

ORIGINAL ARTICLES

Results and Assessment of Photopatch Testing in Spain: Towards a New Standard Set of Photoallergens

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Abstract. *Introduction.* While the standardization of exploration with photoallergy tests or photopatch testing runs its course in Europe, we have carried out an epidemiological study about the current situation of photoallergy in our country.

Material and methods. We have gathered the results of photopatch testing in seven hospital centres of Madrid, Cataluña, Galicia and Comunidad Valenciana during the years 2004 and 2005. The exploration has included, at least, the standard set of the Spanish Photobiology Group (GEF), with 16 (photo) allergens, that have been irradiated with 10 J/cm². We have assessed the total number of explored patients, their sex, present, past or unknown relevance of positive photopatch testing, cross reactions, and allergens responsible for photosensitization.

Results. Of 224 patients explored by photopatch testing, 39.3% show one or more positive tests. Seventy-one percent (103) were considered relevant with respect to clinical history, 14 cases (9.6%) were cross reactions, and 28 (19.3%) were considered of unknown relevance. The most prevalent allergens were nonsteroidal antiinflammatory drugs, specially ketoprofen (43 patients), followed by bencydamine (7 patients) and etofenamate (5 patients). The mixture of four sunscreens from the standard set of the GEF only detected 10 of 16 patients with photoallergy to sunscreens. Photopatch testing of unknown relevance was mainly due to antiseptics (fenticlor) and topical antihistamines.

Conclusions. We propose the modification of the standard set of photoallergens from the GEF, that should include the majority of nonsteroidal antiinflammatory drugs and sunscreens available in Spain. Ketoprofen continues to be the most frequent photoallergen in our country. It is also important for the cross sensitizations that may present. Sunscreens should be explored separately and not in form of a mixture.

Key words: photoallergic dermatitis, photopatch testing, epidemiology, ketoprofen, sunscreens.

RESULTADOS Y EVALUACIÓN DEL FOTOPARCHE EN ESPAÑA: HACIA UNA NUEVA BATERÍA ESTÁNDAR DE FOTOALERGENOS

Resumen. *Introducción.* Mientras que la estandarización de la exploración con pruebas de fotoalergia o fotoparche (FTP) sigue su curso en Europa, hemos realizado un estudio epidemiológico sobre la situación actual de la fotoalergia en nuestro país.

Material y métodos. Hemos recogido los resultados del FTP en 7 centros hospitalarios de Madrid, Cataluña, Galicia y Comunidad Valenciana, durante los años 2004 y 2005. La exploración ha incluido, al menos, la batería estándar del Grupo Español de Fotobiología (GEF), con 16 (foto)alergenos, que se han irradiado con 10 ju-lios/cm². Hemos valorado el número total de pacientes explorados, su sexo, la relevancia presente, pasada o desconocida de los fotoparches positivos, las reacciones cruzadas y los alergenos responsables de la fotosensibilización.

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Resultados. El 39,3% de los 224 pacientes explorados mediante FTP presentaron uno o más fotoparches positivos. Ciento tres (71%) se consideraron relevantes respecto a la historia clínica, 14 (9,6%) fueron reacciones cruzadas y 28 (19,3%) se consideraron de relevancia desconocida. Los alérgenos más prevalentes fueron los antiinflamatorios no esteroideos, particularmente el ketoprofeno (43 pacientes), seguido a distancia de la bencidamina (7 pacientes) y el etofenamato (5 pacientes). La mezcla de 4 filtros solares de la batería estándar del GEF sólo detectó 10/16 pacientes con fotoalergia a filtros solares. Los fotoparches de relevancia desconocida fueron sobre todo por antisépticos (fenticlor) y antihistamínicos tópicos.

Conclusiones. Proponemos modificar la batería estándar de fotoalérgenos del GEF, que debería contemplar la mayoría de los antiinflamatorios no esteroideos y filtros solares que hay en el mercado español. El ketoprofeno sigue siendo el fotoalérgeno más frecuente en nuestro país. Su importancia deriva también de las sensibilizaciones cruzadas que puede presentar. Los filtros solares deben explorarse por separado, y no en forma de una mezcla.

Palabras clave: dermatitis fotoalérgica, fotoparche, epidemiología, ketoprofeno, filtros solares.

Introduction

Photoallergic reactions are cellular immunity reactions to a photoinduced antigen. According to the Gell and Coombs classification system, they are type IV hypersensitivity responses; they include reactions to the topical or systemic administration of a photosensitizing substance in patients who have been previously sensitized, through contact or photocontact, with this substance. Topical administration and systemic administration cause photoallergic contact dermatitis and photoallergic systemic dermatitis, respectively. The diagnosis of a suspected photoallergy is based on clinical manifestations. These can sometimes be similar to those seen in other forms of contact dermatitis (sunscreen-induced, airborne, etc) and photocontact dermatitis (phototoxic dermatitis, polymorphous light eruption, chronic actinic dermatitis, etc). Diagnosis is generally confirmed by photopatch testing, a procedure that is similar to conventional, epicutaneous patch testing except that it involves the application of 2 matching sets of suspected allergens to the patient's skin. One of the sets is then irradiated with ultraviolet (normally UV-A) light.

Photopatch testing protocols have not yet been standardized. In May 2002, a group of experts met in Amsterdam, Holland, under the umbrella of the European Task Force for Photopatch Testing, to draw up a consensus statement regarding photopatch testing methodology and interpretation.¹ The group was formed by 14 dermatologists and photobiologists from 11 European countries. One of the conclusions they reached was that photopatch testing was "significantly underused in Europe and probably worldwide. This is due to a number of reasons, not least of which is the fact that responsibility for photopatch testing has fallen between two areas of dermatology subspecialization, the 'photodermatologists' who have light-related, but lack contact experience, and vice versa for 'contact dermatologists'."

Table 1. Photopatch Test Results Using Allergens in the Standard Set Recommended by the Spanish Photobiology Group (GEF). Percentage of Positive Results With Respect to All Positive Results and Percentage of Relevant Reactions for Each Allergen

| Allergen | Percentage of All Positive Results | Present or Past Relevance, % |
|----------------------------------|------------------------------------|------------------------------|
| Ketoprofen 2.5% | 45 | 95 |
| Sunscreen mix at 2% ^a | 10 | 100 |
| Fenticlor 1% | 8 | 0 |
| Benzydamine 1% | 7 | 85 |
| Fragrance mix at 8% ^b | 7 | 71 |
| Promethazine 0.5% | 7 | 0 |
| Piroxicam 1% | 3 | 100 |
| Demethylchlortetracycline 5% | 2 | 0 |
| Chlorpromazine 0.1% | 2 | 0 |
| Triclosan 2% | 2 | 0 |
| Bithionol 1% | 2 | 0 |
| Musk ambrette 5% | 1 | 100 |
| Hexachlorophene 1% | 1 | 0 |
| Diphenhydramine 1% | 0 | – |
| Fluorescein 10% | 0 | – |
| Chlorhexidine 0.5% | 0 | – |

^aSunscreen mix at 2%: benzophenone-3, butyl methoxydibenzoylmethane, 4-methylbenzylidene camphor, and octyl methoxycinnamate (each at 0.5%)

^bFragrance mix: Cinnamic aldehyde, cinnamic alcohol, amyl cinnamic aldehyde, hydroxycitronellal, eugenol, isoeugenol, oak moss, geraniol (each at 1%).

The first steps towards standardizing photopatch testing in Spain were taken with the creation of the Spanish Contact Dermatitis Research Group (abbreviated in Spanish to GEIDC) in 1976. Efforts were intensified in 1995, in particular, when the Spanish Photobiology Group (abbreviated in Spanish to GEF) decided to standardize the photopatch testing methods followed by its dermatology members, some of whom also belonged to the GEIDC.² It was decided to use a standard set of 16 photoallergens (Table 1) applied in duplicate. One of the sets is then irradiated with UV-A light at a dose of 10 J/cm² at 48 hours. The test results are read 24 hours or, preferably, 24 and 48 hours after irradiation and the intensity and relevance of the reactions are assessed.

At a meeting in Valencia, Spain, on January 29, 2004, the GEF agreed to follow the majority of the recommendations of the European Task Force for Photopatch Testing. One of the changes they made was to irradiate the photopatches at a dose of 5 rather than 10 J/cm². The GEF, however, maintained its standard set of photoallergens, which included certain nonsteroidal antiinflammatory drugs (NSAIDs) such as piroxicam and benzydamine that were not contemplated in the task force's recommendations.¹

With a view to assessing the current situation regarding photoallergies in Spain, we decided to gather further data on photopatch testing in Spain for 2004 and 2005. We were interested in analyzing positive reactions to a range of allergens and not just those in the GEF's standard set. In the course of this paper, we will evaluate this set of allergens and propose several modifications, including the addition and removal of certain photoallergens and changes in the concentrations of others.

Material and Methods

We sent data collection sheets to the dermatology members of the GEF and asked them to record their photopatch test results for the years 2004 and 2005. We received reliable data from 7 hospitals located in the autonomous Spanish communities of Madrid, Catalonia, Galicia, and Valencia. The 7 hospitals were Hospital 12 de Octubre in Madrid, Hospital Clínic in Barcelona, Hospital del Mar in Barcelona, Hospital de Sant Pau in Barcelona, Hospital Gil Casares in Santiago de Compostela, Consorcio Hospital General Universitario in Valencia, and Hospital General in Alicante.

We evaluated the total number of patients who underwent photopatch testing, their sex, the number of positive reactions, the allergens responsible for these reactions, and the relevance (present, past, or unknown) of the reactions.

In total, we analyzed the results of 224 patients (121 women and 103 men).

Two matching sets of patches were placed on each patient's back, using mainly aluminium chambers (Finn chambers) and hypoallergenic tape (Scanpor). At 48 hours, 1 set of allergens was irradiated with UV-A light at a dose of 10 J/cm².

Results were read when the patches were removed and 24 and/or 48 hours after irradiation. Positive reactions on the irradiated side were compared to the corresponding reactions (positive or negative) on the nonirradiated side. We were only interested in photoallergic reactions, that is, reactions that had been positive on the irradiated side and negative on the nonirradiated side. Some authors have reported positive reactions to fragrance mixes on both sides.

We assessed the relevance of the positive photopatch reactions using the same approach as that used in epicutaneous patch testing.³ Relevance refers to the relationship between a positive reaction (allergic, nonirritant, or phototoxic reaction) and the presenting episode of dermatitis. A positive contact or photocontact patch test reaction can have present, past, or unknown relevance. Unknown relevance means that it cannot be explained by either the patient or the investigator. In our study, present relevance was when the sensitization explained, in part or in full, the dermatitis for which the patient was seeking consultation, and past relevance was when there was a known history of dermatitis related to contact or photocontact sensitization. Finally, relevance was considered unknown when the patient reported no previous contact with the allergen in question, or acknowledged previous contact but not intolerance (latent sensitization?). We also evaluated cross-reactions for the first time.

Results

Of the 224 patients studied, 88 (39.3%) had 1 or more positive photopatch reactions. Of these 88 patients, 49 were women (40.5% of all women examined) and 39 were men (37.9% of all men examined). Combined, they had a total of 145 positive reactions (an average of 1.6 positive photopatch reactions per patient).

Of the 145 positive reactions, 103 (71%) were of present or past relevance and 28 (19.3%) were of unknown relevance. Fourteen (9.6%) reactions were considered to be cross-reactions.

Table 1 shows the positive reactions to the allergens from the GEF's standard set and Table 2 shows the positive reactions to other allergens.

NSAIDs were the allergens that produced a photoallergic reaction most often (69 positive reactions in 65 patients), followed distantly by sunscreens (22 positive reactions in 16 patients).

The most common NSAID was ketoprofen (43 patients), followed by benzydamine (7 patients), etofenamate (5

patients), piroxicam and fepradinol (3 patients), piketoprofen (2 patients), ibuprofen, and indomethacin (1 patient).

We made no distinction between sensitization to ketoprofen and sensitization to its active isomer dexketoprofen as we considered that each was a marker for the other.

Ketoprofen is the most common photoallergen in Spain, and in our series, it was relevant in most cases (present in 39 cases and past in 2). Two additional positive reactions to ketoprofen were considered to be cross-reactions, occurring in patients with primary sensitization to benzophenone-3 (oxybenzone). Conversely, 11 positive photopatch reactions to other substances (fenofibrate [7], oxybenzone [3], and piketoprofen [2]) were considered to be cross-reactions with ketoprofen (primary sensitizer).

Of the 16 patients with photoallergy to sunscreens, only 10 had a positive photopatch reaction to the GEF's 2% sunscreen mix. Three patients had a photoallergic reaction to phenylbenzimidazole sulfonic acid, benzophenone-4, and octocrylene, respectively. None of these compounds are in the GEF's standard set of photoallergens. In addition, a further 3 patients had positive photopatch reactions to oxybenzone (benzophenone-3) and/or 2% octyl methoxycinnamate in Vaseline yet their reaction to the sunscreen mix in the standard set (where the concentration of each of the sunscreens is 0.5%) had been negative. In other words, the standard 2% sunscreen mix yielded false negative results.

Of the 28 photopatch reactions of unknown relevance, the most common ones were caused by fenticlor (8) and promethazine (7), followed by triclosan (2), demethylchlortetracycline (2), chlorpromazine (2), fragrance mix (2), bithionol (2), hexachlorophene (1) and benzydamine (1).

No positive photopatch reactions were observed for chlorhexidine, fluorescein or diphenhydramine, which are all included in the GEF's standard set.

Finally, we observed isolated cases of photoallergy to diltiazem (2), atranorin, ciprofloxacin, and valproic acid.

Discussion

Photopatch testing is uncommon in Spain. Of the 7 hospitals that participated in this study, only one (Hospital General de Valencia) performed over 30 photopatch tests a year. In dermatology departments with a photobiology unit and a skin allergy unit, the number of diagnoses made using photopatch testing was higher when both units collaborated closely with one another. Photopatch testing can be performed by photobiologists or skin allergy specialists. The almost invisible line that sometimes separates a photoallergy from a contact allergy means that some patients referred to the photobiology unit end up being diagnosed in the contact unit,⁴ and vice versa, albeit less frequently.

Table 2. Photopatch Test Results Using Allergens Not in the Standard Set Recommended by the Spanish Photobiology Group (GEF)

| Allergen | Relevance | Cross-reaction |
|--------------------------------------|-----------|----------------|
| Etofenamate 1% | 5 | 0 |
| Piketoprofen 2.5% | 2 | 2 |
| Fepradinol 1% | 3 | 0 |
| Ibuprofen 5% | 1 | 0 |
| Indomethacin 10% | 1 | 0 |
| Benzophenone-3 2% | 5 | 3 |
| Octyl methoxycinnamate 2% | 5 | 0 |
| Butyl methoxydibenzoylmethane 2% | 4 | 0 |
| Methylbenzylidene camphor 2% | 2 | 0 |
| Phenylbenzimidazole sulfonic acid 2% | 1 | 0 |
| Benzophenone-4 2% | 1 | 0 |
| Octocrylene 10% | 1 | 0 |
| Fenofibrate 1% | 0 | 7 |
| Diltiazem | 2 | 0 |
| Ciprofloxacin | 1 | 0 |
| Atranorin 0.5% | 1 | 0 |
| Valproic acid | 1 | 0 |

The GEF conducted its first epidemiological study on the prevalence of photoallergies in Spain in 1996⁵; 170 patients in 7 hospitals were examined using the standard set of photoallergens. There were 64 positive test reactions. The most common photoallergens were NSAIDs, mainly ketoprofen (26) and piroxicam (9), followed distantly by the sunscreen mix (4). In 1997 and 1998, the GEF conducted a second photopatch test study in Spain, this time involving 296 patients in 10 different hospitals. It found 151 positive test reactions.⁶ The second study included information on the relevance of the positive reactions. Once again, the most common photoallergens were NSAIDs, mainly ketoprofen (42) and piroxicam (10). These were followed distantly by the sunscreen mix (5).

Comparing our results with those of the above studies, it emerges that the frequency of photosensitization to ketoprofen has remained stable. This contrasts with other NSAIDs such as benzydamine and etofenamate, in which photosensitization has increased, and with piroxicam, in which it has decreased. Many of the photoallergic reactions to piroxicam were cases of secondary sensitization or cross-reactions. In other words, they occurred in patients who had been previously sensitized to thiosalicylic acid from thiomersal and who were seeking consultation for a

photoallergy to topical or systemic piroxicam. Although thimerosal is still a common allergen in Spain,⁷ our study showed that, at least in Hospital General de Valencia, thimerosal sensitization is now more frequently due to exposure to mercuric chloride than to thiosalicylic acid, and mercuric chloride does not cross-react with piroxicam.⁸

Ketoprofen is the most important photoallergen in Spain. Not only is it the most prevalent but it also cross-reacts with other arylpropionic acid derivatives⁹ such as fenofibrate (a lipid-lowering agent) and benzophenone-3 (oxybenzone) (a chemical sunscreen) and other NSAIDs such as dexamethasone, and less frequently, piroxicam.

Although our study detected a higher number of patients with photosensitization to sunscreens than did previous studies conducted in Spain,^{5,6} the number is still low compared to other European^{10,11} and American^{12,13} studies.

Contact and photocontact allergy to sunscreens may be underdiagnosed in Spain for a number of reasons. The GEF's standard set of allergens, for example, contains a sunscreen mix at 2% that includes just 4 sunscreen components (benzophenone-3, butyl methoxydibenzoylmethane, 4-methylbenzylidene camphor, and octyl methoxycinnamate) at very low concentrations (0.5% each). As we have already mentioned in the results section, this can give rise to false negatives. New sunscreens containing potential photosensitizing agents such as octocrylene have also been launched on the market.¹⁴ Another reason for underdiagnosis may be that in certain patients, photoallergy to sunscreens is recorded as intolerance to facial cosmetics and/or lipsticks. Sunscreens are not included in either the GEIDC's standard set of allergens, or in commercial sets of cosmetics and cosmetic preservatives that are used to test patients in Spain. It is therefore relatively easy to miss a diagnosis in a patient who is allergic or photoallergic to a sunscreen in a cosmetic product. It would be useful to test patients with dermatitis of the face and/or cheilitis induced by facial cosmetics and/or lipsticks using a set of sunscreen photopatches. The growing tendency to include sunscreens in all types of cosmetics (face creams, lipsticks, shaving lotions and aftershaves, shampoos, nail products, etc) will almost certainly lead to an increase in the number of patients that experience contact and photocontact allergy to these substances.¹⁵

We believe it would be a good idea to eliminate the 2% sunscreen mix from the GEF's standard set and incorporate each sunscreen separately. In addition, it would be worthwhile testing patients using higher concentrations than 2% to avoid the risk of false negatives.¹⁶ Sunscreens are currently available for patch and photopatch testing at a concentration of 10% in Vaseline (MartiDerm).

We observed a high percentage (19.3%) of photopatch test reactions of unknown relevance. The corresponding allergens were antiseptics (fenticlor, triclosan, bithionol, hexachlorophene), topical antihistamines (promethazine,

diphenhydramine), and tranquilizers (chlorpromazine), among others. Some of them (fenticlor, hexachlorophene, and diphenhydramine) are no longer so pertinent, while others (promethazine and chlorpromazine) should not be included in routine photopatch testing unless there is a history of exposure.

Standard contact and photocontact allergen sets vary over time and in accordance with changing usage and exposure scenarios in different countries. Photoallergen sets also vary from one country to the next. In Spain, for example, the most common allergens are, without a doubt, NSAIDs, and ketoprofen and/or dexamethasone, in particular. The use of topical ketoprofen varies from country to country and region to region depending on commercial availability and prescribing habits. Exposure to ketoprofen, however, seems to cause more photosensitization than exposure to other topical NSAIDs such as diclofenac. Although diclofenac is prescribed more often than ketoprofen in Spain, there are few reports of it causing photoallergic reactions.¹⁷

Based on the findings of this study, we suggest that the GEF's new standard set of photoallergens should include the majority of NSAIDs and sunscreens that are commercially available in Spain. Rather than be analyzed as part of a sunscreen mix, sunscreens should be analyzed separately and at a concentration of 10%.

The GEF is to approve a new standard set of photoallergens at its upcoming meeting in Palma de Mallorca, Spain, in February 2007. We believe that the changes will better reflect the current situation regarding photoallergies in Spain.

Conflicts of Interest

The authors declare no conflicts of interest.

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