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Dear Editor,

We would like to introduce our paper, uploaded to the **Photodermatology Photoimmunology & Photomedicine Journal** website, corresponding to the section "**ORIGINAL ARTICLES**" called "**Standard photopatch test battery? Proposal based on current epidemiology and experience in our Skin Allergy Unit.**"

Photoallergic Contact Dermatitis (PACD) patch testing should be guided by clinicians suspicion, but usually initiates with an standard series. In Spain, the latest PPT battery recommendation dates from 1995. Since testing some allergens in PPT (e.g. phenticlor) has currently an smaller interest and in line with previous recommendations (e.g. solar filters should be tested separately), we show our experience with our *homemade* PPT battery in the last four years, in which fragrances were also tested individually. Based on our results, we propose an algorithm to guide which allergens to patch test in PPT under suspicion of PACD.

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Yours sincerely,

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**Standard photopatch test battery? Proposal based on current epidemiology
and experience in our Skin Allergy Unit.**

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and experience in our Skin Allergy Unit.**

ABSTRACT

Background: The diagnosis of photoallergic contact dermatitis (PACD) is confirmed by photopatch testing (PPT). In Spain, the latest recommendation on which allergens to test in PPT dates from 1995.

Methods: In the last 4 years, we studied 455 patients with epicutaneous tests and performed PPT on 33 of those patients (7.3%).

Results: The most prevalent allergens in PPT were: non-steroidal anti-inflammatory drugs (NSAIDs) (46%), fragrances (21%) and solar filters (18%).

Discussion: In our country, the most common photoallergens continue to be NSAIDs (ketoprofen). The increasingly common use of sunscreens has led to a growing involvement of solar filters in PACD, which can be also contained in other cosmetics. In our experience, PACD due to fragrances is nonetheless at least similar in frequency.

Conclusions: The PPT battery must adapt to the prescription, use and exposure habits of each country. We propose a diagnostic model to guide which allergens to test in PPT, which in our experience should also include fragrances.

KEYWORDS

Photoallergy, photopatch test, standard battery, anti-inflammatory drugs, fragrances, solar filters.

SUMMARY STATEMENT

PACD patch testing should be guided by clinicians suspicion, but usually initiates with an standard series. In Spain, the latest PPT battery recommendation dates from 1995. Since testing some allergens in PPT (e.g. phenticlor) has currently an smaller interest and in line with previous recommendations (e.g. solar filters should be tested separately), we show our experience with our *homemade* PPT battery in the last four years, in which fragrances were also tested separately. Based on our results, we propose an algorithm to guide which allergens could be tested in PPT under suspicion of PACD.

INTRODUCTION

Photoallergic contact dermatitis (**PACD**) occurs after topical application of a photosensitizing substance. It is a type IV hypersensitivity reaction in which a chromophore absorbs radiation, mainly from the ultraviolet A (UVA) spectrum, and is transformed into a photoallergen in the skin. Parallel to non-photoinduced allergic contact dermatitis, patients must be previously (photo)sensitized. Due to the necessary involvement of sunlight in provoking the skin lesions, they do not typically appear in areas that are anatomically protected from the sun, e.g.: upper eyelids and retroauricular folds. Involvement of the rest of the face and neck should raise suspicion on PACD.(1)

Diagnosis is confirmed by photopatch testing (**PPT**), which consists of applying allergens to be studied in duplicate and exposing only half of them to broad-spectrum UVA radiation (320-400nm) at a dose of 5 J/cm² after the first 24-48 hours [day (D)1 or D2] of occlusion (e.g. coinciding with the first reading). Final reading usually takes place on D4 (96 hours).(2)

In Spain, the latest recommendation of an standard PPT battery (1995) included 16 allergens(3). According to European guidelines, proposals of modifications have been made at a national level. Nevertheless, we still lack a more recent, formal and standardized PPT recommendation.

Therefore, the decision on which allergens to test is often guided by clinicians suspicion and the dermatologist's experience in this field.(3)

We would like to show our experience with the PPT battery that we test in our Cutaneous Allergy Unit (Hospital Clínico Salamanca) in the last 4 years (2016-2020). We propose a standard battery model/algorithm for PACD, based on: results in our sample, utility in daily clinical practice and literature reports to date.

METHOD

We conducted an observational and retrospective study of the patients that we studied in our Cutaneous Allergy Unit of the Hospital Clínico in Salamanca from March 1, 2016 to February 28, 2020 (48 months). 455 patients were studied with epicutaneous tests, and we performed PPT on 33 of them (7.3%).

All patients were tested with the standard TRUE Test series (MartiTor®, Barcelona, Spain), and patch testing was complemented according to the Spanish Contact Group (GEIDAC) recommendations.(4) Additional batteries from the same commercial firm were tested if deemed necessary.

If PACD due to cosmetics was suspected, solar filters and fragrances were individually tested (MartiTor, Spain), also including ketoprofen and fenofibrate (in order to detect possible cross-reactions). Under suspicion of PACD because of NSAIDs, if there was no previous history of intolerance to cosmetics, the whole NSAIDs-battery was tested, together with fenofibrate and oxybenzone. These were all tested in duplicate, removed after 48 hours and only one series was exposed to broadband UVA (UV 5002 phototherapy cabin, Waldmann®), at a dose of 5 J/cm², whereas the other set was shielded from light exposure. Readings were performed on day (D) 2, both after removal of the patches and application of UVA irradiation, and on D4. All reactions were graded according to International Contact Dermatitis Research Group Criteria (ICRDG).

RESULTS

Thirty-three patients were photopatch tested: 25 were women (75%) and 8 were men (25%). Their average age was 58 +/- 15 years. The face and the neck were the most frequent locations of eczema (52%), followed by the legs (21%). Other involved locations were: trunk, arms and feet. No occupational involvement was found. The sources of possibly implicated allergens were, in decreasing order: creams (33%), topical NSAIDs (30%), sunscreens (30%), perfumes (12%) and other cosmetics such as gels, shampoos or lip cosmetics (6%). (Table 1)

Thirteen patients (39%) showed at least one positive reaction in PPT, reaching up to a total of 28 positive reactions (including own products). All results of PPT are shown in Table 2. The most prevalent allergens were, in decreasing order: NSAIDs (46%), fragrances (21%) and solar filters (18%). All positivities were interpreted as photoallergic results (positive only on the irradiated side), except for fragrance II mix and resorcinol which had been positive to a lesser extent on the non-irradiated side (contact dermatitis and photoaggravated contact dermatitis). Relevance of all the positive results was present and cross-reactions were frequently encountered. (Table 2)

DISCUSSION

Although suspicion of PACD is mostly attributed to cosmetics, the most frequently demonstrated involvement of photoallergens in our country (Spain) continue to be NSAIDs, followed in increasingly high frequency by sunscreens.(2,5) Other European countries show similar results.(6) As expected, ketoprofen continues to be the most frequent photoallergen. Dexketoprofen is its active isomer, which explains the frequently encountered cross-reactions. Other commonly involved NSAIDs are etophenamate and pyroxicam, whose positivities may vary according to regional, national and international prescription habits.

Published reports list UV filters as the most frequent cause of photoallergy in cosmetics.(7) Increased awareness of their use has led to a growth in the prevalence of allergic contact dermatitis and PACD on behalf of solar filters. Organic solar filters are the most allergenic, from which the para-aminobenzoic acid (PABA) had been classically in the past the main responsible.(2) However, this has been lately unseated by benzophenone-3 or oxybenzone, an

aromatic ketone that is used not only in cosmetics (e.g. sunscreens and moisturizers) but also in industrial and textile products to extend their durability and reduce their photodegradation.(8–10) In our series, PACD to solar filters could be found, being sources of exposure quite different: textiles (Decathlon® T-shirt), sunscreens (Delial ® SPF cream) and moisturizing creams (Bella Aurora ® SPF15).

PACD due to fragrances has been classically attributed to oak moss, among others, but is however scarcely reported.(11) In our series, fragrances positive results outnumbered those of solar filters. In the same way, the number of patients who suffered from PACD to fragrances was higher than that due to UV filters. In addition, we were able to establish that co-sensitization to fragrances and solar filters is not infrequent.

It is mandatory to keep in mind possible cross-reactions among all members of the three groups (NSAIDs, solar filters fragrances) and others (fenofibrate). There is an association between photosensitization to ketoprofen and benzophenone-3, fenofibrate (hypolipemiant) and fragrances (cinnamic alcohol, cinnamic aldehyde, hydroxycitronellal). Cross-reactivity is due to the a benzoic ring attached to a ketone group (benzophenone), which is formed by the action of sunlight.(12) This fact may even explain some patients skin reactions, as we were able to demonstrate in a patient who, being sensitized to ketoprofen on behalf of using topical NSAIDs years before, subsequently developed eczematous lesions in photo-exposed areas after wearing a sports T-shirt containing solar filters at the beach (e.g. hot and humid conditions).

In Spain, the latest PPT battery recommendation included 16 allergens and dates from 1995. Despite European recommendations, we still lack a more recent, formal and standardized proposal. Testing some allergens in PPT (e.g. phentictlor, promethazine, triclosan, diphenhydramine) may have currently an smaller interest, ending in negative or non-clinical relevant results.(3) In 2005, it was demonstrated that solar filters tested as a mixture offered a significant number of false negative results, and did not include new allergens with growing relevance such as octocrylene. On this account, some authors proposed to test solar filters

separately and in an appropriate concentration, recommendation which has been followed since 2007.(3) This is how it is currently done in the European PPT battery, which includes solar filters (separately tested) and NSAIDs (Chemotechnique, Sweden). Neither in the European Photopatch Baseline Series (EP-1000) nor in the Extended one (EPE-1000) are any fragrances included. (1) In our country, photoallergen batteries from MartiTor (Barcelona, Spain) do not include any fragrances either. It is true that PPT significantly varies depending on the country, and only few countries include fragrances in PPT batteries. (13) This fact may account for the lower implication of fragrances in many PPT studies results.

Standard allergen baseline series need to be modified over time and adapted to the prescription, use and exposure habits of each country. Likewise should happen with PPT. In this regard and based on our results, we show our proposal of a diagnostic algorithm to guide which allergens or batteries of allergens could be tested under suspicion of PACD (Table 3). In our experience, we totally support the recommendation to test solar filters individually if suspicion of involvement is present, remembering that they may be furtherly contained in other products apart from sunscreens (e.g.: cosmetics in general and textiles). Fragrances in our series reached a higher prevalence than solar filters, contrasting what has been so far reported. On top of that, source of sensitization was often not easy to be suspected (e.g.: sunscreens). In this regard, we feel the need to show which was, in our experience, such an illustrative case a few years ago (Image 1). Similar cases prompted us to include fragrances in PPT, in order to detect undiagnosed photoallergic sensitizations. This seemed to us even more important when fragrances are the second most frequent allergens to cause sensitization in the general population.(14)

Moreover, cross reactivity among these allergens (NSAIDs, UV filters, fragrances) is well-known. Getting to know such positivities becomes even more relevant when it comes to adjust patients avoidance recommendations (e.g. PACD to ketoprofen and fenofibrate cross-reaction, patient should avoid both; sensitization to ketoprofen with past relevance explained subsequent PACD to oxybenzone contained in a sports T-shirt).

We would like to highlight how useful it may be to include fragrances in PPT, given their possible growing involvement in PACD. In this respect, these could be patched either individually or as a mixture. Whenever suspicion of involvement is high, it could be advisable to patch them separately; otherwise, in our sample, we would not have been able to detect 50% of sensitizations. Similarly, separate testing of fragrances could be useful in the study of chronic actinic dermatitis.

Even when its pathogenesis has not been clearly elucidated, phototesting, patch and photopatch testing is recommended, since it has been related with sensitization to aeroallergens, plants and fragrances.(15) On the contrary, if suspicion of involvement is low, fragrance mixtures I and II might still be good markers in up to half of the cases. As in any case, testing own products is also advisable in PPT.

CONCLUSION

PPT is an essential tool in the diagnosis of PACD. In our experience, our results coincide with previously published reports on this subject, especially in our country where NSAIDs continue to be the main culprits of PACD (specifically ketoprofen). The growing involvement of fragrances is however striking, as well as what it is already known for solar filters. Based on our results, we show our algorithm on how to perform PPT, which might ease this task for other clinicians when it comes to decide which allergens to test, given the lack of an updated standard Spanish PPT battery for this purpose.

LEGENDS

Table 1. PACD in our center (2016-2020). Although cosmetics seem to be the most frequently suspected source of photosensitization, topical NSAIDs are the most prevalent positive results in PPT.

Table 2. Photopatch test (PPT) results. NSAIDs: non-steroidal anti-inflammatory drugs. CR: cross reaction. F: fragrance. SF: solar filters. “n” refers to the number of positive patches for that allergen group. “n*” refers to the number of patients diagnosed of PACD on behalf of that allergen group.

Own products that were tested included two different sunscreens. A positive patch test result on the irradiated side of the back was obtained for one of them.

Table 3. PHOTOPATCH BATTERY RECOMMENDATION. NSAIDs: non-steroidal anti-inflammatory drugs. CAD: chronic actinic dermatitis. In general terms, the standard battery should always be tested. In case photoallergy to NSAIDs is suspected, without previous intolerance to cosmetics and regardless of the location involved, our recommendation would be to test the whole NSAIDs battery, and also include fenofibrate and oxybenzone in order to detect possible cross-reactions. In case photoallergy to cosmetics is suspected, especially if face and neck are involved, we deem it useful to test: fragrances (mix, already included in the standard battery if suspicion of involvement is low, or individually, if suspicion is high or in order to study CAD), solar filters (always individually) and, at least, ketoprofen (as NSAIDs group marker) and fenofibrate (hypolipemiant) for possible cross-reactions.

Image 1. Photoaggravated contact dermatitis due to fragrances and solar filters contained in sunscreen (Solcare®). This male consulted due to facial eczema, and was subsequently photopatch tested (2007) with no positive result. Since suspicion of photoinduced dermatitis was still high, we insisted on strict sun protection. However, he experienced outbreaks of eczema for years until new PPT was performed, being both fragrances and solar filters tested separately (2014). Sensitization to *amyl and hexyl cinnamic aldehyde* was proven, along with photoaggravated results in PPT. PACD to *isoamyl methoxycinnamate* was also demonstrated. Solcare® own product was tested, showing a photoaggravated result. Fragrances and organic solar filters avoidance allowed total recovery and the patient experienced no further outbreaks. Fragrances positivities in PPT are not only cross-reactions but can also make them putative agents of PACD or photoaggravated contact dermatitis.

REFERENCES

1. Russo JP, Ipiña A, Palazzolo JF, Cannavó AB, Piacentini RD, Niklasson B. Dermatitis por contacto fotoalérgica a protectores solares con oxibenzona en La Plata, Argentina. *Actas Dermo-Sifiliográficas*. 2018 Jul;109(6):521–8.
2. Kerr A, Ferguson J. Photoallergic contact dermatitis. 2010;10.
3. De la Cuadra Oyanguren J, Pérez-Ferriols A, Lecha-Carretero M, Giménez-Arnau AM, Fernández-Redondo V, Ortiz de Frutos FJ, et al. Resultados y evaluación del fotoparche en España: hacia una nueva batería estándar de fotoalérgenos. *Actas Dermosifiliogr*. 2007(98):96–101.
4. Hervella-Garcés M, García-Gavín J, Silvestre-Salvador JF. Actualización de la serie estándar española de pruebas alérgicas de contacto por el Grupo Español de Investigación en Dermatitis de Contacto y Alergia Cutánea (GEIDAC) para 2016. *Actas Dermo-Sifiliográficas*. 2016 Sep;107(7):559–66.
5. Consuegra Romero G, Castro Gutiérrez B, González López MA. Photoallergic contact dermatitis. *European Journal of Internal Medicine*. 2017 Mar;38:e4–5.
6. Pérez Ferriols A, De la Cuadra Oyanguren J. La nueva batería europea de fotoalérgenos. *Piel Formación Continuada en Dermatología*. 28(2):66–8.
7. Laguna C, de la Cuadra J, Martín-González B, Zaragoza V, Martínez-Casimiro L, Alegre V. Dermatitis alérgica de contacto por cosméticos. *Actas Dermo-Sifiliográficas*. 2009 Feb;100(1):53–60.
8. Zaragoza-Ninet V, Blasco Encinas R, Vilata-Corell JJ, Pérez-Ferriols A, Sierra-Talamantes C, Esteve-Martínez A, et al. Dermatitis alérgica de contacto a cosméticos, estudio clínico-epidemiológico en un hospital terciario. *Actas Dermo-Sifiliográficas*. 2016 May;107(4):329–36.
9. Ortiz de Frutos FJ. Luces y sombras de los filtros solares, específicamente de la oxibenzona. *Actas Dermo-Sifiliográficas*. 2018 Jul;109(6):468–9.
10. Melé-Ninot G, Iglesias-Sancho M, Bergendorff O, Lázaro-Simó AI, Quintana-Codina M, Salleras-Redonnet M. Photoallergic contact dermatitis due to benzophenone contained in swimming goggles. *Contact Dermatitis*. 2020 Jan;82(1):59–60.
11. Victor FC, Cohen DE, Soter NA. A 20-year analysis of previous and emerging allergens that elicit photoallergic contact dermatitis. *Journal of the American Academy of Dermatology*. 2010 Apr;62(4):605–10.
12. Leroy D, Domp Martin A, Szczurko C, Michel M, Louvet S. Photodermatitis from

ketoprofen with cross-reactivity to fenofibrate and benzophenones. Photodermatology, Photoimmunology & Photomedicine. 1997 Jun;13(3):93–7.

13. Hu Y, Wang D, Shen Y, Tang H. Photopatch Testing in Chinese Patients Over 10 Years. Dermatitis. 2016 May;27(3):137–42.

14. Alinaghi F, Bennike NH, Egeberg A, Thyssen JP, Johansen JD. Prevalence of contact allergy in the general population: A systematic review and meta-analysis. Contact Dermatitis. 2019 Feb;80(2):77–85.

15. Paek SY, Lim HW. Chronic Actinic Dermatitis. Dermatologic Clinics. 2014 Jul;32(3):355–61.

All the authors of this manuscript have substantially contributed to the conception and design of the paper, data acquisition, critical review of the intellectual content and give their final approval of the present version.

Signed: the authors.

A handwritten signature in black ink, consisting of a large, stylized 'S' or 'L' shape followed by several vertical strokes and a long horizontal line extending to the right.

Patients (n)	33
Sex	Female (4:1)
Age	58 y (+/- 15y)
Location	1. Head and neck 2. Legs
Suspected source of sensitization	1. Cosmetics 2. Topical NSAIDs
Positive allergens in PPT	1. Topical NSAIDs (46%) 2. Fragrances (21%) 3. Solar filters (18%)

Table 1. PACD in our center (2016-2020). Although cosmetics seem to be the most frequently suspected source of photosensitization, topical NSAIDs are the most prevalent positive results in PPT.

	n	Culprit allergen	Source of sensitization	n*
Topical NSAIDs	13	Ketoprofen (6)	Topical NSAIDs (3) CR with dexketoprofen (2) Past relevance sensitization (1)	7
		Dexketoprofen (3)	Topical NSAIDs (2) CR with ketoprofen (1)	
		Etophenamate (3)	Topical NSAIDs (1) CR with dexketoprofen (2)	
		Salicylates (1)	Topical NSAIDs (1)	
Fragrances	6	Fragrance mix I (1) Hydroxycitronellal (1) Citral (1)	Sunscreen	2
		Amyl cinnamyl aldehyde (1)	<i>Not specified</i>	
		E : Amyl cinnamyl alcohol (1) SE : Octyl salicylate (1)	Sunscreen	2
		E : Fragrance mix II (1) SE : Octinoxate (1) SE : 2-ethylhexyl-p-dimethylaminobenzoate (1)	Moisturizing cream with UV filter	
Solar filters	5	Oxybenzone (2)	Sports T-Shirt (CR with ketoprofen with past relevance) (1) CR with ketoprofen (1)	1
Others	2	Resorcinol (1)	Sunscreen	1
		Fenofibrate (1)	CR with ketoprofen	

Table 2. Photopatch test (PPT) results. NSAIDs: non-steroidal anti-inflammatory drugs. **CR**: cross reaction. **E**: fragrance. **SE**: solar filters. “**n**” refers to the number of positive patches for that allergen group. “**n***” refers to the number of patients diagnosed of PACD on behalf of that allergen group.

Own products that were tested included two different sunscreens. A positive patch test result on the irradiated side of the back was obtained for one of them.

SUSPICION OF PHOTOALLERGIC CONTACT DERMATITIS							
	NSAIDs Any location			COSMETICS Face and neck			
			LOW SUSPICION			HIGH SUSPICION or CAD	
			STANDARD			STANDARD	
PPT	NSAIDs	NSAIDs	- -	Fragrance mix I Fragrance mix II		Fragrances (individually tested)	Fragrances (individually tested)
	Fenofibrate Oxybenzone	Fenofibrate Oxybenzone	Solar filters	Solar filters		Solar filters	Solar filters
			Ketoprofen Fenofibrate	Ketoprofen Fenofibrate		Ketoprofen Fenofibrate	Ketoprofen Fenofibrate

Table 3. PHOTOPATCH BATTERY RECOMMENDATION. *NSAIDs*: non-steroidal anti-inflammatory drugs. *CAD*: chronic actinic dermatitis. In general terms, the standard battery should always be tested. In case photoallergy to NSAIDs is suspected, without previous intolerance to cosmetics and regardless of the location involved, our recommendation would be to test the whole NSAIDs battery, and also include fenofibrate and oxybenzone in order to detect possible cross-reactions. In case photoallergy to cosmetics is suspected, especially if face and neck are involved, we deem it useful to test: fragrances (mix, already included in the standard battery if suspicion of involvement is low, or individually, if suspicion is high or in order to study CAD), solar filters (always separately) and, at least, *ketoprofen* (as NSAIDs group marker) and *fenofibrate* (hypolipemiant) for possible cross-reactions.

Irradiated

Allergen: tested to detect cross-reactions.



Image 1. Photoaggravated contact dermatitis due to fragrances and solar filters contained in sunscreen (Solcare®). This male consulted in our Dermatology Department due to facial eczema, and was subsequently photopatch tested (2007) with no positive result. Since suspicion of photoinduced dermatitis was still high, we insisted on strict sun protection. However, the patient experienced several outbreaks of eczema for years until new PPT was performed, being both fragrances and solar filters tested separately (2014). Sensitization to *amyl and hexyl cinnamic aldehyde* was proven, along with photoaggravated results in PPT. PACD to *isoamyl methoxycinnamate* was also demonstrated. Solcare® own product was tested, showing a photoaggravated result. Fragrances and organic solar filters avoidance allowed total recovery and the patient experienced no further outbreaks. Fragrances positivities in PPT are not only cross-reactions but can also make them putative agents of PACD o photoaggravated contact dermatitis.