Acta Dermatovenerol Croat 2013;21(4):230-235 CLINICAL ARTICLE

The Frequency and Causes of Photoallergic Contact Dermatitis among Dermatology Outpatients

***Radoslaw Spiewak*[1,2]**

[1]Department of Experimental Dermatology and Cosmetology, Faculty of Pharmacy, Jagiellonian University Medical College, [2]Institute of Dermatology, Krakow, Poland

Corresponding author:
Prof. Radoslaw Spiewak, MD, PhD
Department of Experimental Dermatology and Cosmetology
Faculty of Pharmacy, Jagiellonian University
ul. Medyczna 9
30-688 Krakow
Poland
spiewak.eu@gmail.com

Received: August 21, 2012
Accepted: October 15, 2013

SUMMARY Too many patients with photoallergy remain undiagnosed due to unsatisfactory knowledge among doctors and limited access to photopatch testing. The objectives of this study were to analyze the frequency of patients requiring diagnostic work-up for photoallergic contact dermatitis among dermatology patients, and to identify the causative photosensitizers. This prospective study involved 1000 consecutive, first-referred dermatology outpatients. All patients with a history of dermatitis induced or aggravated by exposure to light were qualified for photopatch testing. In the study group, 36 (3.6%; 95%CI: 2.4-4.8%) persons required photopatch testing based on their clinical symptoms. As the total number of patients requiring patch tests of any kind amounted to 205, the percentage of photopatch tested patients among all patch-tested patients was 17.5% (95%CI: 12.2-22.8%). Photoallergic contact dermatitis was ultimately confirmed in 15 (1.5%; 0.7-2.3%) persons: 7 females and 8 males aged 6-60 (median 33) years. Nine patients turned out photoallergic to at least one nonsteroidal anti-inflammatory drug, with ketoprofen photoallergy being most frequent (5 patients, in each case clinically relevant), followed by etofenamate (4 non-relevant reactions) and diclofenac (1 relevant reaction). Five patients were positive to at least one organic sunscreen, most frequently to benzophenone-3 (2 patients). "Classical" contact allergy to tested photohaptens was found in 15 persons, including 7 with coexisting photoallergy. In conclusion, patients requiring diagnostic work-up for photoallergy constitute a relevant group among dermatology patients, therefore, it seems advisable that all second-level dermatology referral centers be capable of photopatch testing. Due attention should also be paid to photoallergy in dermatology training.

KEY WORDS: photoallergy, photopatch test, photoallergic contact dermatitis, dermatology patients, epidemiology

INTRODUCTION

Photoallergic contact dermatitis (PhotoACD) is a variant of allergic contact dermatitis (ACD), an inflammatory skin disease initiated by specific immune reactions to an exogenous hapten. It occurs in individuals with previously acquired contact allergy (type IV hypersensitivity reaction) following re-exposure to the sensitizing hapten (1). In the photoallergic variant, subsequent irradiation, typically with ultraviolet (UV) light, is required to initiate the pathologic processes. The photons deliver energy for either creating cova-

lent bonds between hapten and endogenous protein (formation of antigenic photoadducts), or converting a prohapten into the actual sensitizing hapten (2). Further immune and inflammatory processes seem not to differ between photoallergic and "classical" (i.e. not dependent on irradiation) ACD (3).

In spite of the fact that patients with PhotoACD outnumber those with phototoxic drug reactions (4), health professionals seem to be much more aware of the latter ones. This may be due to insufficient knowledge and underuse of photopatch tests in dermatology practice. Facing the growing problem of allergic skin diseases, there is a need for improving allergy services within dermatology (5). In order to achieve this, the accessibility of centers capable of diagnosing PhotoACD, as well as the amount of time assigned to teaching dermatology residents about photoallergy should be adjusted to better reflect the frequency of patients requiring diagnostic work-up for photoallergy. Unfortunately, no data are available on the frequency of PhotoACD among dermatology patients to provide solid foundation for such adjustments. The aim of the present study was, therefore, to analyze the frequency of patients requiring diagnostic work-up for PhotoACD among consecutive dermatology outpatients, and to identify the causative photosensitizers.

PATIENTS AND METHODS

This prospective observational study commenced in February 2010 and was continued until the total number of consecutive patients referred for the first time to our dermatology outpatient clinic reached 1000, which happened in February 2012. From this cohort, all patients with suspected photodermatosis were routinely qualified for photopatch testing. The inclusion criterion was a history of chronic or recurrent dermatitis of uncovered skin areas, or dermatitis induced or aggravated by exposure to light (6). All patients were photopatch tested to the baseline series of the European Multi-Centre Photopatch Test Study (EMCPPTS) taskforce (7), as listed in Table 1. Nineteen patients were additionally tested to four organic sunscreens: 4-aminobenzoic acid (PABA) 10% in petrolatum (pet.), 2-ethylhexyl-4-dimethylaminobenzoate (EHDAB, syn. octyldimethyl PABA) 10% pet., 2-hydroxy-4-methoxy-4'-methyl-benzophenone (benzophenone 10) 10% pet., and terepthalylidene

Table 1. Test series of the European Multi-Centre Photopatch Test Study taskforce (7)

No.	Hapten	CAS number	Test preparation
1	Butyl methoxydibenzoylmethane	70356-09-1	10% pet.
2	Homosalate	8045-71-4	10% pet.
3	4-Methylbenzylidene camphor	36861-47-9	10% pet.
4	Benzophenone-3 (Oxybenzone)	131-57-7	10% pet.
5	Ethylhexyl methoxycinnamate	5466-77-3	10% pet.
6	Phenylbenzimidazole sulfonic acid	27503-81-7	10 % pet.
7	Benzophenone 4 (Sulisobenzone)	4065-45-6	2% pet.
8	Drometrizole trisiloxane	155633-54-8	10% pet.
9	Octocrylene	6197-30-4	10% pet.
10	Ethylhexyl salicylate	118-60-5	10% pet.
11	Ethylhexyl triazone (Octyl triazone)	88122-99-0	10% pet.
12	Isoamyl-p-methoxycinnamate	71617-10-2	10% pet.
13	Terepthalylidene dicamphor sulphonic acid	90457-82-2	10% aqua
14	bis-Ethylhexyloxyphenol methoxyphenyl triazine	187393-00-6	10% pet.
15	Methylene bis-benzotriazolyl tetramethylbutylphenol (Bisoctrizole)	103597-45-1	10% pet.
16	Diethylamino hydroxybenzoyl hexyl benzoate	302776-68-7	10% pet.
17	Disodium phenyl dibenzimidazole tetrasulfonate	180898-37-7	10% pet.
18	Diethylhexyl butamido triazone	154702-15-5	10% pet.
19	Polysilicone-15	207574-74-1	10% pet.
20	Ketoprofen	22071-15-4	1% pet.
21	Etofenamate	30544-47-9	2% pet.
22	Piroxicam	36322-90-4	1% pet.
23	Diclofenac	15307-79-6	5% pet.
24	Ibuprofen	15687-27-1	5% pet.
25	Petrolatum (pet.) – control	-	-

Table 2. Rates of positive photopatch test results to haptens from the European Multi-Centre Photopatch Test Study series, routine testing (N=36)

Hapten	Photoallergy	"Classical" contact allergy
NSAID		
Ketoprofen 1% pet.	5 (13.9%)	0
Etofenamate 2% pet.	4 (11.1%)	1 (2.8%)
Diclofenac 5% pet.	1 (2.8%)	0
Sunscreen		
Benzophenone 3 (Oxybenzone)10% pet.	2 (5.6%)	0
Benzophenone 4 (Sulisobenzone) 2% pet.	1 (2.8%)	1 (2.8%)
Methylene bis-benzotriazolyl tetramethylbutylphenol (Bisoctrizole) 10% pet.	1 (2.8%)	1 (2.8%)
Phenylbenzimidazol sulfonic acid 10% pet.	1 (2.8%)	0
Ethylhexyl triazone (EHT, Octyl triazone) 10% pet.	1 (2.8%)	0
Diethylamino hydroxybenzoyl hexyl benzoate 10% pet.	1 (2.8%)	0
Ethylhexyl-methoxycinnamate 10% pet.	0	1 (2.8%)
Octocrylene 10% pet.	0	1 (2.8%)
Polysilicone-15 10% pet.	0	1 (2.8%)

Other substances in this series that remained negative in all patients tested: butyl-methoxy-dibenzoylmethane 10% pet.; homosalate 10% pet.; 4-methylbenzylidene camphor 10% pet.; drometrizole trisiloxane 10% aqua; ethylhexyl salicylate 10% pet.; isoamyl-p-methoxycinnamate 10% pet.; bis-ethylhexyloxyphenol methoxyphenol triazine 10% pet.; disodium phenyl dibenzimidazole tetrasulfonate 10% pet.; diethylhexyl butamido triazone 10% pet.; piroxicam 1% pet.; ibuprofen 5% pet.; pure petrolatum as control.

dicamphor sulfonic acid 10% in aqua. Ten patients were additionally tested to the Scandinavian Photopatch Test Series (Chemotechnique Diagnostics, Sweden). Patients' own drugs or cosmetics were tested in individual cases, whenever it seemed relevant. Patch tests were mounted in IQ Ultra test units (Chemotechnique Diagnostics, Sweden) on the patient's back in two identical sets mounted in and kept under occlusion for 48 hours. After removal of the mounting material, one set was irradiated with 5 J/cm^2 UVA using Waldmann 801 AL phototherapy unit, while the non-irradiated set served as the reference. Skin reactions were recorded 24 and 48 hours after irradiation. The presence of an inflammatory reaction in the irradiated set and no reaction to the same hapten in the non-irradiated area was interpreted as confirmation of photoallergy. In case of positive reactions to a hapten both on irradiated and non-irradiated site, the "classical" contact allergy was recognized (8).

RESULTS

Among 1000 consecutive dermatology outpatients, 36 persons (3.6%; 95% confidence interval (CI): 2.4-4.8%) were qualified for photopatch testing based on their symptoms: 21 females and 15 males aged 6 to 72 (median 31) years. The total number of patients requiring patch tests during the study period amounted to 205, thus the percentage of photo-patch tested patients among all patients qualified for patch testing of any kind was 17.5% (95%CI: 12.2-22.8%). Photo-ACD was confirmed in 15 (1.5%; 0.7-2.3%) persons, 7 females and 8 males aged 6 to 60 (median 33) years. Twelve (1.2%; 0.5-1.9%) patients developed positive photoallergic reactions to at least one hapten of the EMCPPTS series, including nine reacting to at least one nonsteroidal antiinflammatory drug (NSAID) and five to at least one organic sunscreen (Table 2). Five patients developed photoallergic response to more than one photohapten from the EMCPPTS series (Table 3). Results of testing 10 patients from this group to the Scandinavian Photopatch Test Series are collated in Table 4. No reactions were seen to additional organic sunscreens tested in 19 of the 36 patients. Topical ketoprofen preparations predominated among patients' own products brought for testing: three out of five ketoprofen-photoallergic patients brought one each Ketoprom® gel, Ketonal® gel, and Fastum® gel (all containing 2.5% ketoprofen) as suspected causes of their dermatitis, which was confirmed by photopatch tests. In one patient, photoallergic reactions to Advantan® cream and Nanobase® cream were observed, with all other tests negative. Another patient proved photoallergic to Vichy Capital Soleil® sunscreen. Another patient indicated TerbiGen® tablets as the suspected cause, and indeed proved photoallergic to terbinafine, which has been described in detail elsewhere (9). "Classical" contact allergy to the tested photohaptens was found in 15 out of 36 patients qualified for photopatch testing, including seven patients with coexisting photoallergy and "classical" contact allergy.

Table 3. Patients with simultaneous response to more than one photohapten from the European Multi-Centre Photopatch Test Study series (routine testing, N=36)

Photohapten	Patients				
	M, 31	F, 22	M, 48	M, 34	M, 6
Ketoprofen	+	+++			
Etofenamate	+				
Benzophenone 3 (Oxybenzone)		+	+		
Benzophenone 4 (Sulisobenzone)			+		
Diclofenac				+	
Methylene bis-benzotriazolyl tetramethylbutylphenol (Bisoctrizole)				+	
Phenylbenzimidazole sulfonic acid					+
Diethylamino hydroxybenzoyl hexyl benzoate					+

M = male; F = female; photopatch test reactions scored according to the ICDRG scale (8)

DISCUSSION

The present study demonstrated ketoprofen to be a potent photosensitizer. Until 2011, topical ketoprofen preparations were sold in Poland as over-the-counter drugs. During this period, TV networks were regularly broadcasting commercials featuring young people with sport injuries, who could continue their outdoor activities after using the advertised ketoprofen preparations, which ironically seems to be a blueprint for acquiring photoallergy to this drug. Ketoprofen, nevertheless, could never match the popularity of another NSAID, ibuprofen: in a recent survey, 16% of 130 young people admitted using ibuprofen regularly, while none in this group reported ever using ketoprofen (10). In spite of such clear ibuprofen predominance, photosensitization to ketoprofen was found in five participants of the present study, whilst none reacted to ibuprofen, which was also included in the routine photopatch test series. This suggests that ketoprofen may possess certain biological properties predisposing to photosensitization, in analogy with the most frequent "classical" hapten nickel that has sensitized approximately 65 million people in Europe due to widespread exposure (11,12), but also its unique biological properties, as reviewed elsewhere (13). Photosensitizing potency of ketoprofen calls for appropriate actions, like placing a black box warning on the product package that the drug must not be applied on sun-exposed skin areas or taken orally before sun exposure. With regard to reducing the risk of photosensitization to ketoprofen, a change is proposed of drug delivery route to the transdermal delivery system covered with a UV-opaque material (e.g., a layer of metal foil). Data from pharmacodynamics and phototosensitivity studies indicate, however, that such UV protection should be continued for 2 weeks after concluding ketoprofen application, which may seem rather unpractical, thus patient compliance is not warranted (Dr Richard Guy, symposium communication in Malmö, Sweden, June 13, 2012).

In contrast to ketoprofen, where clinical relevance of positive photopatch test results was confirmed in all patients, etofenamate with a comparable sensitization rate remains a mystery: all patients with posi-

Table 4. Positive photopatch test reactions to haptens from the Scandinavian Photopatch Test Series (supplementary testing, N=10)

Hapten	Photoallergy	'Classical' contact allergy
Fentichlor 1% pet.	1 (10%)	1 (10%)
6-Methylcoumarine 1% pet.	1 (10%)	0
Promethazine hydrochloride 1% pet.	1 (10%)	0
Hexachlorophene 1% pet.	0	4 (40%)
Wood mix 20% pet.	0	2 (20%)
3,4,5-Tribromosalicylanilide 1% pet.	0	1 (10%)
3,4,4-Trichlorocarbanilide (TCC) 1% pet.	0	1 (10%)

Benzophenone 3 is listed in both Scandinavian Photopatch Test Series and European Multi-Centre Photopatch Test Study series; results are shown in Table 2. Other substances in Scandinavian series that remained negative in all tested patients were: 3,3',4',5-tetrachlorosalicylanilide 0.1% pet.; triclosan 2% pet.; (+)-usnic acid 0.1% pet.; atranorin 0.1% pet.; balsam of Peru 25% pet.; bithionol 1 % pet.; chlorhexidine digluconate 0.5% aq.; chlorpromazine hydrochloride 0.1% pet.; diphenhydramine hydrochloride 1% pet.; evernic acid 0.1% pet.; perfume mix 6% pet.

tive photopatch reactions to etofenamate insisted that they had never used any of the etofenamate preparations available on the market. Cross-reactivity with ketoprofen seems not a plausible explanation, as co-existence of photoallergies to both these drugs was found in only one patient. In the remaining three patients, etofenamate positivity was the sole reaction observed. With this respect, etofenamate revokes an analogy to the "classical" hapten thiomersal (merthiolate), whose high positivity rates combined with low clinical relevance have intrigued researchers for decades with no definite explanation available until now (14). There is some striking difference between etofenamate and ketoprofen with regard to their biological effects in human keratinocytes; ketoprofen demonstrates a clearly phototoxic effect, which may contribute to the development of photoallergic reactions, while etofenamate exerts an overall toxic effect on keratinocytes, which is only aggravated by light (15). Further studies are needed to clarify whether this toxic effect could explain the observed high prevalence of clinically non-relevant (i.e. possibly toxic) photopatch test reactions.

Five patients demonstrated more than one reaction to photohaptens from the EMCPPTS series, each one with an individual pattern (Table 3). Such simultaneous positivity may result from either co-sensitization (coincidence) or cross-sensitization (structural or functional similarity between photohaptens). Simultaneous photosensitization to ketoprofen or etofenamate in just one out of eight patients photosensitized to either of these drugs seems to hint at a coincidence rather than cross-sensitization. Also, there are no reports on the observed cross-reactivity between ketoprofen or etofenamate in medical literature to date (PubMed and Scopus search on November 1, 2013). A second patient was simultaneously photosensitized to ketoprofen and benzophenone 3. As ketoprofen and benzophenones are structurally related, cross-sensitization seems more probable in this case. In a previous study in seven ketoprofen-photoallergic patients, four patients reacted also to benzophenone 3 (16). Structural similarities between benzophenone 3 and benzophenone 4 also hint at cross-sensitization in the third patient (Table 3). In case of the two remaining patients, there were no previous reports of simultaneous photoallergy either to diclofenac and methylene bis-benzotriazolyl tetramethylbutylphenol (bisoctrizole) or to phenylbenzimidazole sulfonic acid and diethylamino hydroxybenzoyl hexyl benzoate, which put together with the structural differences of the chemicals hints at co-sensitization rather than cross-sensitization.

CONCLUSION

Patients requiring diagnostic work-up for photoallergy constitute a relevant group among dermatology outpatients, therefore, it seems advisable that all second-level dermatology referral centers be capable of photopatch testing in patients with symptoms suggesting this pathology. Also, due attention should be paid to the problem of photoallergy in the dermatology teaching curricula, both for medical students and for dermatology residents.

ACKNOWLEDGMENT

The study was partly financed by the grant K/ZDS/001906 from the Jagiellonian University Medical College in Krakow, Poland.

References

1. Spiewak R. Contact dermatitis in atopic individuals. Curr Opin Allergy Clin Immunol 2012;12:491-7.
2. Spiewak R. Photoallergies. Post Dermatol Allergol 2009;26:347-9.
3. Tončić RJ, Lipozenčić J, Martinac I, Gregurić S. Immunology of allergic contact dermatitis. Acta Dermatovenerol Croat 2011;19:51-68.
4. Fotiades J, Soter NA, Lim HW. Results of evaluation of 203 patients for photosensitivity in a 7.3-year period. J Am Acad Dermatol 1995;33:597-602.
5. Lipozenčić J. Allergic diseases are an important problem nowadays – suggestions for resolving. Acta Dermatovenerol Croat 2011;19:141-2.
6. Spiewak R. The substantial differences between photoallergic and phototoxic reactions. Ann Agric Environ Med 2012;19:888-9.
7. The European Multicentre Photopatch Test Study (EMCPPTS) Taskforce. A European multicentre photopatch test study. Br J Dermatol 2012;166:1002-9.
8. Spiewak R. Patch testing for contact allergy and allergic contact dermatitis. Open Allergy J 2008;1:42-51.
9. Spiewak R. Systemic photoallergy to terbinafine. Allergy 2010;75:1071-2.
10. Plichta D, Dorynska A, Spiewak R. Patterns of drug consumption and the occurrence of adverse drug reactions among students of public health. Pol Merkuriusz Lek 2012;32:232-7.
11. Klimanska M, Zmudzinska M, Jenerowicz D, Czarnecka-Operacz M. The importance of exposure to contact allergens in patients with allergic contact dermatitis. Post Dermatol Alergol 2011;28:203-11.

12. Thyssen JP, Uter W, McFadden J, Menne T, Spiewak R, Vigan M *et al*. The EU Nickel Directive revisited – future steps towards better protection against nickel allergy. Contact Dermatitis 2011;64:121-5.
13. Spiewak R, Pietowska J, Curzytek K. Nickel: a unique allergen – from molecular structure to European legislation. Expert Rev Clin Immunol 2007;3:851-9.
14. Spiewak R. Immunotherapy of allergic contact dermatitis. Immunotherapy 2011;3:979-96.
15. Spiewak R, Gregorius A, Sznelewski P. A new *in vitro* protocol for assessing phototoxic effects of xenobiotics on human keratinocytes. Estetol Med Kosmetol 2012;2:110-4.
16. Leroy D, Dompmartin A, Szczurko C, Michel M, Louvet S. Photodermatitis from ketoprofen with cross-reactivity to fenofibrate and benzophenones. Photodermatol Photoimmunol Photomed 1997;13:93-7.