having been exposed to CSs were, in most cases, also tested with the respective molecules used. Patients with a proven contact allergy to a CS and some presumed to have had such a reaction, according to their history, were later tested with an extended CS series to study simultaneous positive (and cross) reactions.

Sixty-six CSs, including those from the baseline series, as well as 2 sexual hormones, that is, progesterone and testosterone, were thus tested (Table 1). All CSs (except for the 2 screening agents officially added to the baseline series¹⁹) were made up in the Contact-allergy Unit by a laboratory technician; the substances used for these preparations had previously been obtained from the pharmaceutical companies marketing them. Dexamethasone Na-phosphate (introduced in November 1990) and difluprednate (Sicor, Milan, Italy; marketed in 2008 to treat ocular pain²⁰) have been included in the base line series since October 1994. The test solutions were freshly prepared every 6 to 12 months.

Ethanol was the vehicle used to test all CS molecules except for tixocortol pivalate and budesonide where petrolatum worked well.^{21,22} Due to their weak trans-epidermal penetration, hydrocortisone and cortisone acetate were diluted in an equal mixture of ethanol and dimethyl sulfoxide (DMSO).²¹ Both ethanol and ethanol/DMSO were included as controls in the extended series.

The concentrations of the test solutions were defined according to the methods of Isaksson et al.^{23,24} (Table 1). Par-

ticularly for budesonide, lower concentrations were also tested, that is, 0.01% pet. and 0.002% eth.

The patch test materials used were van der Bend chambers (van der Bend, Briele, The Netherlands) on Mepore® (3M), covered on the upper back with Mefix®. The patches were removed after 2 days and the patch test reactions were evaluated at day 2, day 4, and in many cases also after 7 days, in accordance with the International Contact Dermatitis Recommendation Group (ICDRG) criteria. All clearly positive tests were taken into account in this study. Although, in general, dubious reactions were excluded from our analysis, weak irritant reactions to the DMSO/eth (even in the presence of hydrocortisone) could not always be ruled out with certainty.

The results were collected from a computer database containing the following information: sex, date of birth, occupation, personal and familial atopic history, localization and lesion type, use of CSs, and patch test results. The relevance of the reactions was considered on the basis of a history of known or likely contact of the affected skin area with products containing the allergen, as well as according to the follow-up of the patients in whom the dermatitis got better, for example, in the case of an underlying disease such as atopic or seborrheic dermatitis, or disappeared on discontinuing the use of the incriminated CS.

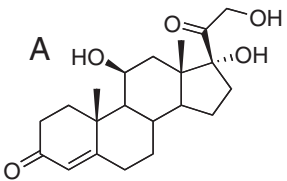
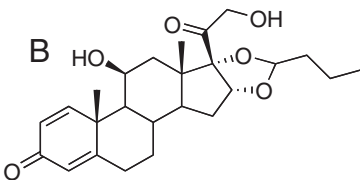
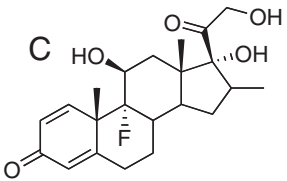
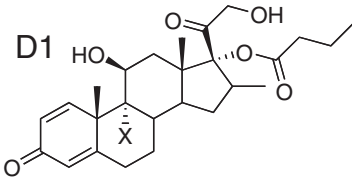
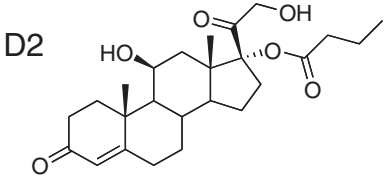
To categorize the multiple positive reactions often observed with CSs, which may be due to simultaneous or subsequent sensitization or to cross-reactivity,²⁵ the CSs were classified into 4 reacting groups: groups A, B, C, and D.²⁶ Group D has been further sub-classified into 2 subgroups: D1 and D2^{18,27,28} (Table 2).

Results

Eighteen (5.7%) out of 315 CS allergic patients (Table 3) presented with facial, periocular, or eyelid eczema, and/or conjunctivitis, following ocular application of CSs. Their symptoms responded to treatment either poorly or not at all; decreased very rapidly when the treatment was stopped; or got worse when CS-based collyria or ointments were re-applied (Figs. 1–2 provide examples of ACD following the ocular use of dexamethasone Na-phosphate).

According to the clinical history, the patients had used ophthalmic preparations containing hydrocortisone, prednisolone, dexamethasone, fluorometholone, and/or triamcinolone acetoneide. All 18 patients tested positively to the group A CSs, that is, hydrocortisone, prednisone, prednisolone, methylprednisolone, and/or particularly to tixocortol pivalate, the latter being the contact allergy marker of this group.

TABLE 2. CLASSIFICATION OF CORTICOSTEROIDS

Group	Characteristics of the group	Typical members	Possible cross reactions outside the group
A 	No substitution on the D ring except a short chain ester or a thioester on C21	Cloprednol acetate Cortisone acetate Dichlorisone acetate Fludrocortisone acetate Fluorometholone Fluprednisolone acetate Hydrocortisone Hydrocortisone acetate Hydrocortisone 21-butyrate Hydrocortisone hemisuccinate Isofluprednone acetate Mazipredone Medrysone Methylprednisolone acetate Methylprednisolone hemisuccinate Prednisolone Prednisolone caproate Prednisolone pivalate Prednisolone sodium metasulpho benzoate Prednisolone succinate Prednisone Tixocortol pivalate	D2
B 	C16, C17 cis Ketal or diol structure Possibly a side chain on C21	Amcinonide Budesonide Desonide Fluchloronide Flumoxonide Flunisolide Fluocinolone acetonide Fluocinonide Halcinonide Triamcinolone acetonide Triamcinolone benetonide Triamcinolone diacetate Triamcinolone hexacetone	
C 	C16 methyl substitution on the D ring Halogen substitution No side chain on C17 Possibly a side chain on C21	Betamethasone Betamethasone sodium phosphate Desoxymethasone Dexamethasone Dexamethasone acetate Dexamethasone sodium phosphate Diflucortolone valerate Flumethasone pivalate Fluocortin butyl Fluocortolone Fluocortolone caprylate Fluocortolone pivalate Fluprednidene acetate Halomethasone Meprednisone	
D1 	Methyl substitution on C16 Halogen substitution Side chain ester on C17 Possibly a side chain on C21	Alclomethasone dipropionate Beclomethasone dipropionate Betamethasone dipropionate Betamethasone 17-valérate Clobetasol propionate Clobetasone butyrate Diflorasone diacetate Fluticasone propionate Mometasone furoate	
D2 	No methyl substitution on C16 No halogen substitution Side chain ester on C17 Possibly a side chain on C21	Difluprednate Hydrocortisone aceponate Hydrocortisone 17-butyrate Methylprednisolone aceponate Prednicarbate	A Budesonide (S isomer)

- Eight patients, all of whom had used hydrocortisone ophthalmic ointment [numbers (nos.) 1, 3, 5, 8, 11, 13, 17, and 18; Table 3], reacted exclusively to group A, particularly to hydrocortisone, and presented with cross-reactions with other CSs from the same group.
- Six patients (nos. 2, 4, 6, 7, 14, and 15; Table 3), who had also used ophthalmic CSs containing hydrocortisone and/or prednisolone, tested positively to group A CSs

with concomitant/cross-reactions with the labile ester molecules from the D2 group, of whom 2 also tested positively to budesonide (nos. 7 and 14). Indeed, budesonide, based on the acetal function, is actually an equal mixture of the R and S diastereoisomers^{29,30} and is able not only to cross-react within the acetonide group (group B) but also with ester molecules (mainly of group D2).

TABLE 3. LIST OF PATIENTS WITH ALLERGIC CONTACT DERMATITIS FOLLOWING OCULAR USE OF CORTICOSTEROIDS

	Sex	Age	Occupation	Lesion location	Date cons.	Positive tests to corticosteroid	Other positive tests	Ophthalmic corticosteroids exposure
1	M	56	Office work	Eyes	02/2005	Tixocortol pivalate++, hydrocortisone acetate++, dichlorisone acetate++		Hydrocortisone
2	F	22	Student	Eyelids	05/2005	Tixocortol pivalate++, hydrocortisone 17-butyrate+	Benzalkonium chloride, polymyxine B, oxytetracycline hydrochloride	Hydrocortisone
3	F	48	Housekeeping	Eyelids and mucosa	02/2004	Tixocortol pivalate+, hydrocortisone+	Neomycin, tobramycin	Hydrocortisone and dexamethasone
4	F	75	Unknown	Periocular	08/2003	Tixocortol pivalate++, cloprednol++, fluorocortin butyl+, Fluprednisolone acetate+, hydrocortisone 21-butyrate+, methylprednisolone acetate+, methylprednisolone hemisuccinate++, prednisolone+, prednisolone metasulpho-benzoate+, prednisone+, Mazipredonum+, Prednicarbate+, methylprednisolone aceponate+, Prednisolone pivalate+, prednisolone caproate+, hydrocortisone 17-butyrate+	Polymyxine B, formaldehyde, quaternium 15	Multiple preparations, that is, hydrocortisone, prednisolone
5	F	56	Unknown	Periocular	06/2002	Tixocortol pivalate+, cloprednol++, hydrocortisone acetate+, hydrocortisone 21-butyrate+, prednisolone++, hydrocortisone++++, prednisolone metasulpho-benzoate++, mazipredonum++	Neomycin, wool alcohols, amercholL101, phenylephrine, chloramphenicol, oxytetracycline hydrochloride	Hydrocortisone and prednisolone
6	F	72	Housekeeping	Periocular	06/2001	Tixocortol pivalate++, cortisone acetate+, fluocortin butyl+, fluprednisolone acetate+, hydrocortisone 21-butyrate+, methylprednisolone acetate++, prednisolone+, prednisolone metasulpho-benzoate+, prednisone++, mazipredonum+, prednicarbate+, prednisolone pivalate+, prednisolone caproate++	Neomycin, nickel, wool alcohols, amercholL101, phenylephrin, oxytetracycline hydrochloride, chloramphenicol	Multiple preparations
7	F	56	Housekeeping	Periocular	03/2001	Budesonide++, cortisone acetate++, diflurasone diacetate+, hydrocortisone acetate+, hydrocortisone 21-butyrate++, methylprednisolone acetate+, prednisolone+, hydrocortisone+, hydrocortisone aceponate+, prednicarbate++, methylprednisolone aceponate++, difluprednate++, testosterone propionate+, ethanol++, ethanol/DMSO++	Colophonium, wool alcohols, amercholL101	Pednisolone, dexamethasone
8	M	31	Office work	Periocular	06/2000	Tixocortol pivalate++, hydrocortisone++		Hydrocortisone

(continued)

TABLE 3. (CONTINUED)

Sex	Age	Occupation	Lesion location	Date cons.	Positive tests to corticosteroid	Other positive tests	Ophthalmic corticosteroids exposure	
9	M	38	Electrician	Periocular	03/1999	Budesonide+++ , amcinonide++ , beclomethasone dipropionate++ , betamethasone++ , cortisone acetate++ , desonide++ , dexamethasone++ , medrysone++ , prednisolone+ , hydrocortisone+ , prednisolone metasulpho-benzoate++ , triamcinolone++ , triamcinolone benetonide+ , triamcinolone acetonide+ , prednisolone caproate++ , testosterone propionate+ , glutaraldehyde+ , glyoxal+ Tixocortol pivalate++ , budesonide++++ , amcinonide++++ , betamethasone++++ , betamethasone Na-Phosphate++ , clobetasone butyrate+ , cloprednol++ , cortisone acetate+++ , desonide++ , desoxymethasone++++ , dexamethasone++++ , dexamethasone acetate++ , dexamethasone Na-Phosphate++ , fluchloronide+ , fludrocortisone acetate+ , flumoxonide+ , flunisolide+ , fluocinolone acetonide+ , pluprednisolone acetate+ , hydrocortisone+ , prednisone+ , procinonide+ , triamcinolone+++ , triamcinolone diacetate+ , triamcinolone hexacetonide+ , flucinonide+++ , triamcinolone benetonide+++ , fluticasone propionate+ , hydrocortisone aceponate+ , mazipredonum+ , alclomethasone dipropionate++ , triamcinolone acetonide+++ , prednicarbate++ , prednisolone pivalate+ , hydrocortisone 17-butyrate+ , prednisolone caproate+ , testosterone propionate+	Neomycin, fragrance mix I, wool alcohols	Pednisolone pivalate and fluorometholone
10	M	54	Office work	Periocular	02/2000	Colophonium, fragrance mix I-II, neomycin, myroxelon pereirae, parabens, paratertiary butyl phenol formaldehyde resins, euxylK400, propylene glycol, sorbitane sesquioletate, cetylalcohol, thiomersal	Hydrocortisone and dexamethasone	
11	F	82	Unknown	Periocular	12/1998	Potassium dichromate, cobalt chloride, nickel, cocamidopropylbetaine	Hydrocortisone	

12	F	56	Housekeeping	Periocular	09/1999	Tixocortol pivalate+, budesonide++, aminonide+, beclomethasone dipropionate++, betamethasone dipropionate++, betamethasone 17-valerate+, clobetasol propionate++, clobetasone butyrate+, cloprednol++, cortisone acetate++, desonide++, desoxymethasone+, dexamethasone+, dexamethasone acetate+, diflorasone diacetate+, diflucortolone valerate+, fluchloronide+, fludrocortisone acetate+, flumoxonide+, flunisolide+, fluocinolone acetonide+, fluocortin butyl+, fluocortolone+, fluocortolone caprylate+, fluocortolone pivalate+, fluorometholone+, fluprednidene acetate+, halcinonide+, halomethasone+, hydrocortisone acetate+, hydrocortisone 21-butyrate+, hydrocortisone hemisuccinate+, isofluprednone acetate+, medrysone+, meprednisone+, methylprednisolone acetate+, methylprednisolone hemisuccinate+, momethasone furoate+, hydrocortisone+, prednisolone metasulpho-benzoate+, prednisone+, procinonide+, triamcinolone+++, triamcinolone diacetate+, triamcinolone hexacetoneide+, dichlorisone acetate+, flucinonide+, triamcinolone benetonide++++, fluticasone propionate++, hydrocortisone aceponate++, mazipredonum+, alclomethasone dipropionate++, triamcinolone acetate+, prednicarbate++, methylprednisolone aceponate++, prednisolone pivalate+, hydrocortisone 17-butyrate+, prednisolone caproate+, progesterone+, testosterone propionate++, ethanol/DMSO+, glutaraldehyde+, glyoxal+	Potassium dichromate, cobalt chloride, myroxolon pereira, fragrance mix I, euxylK400, thiomersal, sulfonilamide, ciprofloxacine, phenylephrine	Dexamethasone, dexamethasone Na-metasulpho-benzoate, triamcinolone acetoneide
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13	F	45	Office work	Eyelids	12/1996	Tixocortol pivalate+, cloprednol++, hydrocortisone+	Potassium dichromate, cobalt chloride, nickel, cocamidopropylbetaine	Hydrocortisone
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(continued)

TABLE 3. (CONTINUED)

Sex	Age	Occupation	Lesion location	Date cons.	Positive tests to corticosteroid	Other positive tests	Ophthalmic corticosteroids exposure	
14	F	83	Unknown	Mucosa	10/1995	Tixocortol pivalate+, budesonide++, cloprednol++, hydrocortisone 21-butyrate++, methylprednisolone acetate+, hydrocortisone+, hydrocortisone aceponate++, mazipredonum+, prednicarbate++, methylprednisolone aceponate++, hydrocortisone 17-butyrate++, prednisolone caproate+	Neomycin, wool alcohols, amerchoLL101, benzocaine, rifamycin	Hydrocortisone
15	F	33	Office work	Periocular	07/1995	Tixocortol pivalate+, cloprednol+, hydrocortisone 21-butyrate+, isofluprednone acetate+, methylprednisolone acetate+, prednisolone+, hydrocortisone+, prednisolone succinate+, prednisone+, methylprednisolone aceponate++, hydrocortisone 17-butyrate+, prednisolone caproate+		Hydrocortisone
16	F	61	Housekeeping	Periocular - face	08/1992	Tixocortol pivalate+++, budesonide++, aminonide+, betamethasone+, betamethasone Na-Phosphate+, cloprednol++, cortisone acetate+, desonide++, dexamethasone+, dexamethasone acetate+, fludrocortisone acetate+, methylprednisolone acetate+, prednisolone+, hydrocortisone+, triamcinolone+++, triamcinolone diacetate+++, triamcinolone hexacetamide+, dichlorisone acetate+, prednisolone caproate+	Neomycin, colophonium, paraphenylenediamine, myroxolon pereirae, fragrance mix I, ethylenediamine, primine, propylene glycol, diaminodiphenylmethane	Hydrocortisone, dexamethasone Na-Phosphate and dexamethasone
17	F	45	Housekeeping	Periocular - neck	03/1993	Tixocortol pivalate+, cloprednol++, methylprednisolone acetate+, hydrocortisone+, prednisone+, alclomethasone dipropionate+, prednisolone caproate+	Neomycin, paraphenylenediamine, diaminodiphenylmethane	Hydrocortisone
18	F	55	Office work	Periocular	01/1990	Tixocortol pivalate+, hydrocortisone acetate+, hydrocortisone+		Hydrocortisone



FIG. 1. Allergic contact dermatitis from corticosteroids, in this case following the ocular use of dexamethasone (ointment) and dexamethasone Na-phosphate (collyrium), respectively: periocular edema and eczema, conjunctivitis, and worsening of the ocular pathology for which the corticosteroid was prescribed.

- Four additional patients (nos. 9, 10, 12, and 16; Table 3) reacted to CSs from different groups. One of them (no. 9) had exclusively used collyria containing group A molecules, that is, prednisolone pivalate and fluorometholone, whereas the other 3 had used ophthalmic ointments containing dexamethasone (nos. 10, 12, and 16), dexamethasone Na-phosphate (no. 16), dexamethasone Na-metasulpho-benzoate, or triamcinolone acetate (no. 12).

Some patients (nos. 2, 3, 4, 5, 6, 9, 10, 12, 16, and 17; Table 3) also tested positively to other allergens present in ophthalmic products, such as benzalkonium chloride and thiomersal (preservative agent), polymyxine B, tetracycline, neomycine, chloramphenicol, and rifamycine (local antibiotics), and wool alcohols (an excipient often used in ophthalmic ointments).

Discussion and Conclusion

Not many cases of allergic reactions due to ophthalmologic use of CSs have been reported in the literature. In this study, out of 315 patients with a CS allergy, 6% presented with ACD and/or conjunctivitis following ocular administration.

Recognizing CS allergy can be difficult as the clinical signs are neither specific nor spectacular, or display a completely atypical chronology, which is due to the anti-inflammatory

properties of the CS. As mentioned by Le Coz,³¹ the clinical manifestation of such reaction depends on 2 competing effects that are of variable intensity and offset in time, namely, the immunological allergic response and the pharmacological antiallergic effect.

Facial and periocular edema and/or eczema, conjunctivitis, a dry sensation, burning, itching (pruritus), or tearing are symptoms that may indicate sensitization. Worsening, rapid increase, and/or absence of response of the ocular pathology for which the CSs was prescribed should alert the clinician to suspect a contact allergy.

All patients presented with multiple positive reactions to CS, which may be due to concomitant but certainly also to cross-sensitivity.^{25–29,32} The potential of CSs to cross-react within and between groups could be related to structural homology and biometabolization of the CS. Foti et al.³³ suggested that the cross reactivity of CS may occur at T-lymphocyte level during antigen presentation. Molecules from group A were mainly implicated, in particular hydrocortisone, the most prescribed ophthalmic CS. Group A CSs classically cross-react with molecules from group D2, which are rapidly metabolized in the skin to group A molecules.^{18,26–29,34} One example of intracutaneous biometabolization is the conversion of hydrocortisone 17-butyrate (group D2) to hydrocortisone 21-butyrate, followed by an enzymatic transformation into hydrocortisone (group A). This illustrates the typical cross-reaction pattern observed between group A and group D2.

Further, besides CSs, multiple positive tests were also observed for other potential allergens present in ocular preparations, that is, topical antibiotics, antiseptics, and even vehicle components.

Conventional patch testing of ocular products as such (as is), in particular beta-blocking agents, is often unsuccessful in diagnosing ACD and the baseline standard series does not seem very useful either.^{35,36} The anatomological and physiological properties of eyelid skin, sometimes previously damaged by dermatitis, may be the cause of a lower threshold to contact allergy in comparison with the thick healthy skin of the back.³⁶ Repeated open application tests on the forearm (1 application 2 or 3 times a day during several days) is sometimes necessary to confirm sensitization.

Extensive patch testing (and sometimes additional tests) with all ingredients (including CSs) of the preparations used, are thus required to detect all relevant allergens, to advise patients about which products should be avoided,³⁷ as well as with regard to the use of future safe alternatives.

Acknowledgments

The authors thank the Foundation Saint-Luc from the Université Catholique de Louvain for supporting this research work.

Author Disclosure Statement

The authors disclose no conflict of interest in connection with the submitted article. The authors indicate no financial conflict of interest. The study and data accumulation were conducted with the approval of the Institutional Ethics Committee, Commission d'Éthique Biomédicale Hospitalo-Facultaire de l'Université Catholique de Louvain (NCT 340320084407).



FIG. 2. Patch test results. Positive patch tests of dexamethasone containing ointment and Na-Phosphate containing collyrium, respectively (Deicol®; Meda Pharma, Brussels, Belgium).

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Received: June 29, 2010

Accepted: November 2, 2010

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