

Photopatch tests: an Italian multicentre study from 2004 to 2006

PAOLO DANIELE PIGATTO¹, GIANPAOLO GUZZI², DONATELLA SCHENA³, MARCELLA GUARRERA⁴,
CATERINA FOTI⁵, STEFANO FRANCALANCI⁶, ANTONIO CRISTAUDO⁷, FABIO AYALA⁸ AND COLOMBINA VINCENZI⁹

¹Department of Technology for Health, IRCCS, Galeazzi Dermatological Clinic, University of Milan, Via Galeazzi 4, 20161 Milan, Italy, ²Italian Association for Metals and Biocompatibility Research, 20122 Milan, Italy, ³Department of Biomedical and Surgical Science, Dermatology Section, University of Verona, 37100 Verona, Italy, ⁴Section of Dermatology, DISEM, University School of Medicine, 16132 Genova, Italy, ⁵Department of Internal Medicine, Immunology and Infectious Diseases, Unit of Dermatology, University of Bari, 70124 Bari, Italy, ⁶Department of Dermatological Sciences, University of Florence, 50121 Florence, Italy, ⁷San Gallicano Dermatological Institute, IRCCS, 00144 Rome, Italy, ⁸Department of Dermatology, University of Naples Federico II, 80131 Napoli, Italy, and ⁹Department of Dermatology, University of Bologna, 40126 Bologna, Italy

Background: Evaluation of possible photoallergic contact dermatitis in at-risk populations is often not undertaken, and an agreed methodology for investigation is uncommonly used.

Objectives: We conducted a retrospective multicentre study to determine the prevalence of photoallergic contact dermatitis in Italy.

Methods: A total of 1082 patients with histories and clinical features suggestive of photoallergic contact dermatitis were evaluated. All the patients had undergone photopatch testing with allergens proposed for Italy as well as other substances suggested by each patient's personal history.

Results: 234 patients (21.6%) were positive to at least one test substance of the standard photopatch testing series or to added substances. 234 patients (21.6%) were positive to at least one substance with a total of 290 reactions. 204 of the reactions were typically photoallergic; 68 reactions were allergic and within this group 10 were photoaugmented reactions; 18 reactions were considered to be phototoxic.

Conclusion: The predominant group of photoallergens was drugs, followed by organic UV filters and antimicrobial agents.

Key words: photoallergic contact dermatitis; photopatch tests; topical arylpropionic derivatives; topical non-steroidal anti-inflammatory drugs; ultraviolet filters. © Blackwell Munksgaard, 2008.

Accepted for publication 22 February 2008

Cases of photoallergic contact dermatitis, caused by the exposure to ultraviolet (UV) radiation on topically applied chemical substances, are uncommonly encountered in clinical practice, accounting for about 10% of all photodermatoses (1). The prevalence of photoallergic contact dermatitis in the general population is unknown. Many substances have been described as 'photoallergens', for example halogenated salicylanilides, sulfonamides, and musk ambrette, but the incidence of reactions has varied over the years as they have been excluded from use or largely replaced by other substances in cosmetics, pharmaceutical, and industrial products.

Photopatch testing is the clinical investigation for evaluating suspected photoallergic contact dermatitis but is underused in Europe and worldwide. There is a lack of standardization in photopatch testing throughout Europe. Although there have been some attempts at uniformity in the past (1–8), even the most recent literature shows significant differences in methodology (9–12): agents used, their test concentration, and interpretation of results. An agreed methodology should respond to local photoallergen exposure patterns. Only a few published studies have dealt with the incidence of photocontact allergy in Italy. In our 1996

multicentre survey of photoallergic contact dermatitis, we attempted to evaluate and standardize diagnostic methods (7). In this study, we tried to standardize photopatch testing after a decade of monitoring changes in the epidemiology of old and new photoallergens.

Patients and Methods

A total of 1082 patients, recruited from eight centres (Table 1) with histories and clinical features suggestive of possible photoallergic contact dermatitis, were assessed.

It was agreed that the primary inclusion criterion should be dermatitis predominantly affecting light-exposed sites, with or without a personal history of sunscreen and/or topical non-steroidal anti-inflammatory drugs reaction. Photopatch testing was also considered in patients with confirmed chronic actinic dermatitis and individuals with a photosensitive eruption without any overt manifestations of dermatitis.

All patients were tested using the series (Table 2) (available through Lofarma, Firma, Hermal-Trolab, or Chemotechnique) proposed in 2004 by the Società Italiana di Dermatologia Allergologica Professionale e Ambientale (SIDAPA), which was based on a European study (13), together with other allergens indicated by the history of each patient. The additional agents used varied among centres. All allergens were diluted in accordance with published information (13).

In our previous multicentre study, photopatch testing focused on topical drugs and organic UV filters and included products suggested by the patient (14–18).

As drometrizole trisiloxane was unavailable on the market, the commercial sunscreen Anthelios™ XL 50+ from LaRoche Posay (Milan, Italy) was tested, and a reaction was considered to have occurred to drometrizole trisiloxane if there was a reaction to the commercial product but not to the other available ingredients of it.

The procedure for photopatch testing involved the application of the photoseries of allergens in duplicate for 2 days to the skin on the upper back,

avoiding 3–5 cm on either side of the spine in I.Q. Chambers™ (Chemotechnique Diagnostics, Malmö, Sweden). At D2, both series were removed and any reaction recorded. Then, with one series covered by opaque material, the other was irradiated with 5 J/cm² UVA (previously 3–10 J/cm²) measured by a radiometer (PUVA meter; Waldmann, VS-Schwenningen, Germany) used for PUVA therapy. Further readings were made at D4 (2D postirradiation) according to the International Contact Dermatitis Research Group scheme. In cases where there was a slight erythema, an additional reading was made at D7.

As the type of lamp used for photoirradiation of allergens may affect the findings (17), PUVA fluorescent lamps were chosen because of their availability, reproducible spectrum, and beam uniformity even though they do emit a small percentage of UVB.

Reactions were interpreted according to the following scheme:

- (1) Photocontact allergy was diagnosed when only the irradiated allergen was positive and the other did not show any reaction. It was agreed that a positive reaction to an allergen after irradiation in the presence of negative controls strongly supported a photoallergic mechanism.
- (2) Contact allergy was diagnosed when allergens in both irradiated and control panels were positive.
- (3) Negative when unirradiated and irradiated sites were negative.
- (4) Photoaugmented contact reaction (contact reaction stronger in the irradiated panel than in the unirradiated site).
- (5) Photoinhibited contact reaction (contact reaction weaker in the irradiated panel than in the unirradiated site).
- (6) Phototoxic type (occurring in photoirradiated panel showing a decrescendo pattern).
- (7) Irritant reaction (occurring in one or both panels showing a decrescendo pattern).

Finally, to determine relevance, patients with positive reactions were re-evaluated on the basis of their clinical history, presence of the allergen, and the existence of an appropriate temporal relationship between UV exposure and the appearance of dermatitis.

Results

Our study population of 1082 patients had a mean age of 44.27 years (16–86 years) with a median age of 41 years; females predominated (602; 55.6%) over males (480; 44.4%).

Table 1. Centres participating in the study

Centre	Tested patients	Positive patients
Genova	174	38
Verona	223	70
Roma	92	22
Bologna	29	5
Firenze	84	38
Bari	78	20
Milano	319	89
Napoli	43	15

Table 2. Photopatch tests: baseline series proposed by Società Italiana di Dermatologia Allergologica Professionale e Ambientale (SIDAPA)

INCI	INN	Common chemical names	CAS	Trade/other names	Vehicle petrolatum (%)
Benzophenone-4 Ethylhexyl triazone	Sulisobenzone	5-benzoyl-4-hydroxy-2-methoxybenzenesulfonic acid Benzoic acid, 4,4',4'-(1,3,5-triazine-2,4,6-triyltriumino)tris, tris(2-ethylhexyl) ester	4065-45-6 88122-99-0	Uvinul T150	10 5
4-methylbenzylidene camphor		(±)-1,7,7-trimethyl-3-[(4-methylphenyl)methyl]enebicyclo[2.2.1]heptan- 2-one	36861-47-9/38102- 62-4	Eusolex 6300	10
Isoamyl <i>p</i> -methoxycinnamate		Isopentyl <i>p</i> -methoxycinnamate	71617-10-2	Neo Heliopan E1000	10
Benzophenone-10	Mexenone	2-hydroxy-4-methoxy-4'-methylbenzophenone	1641-17-4		10
PABA	Aminobenzoic acid	4-aminobenzoic acid	150-13-0		5
Ethylhexyl dimethyl PABA		2-ethylhexyl 4-(dimethylamino)benzoate	21245-02-3	Eusolex 6007	10
Butyl methoxydibenzoylmethane	Avobenzone	1-[4-(1,1-dimethylethyl)phenyl]-3-(4-methoxyphenyl)propane-1,3-dione	70356-09-1	Eusolex 9020	10
Benzophenone-3	Oxybenzone	2-hydroxy-4-methoxybenzophenone	131-57-7	Eusolex 4360	10
Homosalate	Homosalate	Benzoic acid, 2-hydroxy-, 3,3,5-trimethylcyclohexyl ester	118-56-9	Eusolex HMS	5
Drometrizole trisiloxane		Phenol, 2-(2h-benzotriazol-2-yl)-4-methyl-6-[2-methyl-3- [1,3,3,3-tetramethyl-1-[(trimethylsilyl)oxy]disiloxanyl]- 2-propenoic acid, 2-cyano-3,3-diphenyl-, 2-ethylhexyl ester	155633-54-8	Silatrizole	5
Octocrylene	Octocrylene	2-propenoic acid, 2-cyano-3,3-diphenyl-, 2-ethylhexyl ester	6197-30-4	Eusolex OCR	5
Phenylbenzimidazole sulfonic acid		2-phenylbenzimidazole-5-sulfonic acid	27503-81-7	Eusolex 232	10
Ethylhexyl methoxycinnamate petrolatum		2-ethylhexyl 4-methoxycinnamate	5466-77-3	Eusolex 2292	10
	Fenticlor	Bis(2-hydroxy-5-chlorophenyl)sulfide	97-24-5		As is
	Bithionol	2,2'-thio bis(4,6-dichlorophenol)	97-18-7		1
	Ketoprofen	2-(3-benzoylphenyl)propanoic acid	22071-15-4		1 5 2.5
	Ibuprofen	2-[4-(2-methylpropyl)phenyl]propanoic acid	15687-27-1		1 5
	Ibuprofen	<i>N</i> -hydroxy-2-[4-(2-methylpropyl)phenyl]propanamide	Unavailable		5
	Promethazine	<i>N,N</i> -dimethyl-1-(10H-phenothiazin-10-yl)propan-2-amine	60-87-7		10
	Dichlorophene	2,2'-methylenebis(4-chlorophenol)	97-23-4		10
	Triclocarban	3,4,4'-trichlorocarbanilide	101-20-2		5
	Chlorhexidine digluconate		18472-51-0		0.1
	Etofenamate	2-(2-hydroxyethoxy)ethyl 2-[[3-(trifluoromethyl)phenyl]amino]benzoate	Unavailable		10
	Proxicam	(8E)-8-[hydroxy-(pyridin-2-ylamino)methylidene]-9-methyl-10, 10-dioxo-10λ6-thia-9-azabicyclo[4.4.0] deca-1,3,5-trien-7-one	36322-90-4		10

CAS, Chemical Abstracts Service; INCI, International Nomenclature of Cosmetic Ingredients; INN, International Nonproprietary Names; PABA, *para*-aminobenzoic acid.

The majority of the patients were referred to our clinical centres for problems of dermatitis on light-exposed sites (492 patients; 45.47%) or intolerance to UV filters or anti-inflammatory drugs (413 patients; 38.17%). There was also a small group with confirmed chronic actinic dermatitis (29 patients; 2.68%) and a heterogeneous group of patients with an undetermined photosensitive eruption (148 patients; 13.68%). We did not include patients with abnormal UVA sensitivity in this study.

A total of 234 patients (21.6%) were positive to at least one substance (Table 3) with a total of 290 reactions. About 204 of the reactions were typically photoallergic; 68 reactions were allergic and within this group, 10 were photoaugmented reactions; and 18 reactions were considered to be phototoxic. The predominant group of photoallergens was drugs, followed by organic UV filters.

Current clinical relevance was found to be high (75% of the positive allergens) for almost all the

drugs and UV filters but low for perfumes and antimicrobials (Table 3).

Discussion

Most of our patients were female, but with respect to the total number of participants with photo-dermatitis, the proportion of male patients compared with female patients affected by photo-contact dermatitis was greater than ordinary contact dermatitis. Photodermatitis is more frequent in the fifth decade of life, perhaps because for outdoor activities and hobbies.

The most frequent photoallergen was ketoprofen with 110 photoallergic results. It is an arylpropionic-derivative topical anti-inflammatory drug, which is widely used in the Mediterranean area on minor injuries. Ketoprofen is established as an important photosensitizer causing cutaneous reactions with a frequency estimated between 0.008% and 0.023% (18). These reactions are

Table 3. Photopatch test results

Allergen	Total positive reactions	Photoallergic type 1 positive reactions	Allergic contact dermatitis (photoaugmented)	Irritative / phototoxic reactions	Current relevance
Arylpropionic derivatives	116	102	14		100
Ketoprofen	110	97	13		
Ibuprofen	5	4	1		
Ibuprofen	1	1			
Octocrylene	23	14	9		18
Piroxicam	19	10	3	6	18
Fentichlor	16	10	3	4	1
Benzophenone-10	16	9	7		14
Benzophenone-3	15	9	6		13
Ethylhexyl methoxycinnamate	13	10	2	1	11
Promethazine	12	3	3	6	12
Butyl methoxydibenzoylmethane	9	5	4		8
Fragrance mix I	8	5	3		1
Drometizole trisiloxane	5	5			5
Trichlorocarbonyl	5	1	3	1	0
Isoamy <i>p</i> -methoxycinnamate	4	3	1		4
Dichlorophene	4	1	3		2
Benzophenone-4	3	2	1		3
Bithionol	3	2	1		0
Chlorhexidine digluconate	3	2	1		3
PABA	2	2			2
Musk mix	2	1	1		0
Tribromosalicylanilide	2	1		1	0
Ethylhexyl triazone	2	1	1		1
Polyethylene glycol-25 PABA	1	1			1
Sesquiterpene lactone mix	1		1		0
4-methylbenzylidene camphor	1	1			0
Ethylhexyl dimethyl PABA	1	1			1
Thiourea	1		1		1
Triclosan	1	1			0
6-methyl coumarin	1	1			0
Etofenamate	1	1			1
Homosalate	0	0			0
Phenylbenzimidazole sulfonic acid	0	0			0
Total	290	204	68 (10)	19	220 (75%)

PABA, *para*-aminobenzoic acid.

mediated by UV-induced decomposition products of ketoprofen that peroxidate membrane lipids of cutaneous cells and provoke the formation of new antigens (19, 20). Phototoxic reactions to ketoprofen were absent in our patients. However, simple allergic reactions were common, and these reactions were persistent; accordingly, we propose to reduce the concentration of ketoprofen in the testing material from 5% to 2.5% or, in particular cases, down to 1% to avoid strong reactions. The other arylpropionic drugs – ibuprofen and ibuprofen – caused fewer reactions (five and one, respectively) and, therefore, can continue to be tested at a concentration of 5%.

The second most frequent drug causing reactions was piroxicam with 10 photoallergic and 6 phototoxic reactions followed by promethazine, a topical antihistamine widely self-prescribed in Italy for the treatment of sunburn and insect bites. Promethazine also showed a high prevalence of phototoxic reactions (6 of a total of 19 reactions) versus photoallergic reactions (three positives). Promethazine and piroxicam together accounted for almost all the phototoxic reactions (12 of 14 reactions).

Reactions to organic UV filters were more common (95 positives) than in our previous survey (7), but almost half of the UV filters reactions were of a simple allergic type. Octocrylene was the prime allergen of this group. It is a UV filter of the cinnamate family used for UVB and near UVA radiations protection and because of its photostability as adjuvant in sunscreen preparations.

Reactions to other UV filters, in decreasing order, were to benzophenone-10, benzophenone-3, ethylhexyl methoxycinnamate, and butyl methoxydibenzoylmethane.

Anthelios XL 60 (now 50+) produced five reactions, all of which were relevant. We considered that drometrizole trisiloxane (Mexoryl™ XL, Milan, Italy) was the allergen when octocrylene, present in Anthelios, was negative. However, we were able to test only two of these patients with 5% drometrizole trisiloxane (supplied by L'Oréal, Milan, Italy) in petrolatum, and in both patients, a reaction occurred at the photoirradiated sites.

Fentichlor is an allergen that showed a high rate of both allergic and photoallergic sensitivity but a very low relevance rate. Bithionol and chlorhexidine digluconate showed a very low incidence.

The fragrance mix produced a high number of reactions but a low grade of relevance; almost all reactions were evaluated as cross-reactions in patients allergic to ketoprofen. In a previous study, we have considered cross-reactions occurring between ketoprofen and cinnamal, a component of the fragrance mix (21). Therefore, we

thought that in general, fragrances are not photohaptens but cross-reacting agents.

There were only two reactions to the musk mix, one contact and one photocontact. This mix is a 3% mix (Chemotechnique, Malmö, Sweden) of synthetic nitro musk compounds (musk xylene 1%, musk moskene 1%, and musk ketone 1%), which have been used in fragrances.

Conclusions

Our study highlights differences in comparison with the results of our pilot study and, given the small size of the population available, suggests that photopatch testing should be used only by centres able to evaluate the results properly.

On the basis of the present results, we propose changing our recommended photopatch test series by introducing new allergens and modifying concentrations: etofenamate, homosalate, 4-methylbenzylidene camphor, phenylbenzimidazole sulfonic acid, and ethylhexyl dimethyl PABA should be used only by reference to the patient's history and ketoprofen tested at the 2–5% concentration.

Standard fragrance mix chemicals should be considered as improbable photoallergens but that may cross-react with other photohaptens, particularly ketoprofen.

We plan to conduct another study with this new series in the next 4–5 years and to continue monitoring because the problem of photoallergic contact dermatitis is continuously changing.

References

1. Pigatto P D, Legori A, Bigardi A S et al. Gruppo Italiano Ricerca Dermatiti da Contatto ed Ambientali. Italian Multicentre Study of Allergic Contact Photodermatitis: epidemiological aspects. *Am J Contact Dermat* 1996; 7: 158–163.
2. Jansen C T, Wennersten G, Rystedt I, Thune P, Brodthagen H. The Scandinavian standard photopatch test procedure. *Contact Dermatitis* 1982; 8: 155–158.
3. Wennersten G, Thune P, Brodthagen H, Jansen C, Rystedt I. The Scandinavian multicentre photopatch study. *Contact Dermatitis* 1984; 10: 305–309.
4. Holzle E, Neumann N, Hausen B, Przybilla B, Schauder S, Honigsmann H, Bircher A, Plewig G. Photopatch testing: the 5-year experience of the German, Austrian and Swiss photopatch test group. *J Am Acad Dermatol* 1991; 25: 59–68.
5. British Photodermatology Group. Workshop report – photopatch testing – methods and indications. *Br J Dermatol* 1997; 136: 371–376.
6. Neumann N J, Holzle E, Lehmann P, Benedikter S, Tapernoux B, Plewig G. Pattern analysis of photopatch test reactions. *Photodermatol Photoimmunol Photomed* 1994; 10: 65–73.
7. Guarrera M. Photopatch testing: a three-year experience. *J Am Acad Dermatol* 1989; 21: 589–591.
8. Leonard F, Charlier C, Jeanmougin M, Manciet J R, Rousselin X, Kalis B. La batterie des photopatch tests en France. *Nouv Dermatol* 1992; 11: 290–293.

9. Berne B, Ros A-M. 7 years experience of photopatch testing with sunscreen allergens in Sweden. *Contact Dermatitis* 1998; 38: 61–64.
10. Darvay A, White I R, Rycroft R J G, Jones A B, Hawk J L M, McFadden J P. Photoallergic contact dermatitis is uncommon. *Br J Dermatol* 2001; 145: 597–601.
11. Neumann N J, Holzle E, Plewig G et al. Photopatch testing: the 12-year experience of the German Austrian, and Swiss photopatch test group. *J Am Acad Dermatol* 2000; 42: 183–192.
12. Bakkum R S L A, Heule F. Results of photopatch testing in Rotterdam during a 10-year period. *Br J Dermatol* 2002; 146: 275–279.
13. Bruynzeel D P, Ferguson J, Andersen K et al. Photopatch testing: a consensus methodology for Europe. *J Eur Acad Dermatol Venereol* 2004; 18: 679–682.
14. Schauder S, Ippen H. Contact and photocontact sensitivity to sunscreens: review of a 15-year experience of the literature. *Contact Dermatitis* 1997; 37: 221–232.
15. Durbize E, Vigan M, Puzeat E et al. Spectrum of cross-photosensitization in 18 consecutive patients with contact photoallergy to ketoprofen: associated photoallergies to non-benzophenone-containing molecules. *Contact Dermatitis* 2003; 48: 144–149.
16. Przybilla B, Holzle E, Enders F, Gollhausen R, Ring J. Photopatch testing with different ultraviolet A sources can yield discrepant test results. *Photodermatol Photoimmunol Photomed* 1991; 8: 57–61.
17. Bryden A M, Moseley H, Ibbotson S H et al. Photopatch testing of 1155 patients: results of the U.K. multicentre photopatch study group. *Br J Dermatol* 2006; 155: 737–747.
18. Baudot S, Milpied B, Larousse C. Cutaneous side effects of ketoprofen gels: results of a study based on 337 cases. *Therapie* 1993; 53: 137–144.
19. Baudot S, Milpied B, Larousse C. Ketoprofene gel et effets secondaires cutanés; bilan d'une enquête sur 337 notifications. *Therapie* 1998; 53: 137–144.
20. Bagheri H, Lhiaubet V, Montastruc J L, Chouini-Lalanne N. Photosensitivity to ketoprofen. *Drug Saf* 2000; 22: 339–349.
21. Pigatto P, Bigardi A, Legori A, Valsecchi R, Picardo M. Cross reactions in patch testing and photopatchtesting with ketoprofen thiaprofenic acid and cinnamic aldehyde. *Am J Contact Dermatitis* 1996; 7: 220–223.

Address:

Prof. Paolo D. Pigatto, M.D.
Department of Technology for Health
Dermatological Clinic
Italy
Via R. Galeazzi 4
20161 Milan, Italy
Tel: 02-662 141
Fax: 02-662 148 00
e-mail: paolo.pigatto@unimi.it