

ORIGINAL ARTICLE

European photopatch test baseline series: A 3-year experience

Daniela Subiabre-Ferrer  | Altea Esteve-Martínez | Rubén Blasco-Encinas |
Concepción Sierra-Talamantes | Amparo Pérez-Ferriols | Violeta Zaragoza-Ninet

Department of Dermatology, Consorcio
Hospital General Universitario de Valencia,
Valencia, Spain

Correspondence

Daniela Subiabre-Ferrer, Department of
Dermatology, Consorcio Hospital General
Universitario de Valencia, Avenida Tres Cruces
s/n, 46014 Valencia, Spain.

Email: dani_subi@hotmail.com

Background: In 2012, a consensus was reached regarding a baseline photopatch test series on the basis of the results of a European multicentre study.

Objectives: To describe experience with the European photopatch test series.

Methods: A retrospective analysis of 116 patients tested with the European photopatch test series between 2014 and 2016 was performed.

Results: Fifty-five positive photopatch test reactions in 25 subjects were recorded, most commonly caused by the topical non-steroidal anti-inflammatory drugs ketoprofen, dexketoprofen, and etofenamate. Organic ultraviolet (UV) absorbers constituted the second main category of agents eliciting positive photopatch test reactions. Among UV absorbers, benzophenone-3 and octocrylene were the most frequent photoallergens. UV absorbers that have been introduced more recently rarely elicited positive photopatch test reactions. Positive patch test reactions were less commonly observed than positive photopatch test reactions, namely, 21 reactions in 14 patients.

Conclusions: We present the largest clinical experience with the European photopatch test baseline series hitherto reported. The results are similar to those underlying the above consensus process, reaffirming the usefulness of this series.

KEYWORDS

European photopatch test, photoallergic contact reactions, topical NSAIDs, UV absorbers

1 | INTRODUCTION

Photoallergic contact dermatitis is a delayed-type hypersensitivity reaction that occurs when an exogenous agent (photoallergen) is applied to the skin and subsequently exposed to ultraviolet (UV) and/or visible radiation.¹ Historically, several agents have been identified as photoallergens. Currently, the 2 most common groups of photoallergens are organic UV absorbers used in sunscreens and topical non-steroidal anti-inflammatory drugs (NSAIDs). The frequency of positive photopatch test reactions is unknown, but they are thought to be uncommon, with frequencies of 2%-10% having been reported among patients referred for investigation of dermatitis on photoexposed skin. The investigation of choice for the diagnosis of photoallergic contact dermatitis is photopatch testing.²

In 2012, a consensus photopatch test series was established on the basis of the results of a European multicentre study³ that was conducted in 30 different hospitals between 2008 and 2011, on

previous publications reporting photoallergy and on the presence or absence of these agents in consumer products within the European market.^{4,5} Twenty substances were chosen to constitute the European photopatch test baseline series, and 15 additional substances that might be important to study in selected cases were recommended to be included in an extended photopatch test series.⁶

The European photopatch test series has been routinely tested in our department since May 2014 in patients referred for photopatch testing. The aim of this study was to analyse the data from patients who underwent photopatch testing with the European series at our department during the period between May 2014 and December 2016.

2 | METHODS

During the period May 2014 to December 2016, all consecutive patients undergoing photopatch testing at the dermatology

TABLE 1 Positive photopatch and patch test reactions

Allergen	Positive photopatch test reactions	Positive patch test reactions
Ketoprofen	16	1
Dexketoprofen	16	1
Etofenamate	7	6
Fenofibrate	6	0
Diclofenac	2	2
Benzophenone-3	2	2
Benzophenone-10	2	0
Chlorpromazine	2	0
Octocrylene	1	1
Triclosan	1	0
Fragrance mix I	0	4
Decyl glucoside	0	2
Butyl methoxydibenzoylmethane	0	1
4-Methylbenzylidene camphor	0	1

department of Hospital General de Valencia, Valencia, Spain were included. Photopatch testing was conducted according to the European consensus methodology.² The European photopatch series was applied to the skin of the mid-back with Finn Chambers (Biodiagnostics, Upton on Severn, UK) in duplicate. The allergens included were all from the European photopatch series—both the baseline series and the extended series⁴—supplemented with fragrance mix I (FM I) 8% pet. and decyl glucoside 5% pet.

After 24 hours, the test preparations were removed, and 1 series was exposed to broadband UVA (5 J/cm², 310-400 nm, Waldmann UVAL 801; Herbert Waldmann, Villingen-Schwenningen, Germany), whereas the other set was shielded from light exposure. The readings were performed on day (D) 2, immediately after removal of the patches and application of UV irradiation, and then on D4, 2 days later. All reactions were graded according to ESCD/ICDRG criteria.⁷ The relevance of positive photopatch test reactions was assessed on the basis of the patient's history and the presence of the allergen(s) in the list of ingredients of the products used by the patients at the sites of dermatitis that motivated photopatch testing (present relevance), or at the sites of previous dermatitis (past relevance), or the allergens found in photopatch testing not being apparently related to a previous dermatitis (uncertain relevance). All patients were additionally patch tested with the Spanish Contact Dermatitis and Cutaneous Allergy Research Group (GEIDAC) baseline series⁸ at the same time, and evaluated on D2 and D4; the results were interpreted as above.

3 | RESULTS

Photopatch testing was performed in 116 patients (80 women and 36 men; mean age 55.9 years, range 18-93 years). In total, 31 (26.7%) of the 116 patients had at least 1 positive reaction. In these patients, the median number of positive reactions was 2.4 per patient, and 41.9% had ≥ 3 positive reactions. A total of 76 positive reactions (including photopatch and patch test reactions) were recorded.

**FIGURE 1** Positive photopatch test reactions to ketoprofen, dexketoprofen and etofenamate on day 4**FIGURE 2** Positive photopatch test reactions to benzophenone-3, octocrylene, ketoprofen and fenofibrate on day 4

Positive photopatch test reactions (55/76) were more frequently observed than positive patch test reactions (21/76).

A total of 55 positive photopatch test reactions in 25 (21.5%) patients were recorded; the results are shown in Table 1. Topical NSAIDs were the most frequent causes, eliciting 41 positive photopatch test reactions. Among these, ketoprofen and dexketoprofen (16 each) were the most frequent causes, and 11 patients had positive reactions to both NSAIDs and to piktetoprofen. Etofenamate elicited 7 positive photopatch test reactions (Figure 1) and diclofenac elicited 3. Two of these patients had been topically exposed to 3% diclofenac for the treatment of actinic keratosis, and 1 had been exposed to 1% diclofenac for pain treatment.

Organic UV absorbers constituted the second most frequent cause of positive photopatch test reactions. Among UV absorbers, benzophenone-3 and octocrylene most frequently elicited positive reactions (Figure 2). A few further positive photopatch test reactions were seen to fenofibrate, chlorpromazine, and triclosan. No photoaggravated contact reactions were observed.

Among the patients who had been photopatch tested, a total of 21 positive patch test reactions in 14 (12.1%) patients were recorded

TABLE 2 Relevance for positive photopatch test reactions

Allergen	Current, n (%)	Past, n (%)	Uncertain, n (%)
NSAIDs	29 (56.9)	19 (37.2)	3 (5.9)
UV absorbers	8 (56.9)	0	4 (33.3)
Fenofibrate	0	0	6 (100)
Fragrance mix I	2 (50)	2 (50)	0
Chlorpromazine	0	0	2 (100)
Triclosan	0	0	1 (100)

NSAID, non-steroidal anti-inflammatory drug; UV, ultraviolet.

(Table 1). Topical NSAIDs were the agents most frequently eliciting positive patch test reactions (in 10 cases), most often to etofenamate ($n = 6$) and diclofenac ($n = 2$). Organic UV absorbers constituted the second main category of agents eliciting positive patch test reactions, namely to benzophenone-3 in 2 cases, to octocrylene in 1 case, and to the surfactant decyl glucoside in 2 cases. Among the baseline patch test series allergens, 12.7% positive reactions to methylchloroisothiazolinone/methylisothiazolinone (MI) or to MI alone were seen that were considered to be current clinically relevant.

Analysis of clinical relevance showed that the majority (51.3%) of positive reactions were of current relevance, 27.6% were of past relevance, and 21.1% were of uncertain relevance. The relevance of each allergen is shown in Table 2. Current relevance was documented in 56.9% of patients with positive reactions to topical NSAIDs and UV absorbers.

Concerning the groups of (photo)allergens, NSAIDs were the most frequent allergens in our study (51 positive reactions in 27 patients). Positive photopatch test reactions (41/51) were more frequent than positive patch test reactions (10/51). Current relevance concerning topical NSAIDs was found for 56.9% of reactions. Ketoprofen and dexketoprofen most frequently elicited positive photopatch test reactions, followed by etofenamate, the latter being the agent most frequently eliciting positive patch test reactions. Among NSAIDs, diclofenac was the third commonest cause of photoallergic reactions. Ten of 27 (37%) of patients with positive reactions to NSAIDs showed co-sensitizations, mainly to fenofibrate (6 patients), UV absorbers (octocrylene and benzophenone-3) (4 patients), and FM I (2 patients).

UV absorbers were the second most frequent allergens in our study, with 12 positive reactions in 10 patients. Positive patch test reactions (6/12) were more frequent than positive photopatch test reactions (4/12). The most common agents were benzophenone-3 (4 patients) and octocrylene (2 patients). The surfactant decyl glucoside elicited 2 positive patch test reactions. Butyl methoxydibenzoylmethane and 4-methylbenzylidene camphor elicited 1 positive patch test reaction each. Analysis of clinical relevance showed that UV absorbers were commonly assigned current relevance (56.9%). Seven of 10 subjects with positive reactions to UV absorbers showed co-sensitizations, mainly to NSAIDs and fenofibrate (6 patients).

Fenofibrate was the third commonest cause of positive photopatch test reactions. All reactions were considered to be cross-reactions with NSAIDs and UV absorbers, because none of the patients had previously been exposed to this drug. FM I elicited 4 positive patch test reactions, chlorpromazine elicited 2 positive patch test reactions, and triclosan elicited 1 positive photopatch test reaction.

4 | DISCUSSION

To our knowledge, the current study represents the largest reported clinical experience with the European photopatch test baseline series up to now. Overall, the frequency of positive photopatch test reactions was similar to that recorded in the European multicentre photopatch study, in which 19.4% positive reactions were seen.³

Positive photopatch test reactions were most commonly caused by topical NSAIDs. Previous studies have suggested that ketoprofen could be a potent photoallergen, with cross-reactions to various photosensitizers, some of which have structural similarities. Ketoprofen and dexketoprofen showed co-sensitization with the UV absorbers benzophenone-3 and octocrylene, fenofibrate, and also with FM I, as in previous reports. The cross-reactivity between ketoprofen and fenofibrate and benzophenones is well known, and involves the benzophenone moiety of ketoprofen. A possible explanation for the co-sensitization with fragrances could be the presence of an aldehyde function in ketoprofen and cinnamal, which is a component of FM I.^{9–12}

Authorities have taken account of these findings, and have promoted changes in recommendations for patients and regulation of topical NSAIDs on the market (prescription only by clinicians, and warnings given to the patients about the risks of photoreactions). The same was done by sunscreen manufacturers who limited the use of benzophenone-3 and octocrylene in sunscreens because of its relation with photoreactions in previously ketoprofen sensitized individuals.

The topical NSAID etofenamate caused the second largest number of positive photopatch test reactions. This anthranilic acid derivative is often used in Mediterranean countries, which explains why its relevance could be fully established in most sensitized individuals. Etofenamate also elicited many positive patch test reactions, being the leading patch test allergen, which may suggest that it has photoallergenic and allergenic properties.^{13,14} Diclofenac was the third commonest cause of positive photopatch test reactions. Its ongoing use for the treatment of actinic keratosis may lead to an increased number of photoreactions.

Organic UV absorbers constituted the second main category of agents eliciting positive photopatch test reactions. Benzophenone-3 and octocrylene elicited positive reactions more frequently than previously reported. Octocrylene is both a photocontact allergen and a contact allergen. It can cause contact allergy probably because of its reactivity towards lysine. Co-sensitization with NSAIDs was frequently found, but so was co-sensitization with fenofibrate, similarly as with NSAIDs. Photosensitivity to ketoprofen is linked with that to benzophenone-3 in the majority of cases, but also with that to octocrylene. The reverse is also possible, but this hypothesis needs further investigation.^{15–17} The “newer” organic UV absorbers did not elicit any reactions. It is of note that 2 patients with positive patch test reactions to sunscreens containing Tinosorb M showed positive patch test reactions to decyl glucoside but not to methylene bis-benzotriazolyl tetramethylbutylphenol (MBBT). In accordance with our results, the European multicentre photopatch test study task force found that Tinosorb M was the agent most frequently eliciting positive patch test reactions.³ Further studies showed that, in most published cases with positive patch test reactions to Tinosorb M, positive

patch test reactions to decyl glucoside were found, but not to pure MBBT. This stresses the importance of individually including the surfactant and the pure sunscreen in the photopatch test, as in our study.^{18–20}

Fenofibrate reactions were of uncertain relevance in all positive patients, and co-sensitization with other allergens such as ketoprofen, octocrylene and benzophenone-3 was found, which is why we consider fenofibrate reactions to be cross-reactions.

It has to be emphasized that the patch test baseline series should also be tested when suspected “sun-exposed dermatitis” is investigated, because (photoaggravated) allergic contact dermatitis, for example, to isothiazolinones can mimic photoallergic contact dermatitis, as shown in our patients and as previously described in the literature.^{21–28}

In conclusion, our results are in accordance with those published for the consensus photopatch test series. They stress the usefulness of the European photopatch test baseline series.

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Conflict of interest

The authors declare no potential conflict of interests.

ORCID

Daniela Subiabre-Ferrer  <http://orcid.org/0000-0001-8818-4948>

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