Are the Spanish baseline series markers sufficient to detect contact allergy to corticosteroids in Spain? A GEIDAC prospective study

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Summary

Background. Corticosteroids are among the most commonly used topical drugs. Contact allergy to these exists, but can be easily missed. Corticosteroid screening markers have been included in the baseline series with the aim of detecting most of the sensitized patients.

Objectives. To assess the prevalence of contact allergy to topical corticosteroids in Spain and examine the usefulness of corticosteroid markers to detect contact allergy to corticosteroids.

Methods. In total, 3699 patients referred to 20 dermatology departments across Spain for patch testing with the baseline series, including budesonide and tixocortol pivalate, were also tested with six supplementary corticosteroids (methylprednisolone aceponate, mometasone furoate, prednicarbate, clobetasol propionate, betamethasone 17-valerate, and betamethasone 17,21-dipropionate). Additionally, 2547 (68.8%) patients were tested with hydrocortisone 17-butyrate.

Results. Fifty-four patients showed positive reactions to at least one of all tested corticosteroids (1.46%). Thirty-nine (1.05%) reacted to at least one of the additionally tested corticosteroids; among these, 24 of 39 (61.5%) did not react to any of the corticosteroid allergy screening markers tested.

Conclusions. More than half of the patients who were allergic to the additionally tested corticosteroids were not detected with the corticosteroid allergy markers. An update of the corticosteroid allergy screening markers is encouraged, with consideration of group 3 corticosteroids.

Key words: budesonide; contact allergy; hydrocortisone 17-butyrate; tixocortol pivalate; topical corticosteroids.

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Since their first use for the treatment of dermatological diseases (1), topical corticosteroids have become widely prescribed. Allergic contact dermatitis is a well-known side-effect of corticosteroids that can be easily missed, in particular by physicians other than dermatologists. Contact allergy to corticosteroids should be suspected whenever their application makes certain conditions deteriorate that usually improve after treatment with them; however, clinical findings might be subtle and easily overlooked. Although hypersensitivity to corticosteroids was previously thought to be infrequent (2), during the 1990s several studies showed high prevalences of sensitization to topical corticosteroids (3–5), in some centres even > 5% (6, 7). To better diagnose such patients, two markers of corticosteroid sensitization were added to the baseline series in 2000 (8), namely, budesonide and tixocortol pivalate. Both of these, as well as hydrocortisone 17-butyrate, were included in the third panel of TRUE Test® (9).

The rationale for using these markers is based on the potential of corticosteroids to be involved in cross-reactions. Several classifications (10–12) have been proposed, based on the clinical patterns of cross-reactions and chemical structures. Accordingly, cross-reactions are supposed to involve predominantly corticosteroids belonging to the same group. The last of these classifications was established by Baeck et al. (12), and divides corticosteroids into three groups: group 1, the non-methylated, most often non-halogenated molecules, accounting for most of the allergic contact reactions to corticosteroids; group 2, the halogenated molecules with a C16/C17 *cis*-ketal/diol structure; and group 3, the halogenated and C16-methylated molecules, which are not commonly reported to cause allergy. This classification also allows the identification of two patient profiles for patient management: profile 1 – patients with hypersensitivity only to one group of corticosteroids; and profile 2 – patients who react to different groups of corticosteroids.

Currently, all corticosteroid allergy markers included in the Spanish baseline series or TRUE Test® belong to group 1, and might not detect contact allergy to corticosteroids from the other two groups. Notwithstanding this, several studies supporting the use of the above markers showed 80% sensitivity in detecting allergy to other corticosteroids (7, 13, 14). However, most of these studies are retrospective and limited to single centres. A selection bias may therefore exist. The aims of our study were: (i) to examine the prevalence of contact allergy to corticosteroids in Spain and the usefulness of corticosteroid allergy markers to detect contact allergy to some of the most commonly used corticosteroids in Spain; and (ii) to assess differences in the patient characteristics summarized in the MOAHLFA index between the group of corticosteroid-allergic patients and the group of non-allergic individuals.

Materials and Methods

In September 2014, all GEIDAC members were asked to answer an online survey and provide their opinion regarding the four corticosteroids most frequently used in their hospitals. Twenty-one of 27 GEIDAC members, all working as specialist dermatologists in different dermatological clinics across Spain, answered the survey and were invited to participate in our study. Twenty of them were able to submit data. The six most frequently mentioned corticosteroids were added to the baseline series to be patch tested in these clinics. The haptens were supplied by Marti Tor® (Barcelona, Spain), which is the AllergEaze® (Calgary, Canada) distributor in Spain. Dilutions as suggested by Baeck et al. in ethanol (eth.) were used (13). Two of the selected corticosteroids belonged to group 1 (methylprednisolone aceponate 0.1% eth. and prednicarbate 1% eth.) and four to group 3 (mometasone furoate 0.1% eth., clobetasol 17-propionate 0.1% eth., betamethasone 17,21-dipropionate 0.1% eth., and betamethasone 17-valerate 0.1% eth.) (Fig. 1). Two betamethasone derivatives (valerate and dipropionate) are available in commercial formulations in Spain, and both were included, as the survey had not taken this into consideration.

From February 2015 to January 2016, all patients who were referred to the 20 participating dermatological clinics to be patch tested for clinically suspected allergic contact dermatitis were eligible to be tested with an extended baseline series including the six above-mentioned additional corticosteroids. Written informed consent was obtained from those agreeing to participate. Exclusion criteria were: age < 18 years, inability to sign a written consent form, and refusal to be tested with the additional corticosteroid allergens. Corticosteroid allergy markers were tested as part of the baseline series: 12 centres used TRUE Test® allergens, namely, tixocortol 21-pivalate 3 μg/cm^2, budesonide 1 μg/cm^2, and hydrocortisone 17-butyrate 20 μg/cm^2 (MEKOS Laboratories, Hillerød, Denmark); five used budesonide 0.01% pet. and tixocortol pivalate 0.1% pet. supplied by AllergEaze®; and three used budesonide 0.01% pet. and tixocortol pivalate 0.1% pet. supplied by Chemotechnique® (Vellinge, Sweden). In three centres (Hospital Morales Meseguer, Hospital Virgen de la Arrixaca, and Hospital General de Alicante), hydrocortisone 17-butyrate 1% eth. supplied by Chemotechnique was

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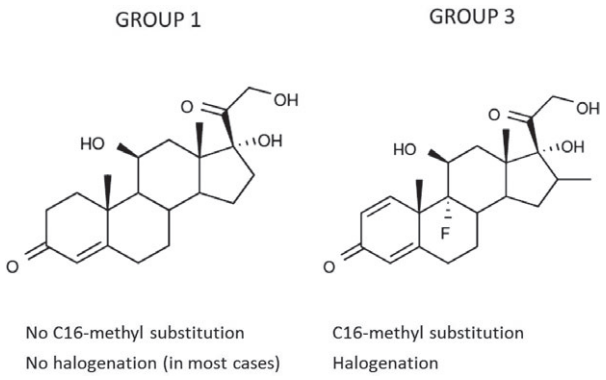

Fig. 1. Chemical structure of corticosteroids belonging to groups 1 and 3.

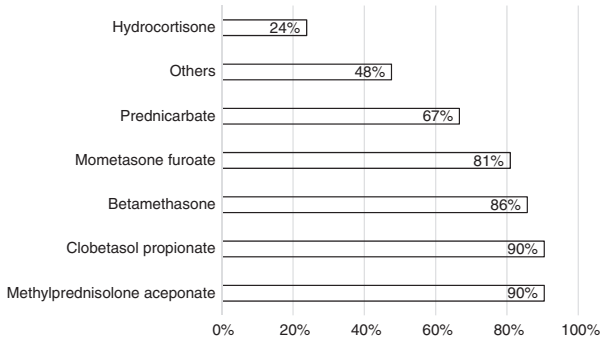

Fig. 2. Results of a survey among 21 GEIDAC members performed across Spain concerning the four most commonly prescribed topical corticosteroids in each institution.

also tested. Finn Chambers® (diameter, 8 mm) (Epitest, Tuusula, Finland) secured with Scanpor® tape (Norgesplaster, Vennesla, Norway) were used, except when using the TRUE Test®. Allergens were applied on the back for 48 h, and readings were performed on day (D)2, D4, and D7, and scored according to ESCD patch test guidelines (15). Irritant, doubtful or negative readings were not recorded.

A database including the clinical information (sex, age, distribution of skin lesions, atopic dermatitis, or occupational dermatitis) and patch test results was created. These characteristics constitute the MOAHLFA index; they were compared between those allergic to topical corticosteroids and those not allergic and classified as significant when the p-value was < 0.05. Moreover, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for each of the corticosteroid markers were calculated, accompanied by a 95% confidence interval. In assessment of the value of tixocortol pivalate, budesonide and hydrocortisone 17-butyrate as markers of allergy to the other corticosteroids tested, true positives were considered to be those patients who showed positive reactions when patch tested with at least one of the markers and at least one of the additional tested corticosteroids. False positives were considered to be those patients who showed positive reactions to at least one of the markers and negative to all of the additional corticosteroids. False negatives were considered to be those patients who did not show positive reactions to the markers but showed positive reactions to at least one of the additional tested corticosteroids. True negatives were those who did not show positive reactions to either the markers or the additional allergens. The study protocol was vetted by the Morales Meseguer Hospital Research Ethics Committee (EST-06-15), approved by the Research Ethics Committees of all of the involved centres, and conducted in accordance with the Helsinki Declaration and in compliance with local and European regulations.

Results

The results of the survey among the GEIDAC members are shown in Fig. 2. Altogether, 3699 patients were tested with the Spanish baseline series including the corticosteroid allergy markers, budesonide, and tixocortol pivalate, and the six additional selected corticosteroids. Two thousand one hundred and thirty-eight patients (58%) were tested with TRUE Test®, 1137 (31%) were tested with AllergEaze® allergens, and 424 (11%) were tested with Chemotechnique allergens. Overall, 2547 patients were also tested with hydrocortisone 17-butyrate: 2138 (84%) with TRUE Test® and 439 (16%) with hydrocortisone 17-butyrate 1% eth. Fifty-four patients showed positive reactions to at least one corticosteroid marker or additional tested corticosteroid (1.46%). In total, 122 positive test reactions to corticosteroids were recorded. The positive results are summarized in Table 1. The mean age of the corticosteroid-allergic patients was 56 years (range: 21–82 years). Thirty patients (55.6%) were male. Occupational cases were not recorded, in corticosteroid(s) allergic patients compared to the remaining patients ($p = 0.018$). The MOAHLFA indices of both all patients patch tested and those sensitized to corticosteroid(s) are summarized in Table 2. Allergy to corticosteroids was found to involve mainly male patients ($p = 0.0003$) and individuals aged > 40 years ($p = 0.005$).

Thirty of 54 patients (55.6%) had positive reactions to corticosteroid markers, mainly to budesonide, which was positive in 23 of 54 tested patients (44.4%). Tixocortol pivalate yielded the lowest number of positive reactions (11/54; 20.4%). Budesonide was positive in all hydrocortisone 17-butyrate-allergic patients and in

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Table 1. Tested patients in each centre, baseline series used, and number of patients sensitized to each allergen

Test centre	No. of patients tested	Baseline series	No. of sensitized patients	Bude	Tixo	HBut	MetP	Pred	Clob	MomF	BetD	BetV
Alcorcon	139	TRUE Test®	1	1(+)	–	1(+)	1(+)	1(+)	–	–	–	–
Alicante	227	Chemotechnique	1	1(+)	1(+)	1(+)	–	1(+)	–	–	–	–
Arganda	43	TRUE Test®	0	–	–	–	–	–	–	–	–	–
Barcelona (Hospital del Mar)	441	AllergEaze®	2	1(+)	–	NT	2(+)	1(+)	–	–	–	–
Barcelona (Hospital Sant Pau)	261	TRUE Test®	4	4(+)	2(+)	2(+)	–	1(+)	–	–	–	–
Badalona	172	AllergEaze®	1	1(+)	1(+)	NT	1(+)	1(+)	1(+)	1(+)	1(+)	1(+)
Cádiz	108	Chemotechnique	1	–	1(+)	NT	–	–	–	–	–	–
Fuenlabrada	241	AllergEaze®	1	1(+)	–	NT	–	–	–	–	–	–
Guadalajara	270	TRUE Test®	8	3(+)	2(+)	1(+)	1(+)	1(+)	–	1(+)	2(+)	2(+)
Las Palmas	130	TRUE Test®	0	–	–	–	–	–	–	–	–	–
León	191	TRUE Test®	4	–	1(+)	–	3(+)	1(+)	2(+)	2(+)	2(+)	1(+)
Madrid (D. Guimaraens)	17	TRUE Test®	0	–	–	–	–	–	–	–	–	–
Madrid (Hospital La Princesa)	146	TRUE Test®	4	1(+)	2(+)	1(+)	1(+)	1(+)	2(+)	1(+)	1(+)	1(+)
Murcia (Hospital Morales Meseguer)	93	AllergEaze®	2	1(+)	–	1(+)	2(+)	1(+)	–	–	–	–
Murcia (Hospital Virgen de la Arrixaca)	89	Chemotechnique	4	3(+)	1(+)	3(+)	3(+)	2(+)	–	–	–	–
Pamplona	190	Allergeaze®	1	1(+)	–	NT	–	–	–	–	–	–
Sevilla	146	TRUE Test®	8	1(+)	–	1(+)	3(+)	1(+)	3(+)	1(+)	4(+)	2(+)
Toledo	235	TRUE Test®	7	4(+)	–	1(+)	1(+)	3(+)	2(+)	1(+)	2(+)	2(+)
Vigo	269	TRUE Test®	0	–	–	–	–	–	–	–	–	–
Vitoria	291	TRUE Test®	5	–	–	–	–	2(+)	3(+)	–	–	–
Total	3699		54	23	11	12	18	17	13	7	12	9

BetD, betamethasone 17,21-dipropionate; BetV, betamethasone 17-valerate; Bude, budesonide; Clob, clobetasol propionate; HBut, hydrocortisone 17-butyrate; MetP, methylprednisolone aceponate; MomF, mometasone furoate; NT, not tested; Pred, prednicarbate; Tixo, tixocortol pivalate; n(+), number of patients positive for each allergen.

Table 2. MOAHLFA index of corticosteroid-sensitized and non-sensitized patients, respectively

	Male	Ocupational	Atopy	Hand	Leg	Face	Age > 40 years
Non-allergic (%)	31.7	11.1	16.0	35.3	11.6	24.6	59.6
Allergic (%)	55.6	0	22.2	31.5	9.3	27.7	79.6
Chi^2 test: *p*-value	0.0003	0.018	0.30	0.66	0.76	0.71	0.005

Differences in proportions were statistically tested with the chi^2 test with Yate's correction.

4 tixocortol pivalate-allergic patients (4/11) (Fig. 3). On the other hand, 39 of 54 (72.2%) patients had positive reactions to at least one of the additional corticosteroids. Among the latter, the most frequently found positive allergens were methylprednisolone aceponate (18/54; 33.3%) and prednicarbate (17/54; 31.5%), both belonging to group 1, and the least frequently positive substance was the group 3 corticosteroid mometasone furoate (7/54; 13.0%). Furthermore, the five tested group 1 corticosteroids (budesonide, hydrocortisone 17-butyrate, tixocortol pivalate, methylprednisolone aceponate, and prednicarbate) were positive in more patients (43/54; 79.6%) than the four tested group 3 corticosteroids (mometasone furoate, clobetasol 17-propionate, betamethasone 17,21-dipropionate, and betamethasone 17-valerate) (21/54; 38.9%). There was a subset of 11 of 54 patients (20.4%) who were allergic to at least one corticosteroid from both groups. Twenty-seven patients (27/54; 50.0%) were sensitized to only one compound: 13 (24%) to only one marker, and 14 (25.9%) to only one of the additionally tested corticosteroids. Twenty-four patients reacting to additional corticosteroids (24/39; 61.5%) showed negative results when patch tested with corticosteroid allergy markers (Fig. 4). This was more frequent for group 3 corticosteroids, namely clobetasol propionate (10/13), betamethasone 17-valerate (6/9), betamethasone 17,21-dipropionate (7/12), and mometasone furoate (4/7), than for group 1 corticosteroids, namely methylprednisolone aceponate (10/18) and prednicarbate (6/17). The predictive properties of each corticosteroid marker as a diagnostic test to detect allergy to any of the other tested corticosteroids in

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Table 3. Predictive capability of each corticosteroid marker as a diagnostic test to detect allergy to any of the other tested corticosteroids

	Budesonide (%)	95%CI	Tixocortol pivalate (%)	95%CI	Hydrocortisone 17-butyrate (%)	95%CI
Sensitivity	44.8	27.0–64.0	15.2	5.7–32.7	30.3	16.2–48.9
Specificity	99.7	99.5–99.9	99.8	99.6–99.9	99.9	99.7–100
PPV	56.5	34.9–76.1	45.5	18.1–75.4	83.3	50.9–97.1
NPV	99.6	99.3–99.7	99.2	98.9–99.5	99.1	98.6–99.4

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

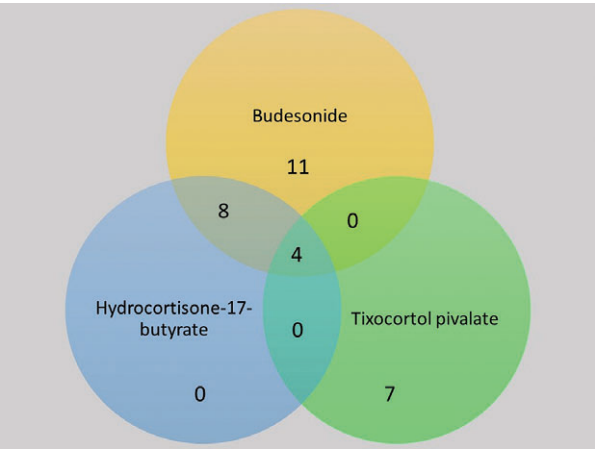

Fig. 3. Concomitant sensitization was frequent among patients allergic to the corticosteroid markers.

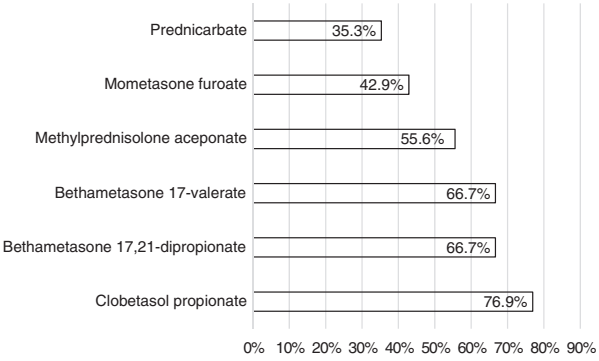

Fig. 4. Percentage of patients with positive reactions to an additional corticosteroid steroid but not to corticosteroid steroid markers.

terms of sensitivity, specificity, PPV and NPV are shown in Table 3. Budesonide showed the highest sensitivity, and tixocortol pivalate the lowest.

Discussion

The prevalence of contact allergy to topical corticosteroids found in the present study (1.46%) is similar to previously reported values in Spain (14, 16). Berbegal et al. (14), in a single-centre retrospective study, found 1.16% of 2587 tested patients with corticosteroid contact allergy in an 11-year period. These proportions are lower than the described prevalences in North America (4.12%) (17), Thailand (3.29%) (18), or Belgium (2.7%) (13). Geographical differences between Spain and other European regions have apparently not changed over time. For instance, in a multicentre European study completed in 1996 (6), the lowest relative frequency of corticosteroid allergy among 14 hospitals across Europe was found in a Spanish centre (0.4% as compared with an overall 2.6% in the rest of Europe). This low prevalence could be explained by the lack of over-the-counter corticosteroids available in Spain, unlike in other countries (17, 18, 19), but could also be attributable to different prescription habits among physicians in Spain, who would probably tend to use less allergenic corticosteroids. As suggested by our internet survey, class 3 corticosteroids, which are known to be less sensitizing, are widely used by Spanish dermatologists. These data were confirmed by one of the authors (Pedro Mercader-García, data from 2014, unpublished), who obtained information from the local health authorities regarding the number of prescription corticosteroids sold in 2013 in Murcia (Spain), a region with a population of 1 309 407 inhabitants in that year. In that area, group 3 corticosteroids were prescribed in 51% of cases, group 1 corticosteroids in 45%, and group 2 corticosteroids in only 4%, which is why none of the group 2 corticosteroids was included in the present study.

Our corticosteroid-allergic population showed a statistically significantly higher proportion of males than the non-allergic population. Berbegal et al. (14) published similar findings, in contrast to Baeck et al. (13) and other previous studies (6), which found threefold more frequent involvement of female patients in their corticosteroid-allergic populations. These wide differences among studies could be related to regional differences in prescription habits. In our study, the prevalence of atopy was low, and no statistically significant differences between the allergic and non-allergic populations were observed. This fact could be related to the exclusion of patients aged < 18 years from our study,

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as atopic dermatitis is more often described in children. Berbegal et al., however, found that only 9% of their corticosteroid-allergic population were atopic (14). These differences might be related to geographical variations in prevalences of atopy in relation to genetic or environmental factors. The exclusion of patients aged < 18 years could explain the high mean age of our population (56 years). The significantly higher proportion of patients aged > 40 years in the corticosteroid-allergic population might indicate that a longer duration of exposure to corticosteroids is needed before sensitization occurs. An occupational origin of corticosteroid allergy has been uncommonly described in previous series, and we did not identify any occupational cases in the study period. Also, the overall proportion of occupational dermatitis in our series was low, probably because occupational diseases are usually treated outside the public health system in Spain. Although leg ulcers and stasis dermatitis are established risk factors for the development of corticosteroid allergy (20), we were unable to find significant differences concerning the legs or any other anatomical site. This fact also highlights the difficulties in the detection of corticosteroid allergy, as there are no typical anatomical sites that could raise suspicion.

Only 55.6% of our corticosteroid-allergic patients were detected by patch testing with the corticosteroid markers included in the European baseline series. This is the lowest proportion reported in the literature. As a limitation of our study, this low prevalence could be attributable to the allergen preparations tested, as 58% of our patients were assessed with TRUE Test®. However, in 2009, Andersen and Paulsen compared budesonide and tixocortol pivalate from TRUE Test® with the pet.-based allergens, and concluded that they are equivalent. Additionally, TRUE Test® offers the advantage of testing exact amounts of the allergens during the patch test procedure (21). The reliability of hydrocortisone 17-butyrate before its commercialization has also been assessed (9). However, all of our cases of allergy to hydrocortisone 17-butyrate were detected by budesonide, which is why we believe that the added value of hydrocortisone 17-butyrate as a marker is uncertain. This is related to the molecular structure of budesonide and one of its isomers, namely the *S*-isomer, which can mimic the hydrophobic pocket of molecules of the former group D2, such as hydrocortisone 17-butyrate (11).

In our opinion, one of the reasons for the low level of detection provided by the markers is the relatively high proportion of group 3 corticosteroid contact allergy found in our study (21 of 54 patients; 38.9% with at least one positive patch test reaction to any corticosteroid of group 3). Sixteen of these (16/21; 76.2%) showed negative results when tested with corticosteroid allergy markers. These results are similar to those of a previous study published in the United Kingdom (22), in which clobetasol propionate and betamethasone valerate were routinely tested. In this study, 81% of the patients who were allergic to these compounds would have been missed if they had been patch tested with only budesonide and tixocortol pivalate. Clobetasol propionate seems to be the most valuable marker among this group, and is already included in the North American baseline series (17), yielding 0.32% positive reactions in a series of 17 978 patients, similar to what was found in our series (0.35%, 13/3699). In our study, mometasone furoate showed the lowest allergy prevalence among all tested corticosteroids, which is similar to what has been previously reported (23).

Corticosteroid markers also proved to be unsuccessful in detecting allergy to group 1 corticosteroids in many cases; for instance, 55.6% of patients with positive test reactions to methylprednisolone aceponate and 35.3% with positive test reactions to prednicarbate had negative results with the markers. Contact allergy to these molecules might have been common in our study because of their widespread use in Spain. For example, in the region of Murcia, prescriptions for methylprednisolone aceponate and prednicarbate, respectively, account for 21% and 11% of the total number of prescribed topical corticosteroids. Also, in the publication from Baeck et al., both allergens were the most common allergens after budesonide and tixocortol pivalate (methylprednisolone aceponate, 105/315; prednicarbate, 111/315) (13).

A proportion of patients (27; 50%) were contact-allergic to only one compound. This could make contact allergy to such compounds very difficult to detect if testing is performed with only one representative of their group. These findings may indicate some practical limitations of the concept of cross-reaction profile proposed by Baeck et al. The sensitivity, specificity, PPV and NPV of the current corticosteroid allergy markers were assessed in an attempt to establish their value as screening markers for diagnosing contact allergy to the additionally tested corticosteroids. All corticosteroid markers showed high NPVs, and, taking into account the low prevalence of allergy to corticosteroids in the general population (17), their inclusion in the baseline series should be recommended, because, whenever they give negative results, corticosteroid allergy can be ruled out reliably. However, all markers show limited sensitivity, which is why the addition of new markers should be considered in order to increase the case detection rate. In our series, if we had only tested clobetasol propionate, methylprednisolone aceponate, and betamethasone 17,21-dipropionate, we

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would have detected sensitization in 21 of 24 patients (87.50%) not detected by the markers.

Conclusions

Corticosteroid contact allergy in Spain is rare, probably because of both legal restrictions on access to over-the-counter corticosteroids, and the prescription habits of physicians, who mainly recommend group 3 corticosteroids. However, contact allergy may be underdiagnosed in a significant number of cases, owing to the failure of the corticosteroid allergy markers included in the baseline series to detect allergy to group 3 corticosteroids in most cases and also to some of the most frequently used group 1 corticosteroids. Among the markers, budesonide proved to be more useful than tixocortol pivalate (sensitivity of 44.8% versus 15.2% respectively). Although hydrocortisone 17-butyrate had a high NPV and a high PPV, its importance as a screening marker was low in our series, because all cases detected by it were also detected by budesonide. It is our recommendation to maintain a high level of awareness regarding corticosteroid allergy. The inclusion of group 3 corticosteroid representatives as markers within the baseline series seems advisable. We also recommend that, when a specific corticosteroid series is used, this should be modified according to local corticosteroid use patterns and the frequency of allergy.

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