Actas Dermosifiliogr. 2009;100:291-7

ORIGINAL ARTICLES

Allergic Contact Dermatitis Due to Corticosteroids: A 3-Year Retrospective Study in a Hospital Skin Allergy Unit

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Abstract. *Background.* Corticosteroid contact dermatitis and its patch testing are subject to certain peculiarities that we should be aware of.
Materials and methods. We performed a retrospective study of all patients who underwent patch tests with a corticosteroid battery in the Skin Allergy Unit of the Dermatology Department of Hospital General Universitario, Alicante, Spain, between October 2004 and June 2007.
Results. During the study period, patch tests were performed on 1065 patients in our allergy unit. A corticosteroid battery was used in 34 patients (3.1%). Fourteen patients were positive for budesonide or tixocortol in the standard battery; 20 were negative for these allergens but there was a clinical suspicion of steroid allergy. At least one positive reaction in the corticosteroid battery was observed in 15 patients (44.1%).The substance most commonly implicated was budesonide (13 patients sensitized). The corticosteroid battery revealed sensitization to other groups of corticosteroids in 4 of the 15 patients with corticosteroid sensitization. Seventeen patients brought drugs that were also tested, obtaining positive results for 10 substances.
Conclusions. Allergens for contact dermatitis due to corticosteroids included in the standard battery (budesonide and tixocortol) detected 93% of patients who are sensitized to steroids; there would appear to be little benefit in performing a corticosteroid battery if those markers are negative. The battery of corticosteroids and the drugs provided by patients were useful to define more exactly the corticosteroid classes that the patient should avoid.

Key words: allergic contact dermatitis, corticosteroids, patch test, standard battery.

DERMATITIS DE CONTACTO POR CORTICOIDES. ESTUDIO RETROSPECTIVO DE 3 AÑOS EN UNA UNIDAD DE ALERGIA CUTÁNEA HOSPITALARIA

Resumen. *Introducción.* La dermatitis de contacto por corticoides y la realización de las pruebas epicutáneas con estas sustancias presentan peculiaridades que hay que conocer.
Material y métodos. Realizamos un estudio retrospectivo de todos los pacientes en los que se aplicó la batería de corticoides en la Unidad de Alergia Cutánea de la Sección de Dermatología del Hospital General Universitario de Alicante, durante el período comprendido entre octubre de 2004 y junio de 2007.
Resultados. Durante el período de estudio se atendieron 1.065 pacientes, a 34 de ellos (3,1 %) se les aplicó la batería de corticoides, 14 pacientes con budesonida o tixocortol positivos en la batería estándar y 20 con estos marcadores negativos pero con sospecha clínica de alergia a corticoides. Quince pacientes (44,1 %) obtuvieron algún positivo en la batería de corticoides. La sustancia que más positivos obtuvo fue budesonida (13 pacientes sensibilizados). En 4 de 15 pacientes el uso de la batería de corticoides informó de sensibilización a otros grupos de corticoides. A 17 pacientes se les aplicaron los medicamentos aportados por ellos, obteniéndose 10 sustancias positivas.
Conclusiones. Los marcadores para la dermatitis de contacto por corticoides presentes en la batería estándar (budesonida y tixocortol) detectaron el 93 % de pacientes sensibilizados a corticoides, por lo que no parece rentable aplicar la batería de corticoides si dichos marcadores son negativos. La batería de corticoides y los propios fármacos aportados por los pacientes fueron útiles para definir mejor los grupos de corticoides que estos no pueden utilizar.

Palabras clave: dermatitis de contacto alérgica, corticoides, pruebas epicutáneas, batería estándar GEIDAC.

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Manuscript accepted for publication July 24, 2008

Introduction

There has been increasing awareness in recent years of the sensitizing capacity of corticosteroids, which are among the most widely used drugs in dermatology. In 2000, for example, the European Environmental and Contact Dermatitis Research Group (EECDRG) recommended the inclusion of tixocortol pivalate 0.1% and budesonide 0.01% in the European standard series of patch test allergens.[1] Three years later, the American Contact Dermatitis Group also added these 2 substances to their standard series, in addition to triamcinolone acetonide and clobetasol-17-propionate. Furthermore, in 2005, it named corticosteroids contact allergen of the year.[2]

Because corticosteroids have antiinflammatory properties, both corticosteroid-induced contact dermatitis and the reading of corticosteroid patch tests have certain peculiarities.

We performed a retrospective study of all patients who underwent corticosteroid patch testing at our skin allergy unit over a period of 3 years. We then analyzed patients with a positive test and examined our findings in terms of the corticosteroids implicated and the classes to which they belonged.

Materials and Methods

We performed a retrospective study at the skin allergy unit of the dermatology department at Hospital General Universitario de Alicante, Alicante, Spain, between October 2004 and June 2007. We reviewed the data for all patients tested with the Chemotechnique corticosteroid series during this period and analyzed patients with a positive result to at least 1 corticosteroid.

Data were obtained from the allergy unit's computerized database, which contains information on patients, allergen series used, and patch test results and their relevance. In an initial step, we identified all patients who underwent skin patch testing using the corticosteroid series; this group included all those patients with a positive reaction to either of the 2 corticosteroids—budesonide 0.01% and tixocortol pivalate 0.1%—present in the standard series of the Spanish Contact Dermatitis Research Group (abbreviated in Spanish to GEIDAC) as well as those patients with a high suspicion of sensitization despite a negative result in the standard series. The corticosteroid series used contained 7 substances: budesonide (0.01% in petrolatum), triamcinolone acetonide (1% in petrolatum), tixocortol (0.1% in petrolatum), dexamethasone (1% in petrolatum), clobetasol-17-propionate (1% in petrolatum), hydrocortisone-17-butyrate (1% in alcohol), and betamethasone valerate (1% in petrolatum). The allergens used in both the standard and the corticosteroid series were supplied by Chemotechnique Diagnostics AB, Malmo, Sweden. We also collected data for patients tested with corticosteroid drugs they had brought along. Finally, we analyzed positive reactions to any of the corticosteroids tested and examined our results by corticosteroid and by corticosteroid class.

The following clinical data were recorded for each patient: medical record number, age, sex, profession, location of lesion(s), allergen series use, number, type and relevance of positive reactions, sensitization source, and diagnosis. All the patients were tested with the GEIDAC standard series and the corticosteroid series, and with other allergens as appropriate. If the patient remembered which corticosteroid products they had used, these were also tested. The patches were applied to the skin using adhesive Finn-Chamber strips and Scampor tape and left on for 48 hours. Test results were read at 48 and 96 hours and positive reactions were graded as +, ++, or +++. In patients with equivocal reactions, the patches were left on and read on day 7. Results were considered to be relevant if the patient's condition could be attributed to or could have been exacerbated by the use of systemic or topical corticosteroids. Because cross-reactions occur between corticosteroids, we considered a reaction to be relevant if it was caused by a substance that belonged to the same group of substances as the corticosteroid used by the patient. Relevance was considered unknown when no proven relationship between the reaction and exposure to the allergen could be established.

Results

In total, 1065 patients underwent patch testing in our allergy unit between October 2004 and June 2007; they were all tested with the GEIDAC standard series and other series as appropriate. Thirty-four patients (14 women, 20 men; mean age, 45 years) were tested with the corticosteroid series (Table 1); 14 of these patients had had a positive reaction to a corticosteroid marker in the standard series. Three or more allergen series were tested in 19 (55.8%) of the patients during the period analyzed and 17 patients were tested with products they had brought in. Patch test results were read after 7 days in 15 (44%) of the 34 patients. These were patients with equivocal results or patients who had tested negative after 4 days but in whom there was a strong suspicion of sensitization to corticosteroids. The majority of patients (10 of 34) had lesions involving multiple sites (≥3 body regions). The most common single location of lesions was the hands (5/34). We detected a history of atopic dermatitis in 18% of these patients and of chronic ulcers or stasis dermatitis in 12%.

Fifteen patients (9 women and 6 men) were found to be sensitized to corticosteroids; this represents 1.4%

Table 1. Characteristics of Patients Tested With the GEIDAC[a] Corticosteroid Series

Sex/Age, y	*Lesion Site(s)*	*No. of Positive Reactions*	*Corticosteroid Positivity*	*History of Atopy*	*History of Ulcers*	*Reading at Day 7*
M/42	Hands	1	Yes	No	No	Yes
F/70	Legs	9	Yes	No	Yes	Yes
F/77	Multiple	16	No	No	Yes	Yes
F/22	Multiple	6	Yes	Yes	No	No
F/33	Hands	2	No		No	No
M/21	Legs	0	No	No	Yes	No
F/55	Hands	1	No	No	No	No
F/41	Hands	2	No	No	No	No
F/13	Multiple	2	No	Yes	No	Yes
F/53	Multiple	2	No	No	No	No
M/66	Palmar-plantar	2	No	No	No	No
F/68	Multiple	5	Yes	No	No	Yes
F/24	Trunk	0	No	Yes	No	Yes
F/36	Multiple	10	Yes	No	No	No
M/37	Trunk	3	No	Yes	No	No
F/6	Multiple	0	No	Yes	No	No
M/81	Arms	0	No	No	No	Yes
F/58	Legs	12	Yes	No	No	Yes
F/39	Around eyes	4	Yes	No	No	Yes
M/51	Genitals	6	Yes	No	No	Yes
M/35	Palms	0	No			No
F/50	Lips	1	No	No	No	No
M/78	Trunk	0	No	No	No	No
M/68	Multiple	5	No	No	No	Yes
F/26	Multiple	5	Yes	No	No	No
M/57	Multiple	8	Yes	No	No	No
F/72	Lips	1	No	No	No	No
M/31	Arms and legs	7	Yes	No	No	Yes
M/36	Face	0	No	No	No	No
M/37	Hands and feet	4	Yes	Yes	No	No
F/26	Face	5	Yes	No	No	No
F/56	Face	2	No	No	No	Yes
M/41	Legs	8	Yes	No	Yes	Yes
F/63	Trunk and legs	19	Yes	No	No	Yes

Abbreviations: M, male; F, female.
[a]Spanish Contact Dermatitis Research Group.

Table 2. Characteristics of Patients Sensitized to Corticosteroids (CS)

Sex/Age, y	*Lesion Site(s)*	*Own Medicinal Products Tested*	*No. of Positive Reactions*	*Corticosteroid(s) involved*	*History of Atopy*	*History of Ulcers*	*Reading at Day 7*
M/42	Hands	Yes	1	Budesonide	No	No	Yes
F/63	Legs	Yes	9	Tixocortol-21-pivalate, Budesonide	No	Yes	Yes
F/22	Multiple	Yes	6	Budesonide, Hydrocortisone aceponate, Prednicarbate	Yes	No	No
F/68	Multiple	No	5	Budesonide	No	No	Yes
F/36	Multiple	No	10	Budesonide	No	No	No
F/58	Legs	Yes	12	Budesonide, Betamethasone-17-valerate, Triamcinolone acetonide, Clobetasol-17-propionate, Dexamethasone, Hydrocortisone-17-butyrate, Mometasone, Diflucortolone valerate, Methylprednisolone aceponate, Betamethasone dipropionate, Betamethasone	No	No	Yes
F/39	Around eyes	No	4	Budesonide	No	No	Yes
M/51	Genitals	Yes	6	Budesonide	No	No	Yes
F/26	Multiple	Yes	5	Budesonide, Triamcinolone acetonide	No	No	No
M/57	Multiple	Yes	8	Budesonide Mometasone, Clobetasol-17-propionate	No	No	No
M/31	Arms and legs	No	7	Clobetasol-17-propionate	No	No	Yes
M/37	Hands and feet	No	4	Budesonide,	Yes	No	No
F/26	Face	Yes	5	Budesonide Triamcinolone acetonide	No	No	No
M	Legs	No	8	Tixocortol-21-pivalate	No	Yes	Yes
F/63	Trunk and legs	Yes	19	Budesonide Tixocortol-21-pivalate Prednicarbate Hydrocortisone	No	No	Yes

Abbreviations: M, male; F, female.

of all the patients tested and 44.1% of those tested with the corticosteroid series (Table 2). Tixocortol pivalate and budesonide (corticosteroid allergy markers from the GEIDAC series) were positive in 14 cases. Only 1 of the 20 patients with a negative result on the standard series was found to be sensitized to a corticosteroid (clobetasol-17-propionate) that could only have been detected by using the corticosteroid series. Identical percentages of patients (13%) had a history of atopy and of chronic ulcers. Multiple site involvement was the most common type of allergic reaction (5 patients), followed by leg involvement (4 patients). The mean number of allergens producing a positive reaction over the study period was 7.2 per patient. Balsam of Peru was the most common noncorticosteroid allergen, producing a positive result in 40% of patients. Seven patients (46.6%) tested positive to more than 1 allergen in the corticosteroid series. Four of the 15 patients were sensitized to a corticosteroid from a class other than class A or B, represented by tixocortol pivalate and budesonide, respectively, in the GEIDAC standard series.

Sensitization was due to topical application in all but 1 patient, who had received an intramuscular injection. Three of the patients used topical corticosteroids frequently

to treat hemorrhoids, chronic discoid lupus, and long-standing eczema.

Of all the substances in the corticosteroid series, budesonide produced positive reactions in the greatest number of patients (n = 13, 86%) (Table 3). Tixocortol pivalate, triamcinolone acetonide, and clobetasol-17-propionate each produced a positive reaction in 3 patients, while the rest of the substances in the series (dexamethasone, hydrocortisone-17-butyrate, and betamethasone valerate) were responsible for 1 reaction each. All of the reactions but 1 were considered to be of present relevance. In 1 case, the patient's symptoms could not be linked to exposure to budesonide or any other class-B corticosteroid.

Four of the 17 patients that were patch tested with medicinal products they had brought in had positive reactions. Prednicarbate and mometasone produced positive reactions in 2 of these patients while the other substances (hydrocortisone aceponate, diflucortolone valerate, methylprednisolone aceponate, betamethasone dipropionate, and betamethasone) produced just 1 positive reaction each. Although the patch tests were performed using the whole product rather than individual ingredients, we are reasonably confident that 3 of the 4 patients were truly sensitized to corticosteroids as they tested negative to the excipients used. The fourth patient, who tested positive to Brentan cream and Batmen cream also tested positive to excipients present in Batmen (benzyl alcohol and sorbitan monostearate) and to clotrimazole, present in Brentan. Sensitization to these substances might explain the positive reaction to the medicinal products tested in this patient, although he also tested positive to tixocortol pivalate, the marker for hydrocortisone (which is present in Brentan cream).

On analyzing the positive results by corticosteroid class, we found that class B was responsible for the greatest number of positive patch test results (n = 16) and was the cause of sensitization in the greatest number of patients (n = 13). Tixocortol pivalate was the only corticosteroid in class A that produced a positive reaction (n = 3). The situation was similar in class C, with just 1 positive patch result, caused by dexamethasone. In class D1, there were 9 positive reactions in 3 patients; 6 of the reactions were caused by patch tests performed with medicinal products brought in by the patients. Finally, 5 positive reactions in 3 patients were found for class-D2 corticosteroids. Just 1 of these reactions was detected using the corticosteroid series; the other 4 were detected by performing patch tests with the topical products brought in by the patients.

Table 3. Positive Results for Corticosteroid Series

Corticosteroid Series	*Absolute Frequency, No.*	*Relative Frequency, %*	*Corticosteroid Class*
Tixocortol pivalate	3	20	A
Budesonide	13	86	B
Triamcinolone acetonide	3	20	B
Dexamethasone	1		C
Clobetasol-17-propionate	3	20	D1
Hydrocortisone-17-butyrate	1		D2
Betamethasone valerate	1		D1

Discussion

The incidence of sensitization to corticosteroids varies according to many factors such as the type and amount of corticosteroids used in a given country, prescription habits, physician awareness of the importance of corticosteroid allergy, allergy tests used, and corticosteroid use.[3] On the basis of reactions to budesonide, tixocortol, and hydrocortisone butyrate, the prevalence of corticosteroid sensitization in the United States of America (USA) is 4.6%.[2] In Europe, the mean prevalence is 2.6%, based on test results for 5 corticosteroids, although rates vary greatly from country to country.[4] In the most recent epidemiologic study of contact allergic dermatitis conducted in Spain (in 2001), a prevalence rate of 1.01% was found for reactions to budesonide and tixocortol (at concentrations of 0.83% and 0.18%, respectively) but very few studies of corticosteroid allergy prevalence have been conducted in Spain.[6,7] We detected a prevalence rate of 1.4% in our series, which is consistent with data published for Spain.

In 2000, the EECDRG recommended adding 2 corticosteroid sensitization markers—budesonide 0.01% in petrolatum and tixocortol pivalate 0.1% in petrolatum—to the European standard series for patch testing.[2] These substances are also in the standard series recommended by the American Contact Dermatitis Group, although at higher concentrations (0.1% in the case of budesonide and 1% in that of tixocortol). The American series also includes hydrocortisone-17-butyrate, triamcinolone acetonide, and clobetasol-17-propionate. It should also be borne in mind that not all manufacturers that produce test allergens for use in Spain use the same corticosteroids or the same concentrations.

There are striking differences between the USA and Europe in terms of the prevalence of sensitization to particular corticosteroids. The most common sensitizer in

the USA is tixocortol pivalate, followed by budesonide.[8] In Europe, these 2 substances seem to be responsible for similar sensitization rates.[5] In our series, the most common sensitizer was budesonide (1.2%) followed by tixocortol pivalate and others (0.2%). These findings are similar to those previously reported for Spain.[6]

When analyzing positive reactions and relevance with corticosteroids, it should not be forgotten that cross-reactions between different types of corticosteroids are very common. In 1989, Dooms-Goznes et al[4] divided corticosteroids into 4 empirical classes, named A, B, C, and D. Further investigation led to class D, containing ester-type molecules, being divided into 2 subclasses, D1 and D2 (Table 3). The sensitization markers for class A and B corticosteroids are tixocortol pivalate and budesonide, respectively. For a molecule to be considered a marker for a particular class, it must be capable of producing a sufficient number of positive patch test results and also strongly correlate with sensitization to the other corticosteroids in the class. There are no markers for either class C, which appears to be the least allergenic group, or class D1. Several authors have proposed hydrocortisone-17-butyrate as a marker for class D2, which is more allergenic than D1 as its molecules are not halogenated. Budesonide (class B) cross-reacts with substances in class D2, while concomitant reactivity has been observed for class A and class D2.[9] Because of the frequency of budesonide reactions, class B was the most allergenic group in our series. The second most allergenic group was class D1, although this was because 1 patient had 5 concomitant positive results, probably due to cross-reactions.

In our series, patients with suspected corticosteroid contact dermatitis were tested with many allergen series (≥3 in 55.8%). Patients sensitized to corticosteroids had a high total number of positive patch tests (mean for study period, 7.2) and almost half of the group had 2 or more positive reactions to the allergens in the corticosteroid series. Balsam of Peru was the most common noncorticosteroid allergen. On analyzing the group tested specifically for corticosteroid sensitization, we found no differences between patients with positive reactions and those with negative reactions for history of atopy or chronic ulcers (which does not concur with findings from other studies[10]) or for lesion site, which was multiple in both groups. A European-based study found that the most common location for lesions was the hands, followed by the legs, the face, and the arms.[5]

Medicinal products brought in by the patients were tested in many cases (17 of 34 patients). In view of our encouraging results, we believe that such medicines should always be tested. In our case, 10 substances produced positive reactions in 4 patients. Testing these products is also helpful because many of them are not found in standard corticosteroid series, as occurred with prednicarbate, which produced 2 positive patch tests in our series. Furthermore, in 2 cases, we discovered sensitization to corticosteroids from different classes to those tested in the allergen series used. When testing medicinal products brought in by patients, however, it is important to always check that a positive result is not due to any of the excipients.

The sensitization markers budesonide and tixocortol pivalate from the standard series proved to be very useful as only 1 of the 15 patients with corticosteroid sensitization would not have been diagnosed had only these allergens been used. Furthermore, we do not believe that hydrocortisone-17-butyrate needs to be included in the standard series as in no case was it the only corticosteroid to produce a positive reaction, either over all or within class D2.

It should be remembered that corticosteroid contact dermatitis tends to be characterized by mild, persistent symptoms in the form of chronic eczema. Corticosteroid contact dermatitis is indeed believed to be underdiagnosed because its symptoms are often attributed to a condition with an endogenous origin. Many of the patients in our series had symptoms of chronic eczema that did not respond well to treatment with topical corticosteroids.

There have been reports of systemic allergic dermatitis reactions following the administration of nontopical corticosteroids,[11,12] including those administered by inhalation[10,13] and intraarticular injection. In our series, only 1 patient had symptoms caused by a nontopical corticosteroid (in this case, intramuscular). All of the patients had eczema symptoms, although other symptoms, though much rarer, may also occur. Examples are urticaria, angioedema,[14,15] erythema multiforme-like reactions,[16] and edema.[17]

Patients diagnosed with corticosteroid allergy should be advised to avoid corticosteroids from either the same class as the marker that produced a positive reaction or from classes in which cross-reactions can occur, unless, of course, they have tested negative to these substances. This is true for both topical and systemic preparations. It is a good idea to provide a list of compounds to avoid for both patients and their general practitioners

Conclusions

Use of the allergy markers budesonide and tixocortol pivalate from the GEIDAC standard series permitted the detection of contact dermatitis in 93% of the patients with corticosteroid sensitization in our series. The use of a corticosteroid series in patients who test negative to these markers would therefore seem to be of little benefit. The use of the corticosteroid series enabled the detection of sensitization to corticosteroids from other classes in 4 of 15 patients, and testing medicinal products brought in by

patients produced a positive reaction in 4 patients; in 2 of these, sensitization to a new class of corticosteroids was detected.

Because corticosteroids are one of the main therapeutic tools available to dermatologists, sensitization to these antiinflammatory drugs can cause major diagnostic and therapeutic problems. Recognizing the symptoms of corticosteroid contact dermatitis is essential for performing appropriate patch tests. Finally, the detection of corticosteroid sensitization can help to prevent systemic and potentially serious reactions and to determine the origin of chronic eczema that does not respond to corticosteroid treatment.

Conflicts of Interest
The authors declare no conflicts of interest.

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