DOCTOR OF MEDICINE

Photoallergic contact dermatitis in Europe

Kerr, Alastair

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Alastair Kerr

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University of Dundee

8. A new European Baseline photopatch test series

In the previous Chapters of this thesis, the studies presented contained information which would be of relevance when deciding upon the composition of a new European Baseline photopatch test series. This Chapter outlines the actual method that was adopted to decide upon the form of this series, as well as presenting its content.

8.1 A second Amsterdam meeting in February 2012

The results of the pilot irritancy study, the UK sunscreen survey and particularly the EMCPPTS, were discussed as an integral part of a one day workshop meeting held under the auspices of the ESPD and ESCD in Amsterdam, The Netherlands in February 2012. The purpose of the meeting was to decide upon the agents that would be included in a new European Baseline photopatch test series. The attendees at this meeting were 13 clinicians from across Europe with an established interest in photoallergy and PPT who had all recruited subjects to the EMCPPTS. Also present was the head of the patch and photopatch test agent supply company Chemotechnique Diagnostics Ltd, who was able to advise on the feasibility of manufacturing individual agents. A total of 65 agents, each of which could potentially have been included in such a series, were chosen for discussion. Agents were included on this list if they had been previously reported as photoallergens in the literature or were listed in Annex VII. Therefore, all 24 EMCPPTS test agents, as well as carprofen and CPE were among the agents for discussion.

Each attendee had been assigned four or five agents before the meeting to research and prepare slides for. Over the course of this one day meeting, each attendee was

given approximately five minutes to present the pertinent information on each agent they had researched. This served as the basis for an open discussion on which agents should be included in a new European Baseline photopatch test series. It was agreed between the attendees that after discussion, each agent would be assigned into one of three main groups, as given below:

1) Inclusion in a new European Baseline series. These agents were felt to be of great enough clinical significance to warrant inclusion in the main series, which would be used by future clinicians to routinely investigate possible cases of PACD in patients.
2) Inclusion in an "additional" European photopatch test series. These agents were not deemed to be of great enough clinical significance to be included in the main European Baseline series. However, they were considered of enough significance to warrant having them commercially available to investigators for PPT in certain instances. Examples of such agents were those felt to be of low photoallergenic potential, those of decreasing availability and those requiring further study.
3) Exclusion from either photopatch test series. These agents were not deemed suitable for inclusion in either of the other two series.

8.2 The agents in a new European Baseline series

After discussion, 20 agents were considered appropriate for inclusion in a new European Baseline photopatch test series, as given in Table 8.1. A concentration of 10% was chosen for all UV absorbers, except benzophenone-4, to increase the sensitivity of the series as discussed at the end of Chapter 4. A consensus opinion was reached among attendees that the total number of 20 agents was appropriate for

a series which would hopefully become widely used by clinicians. This number was felt to be not so large as to put clinicians off using PPT to investigate patients who may also be required to have different standard patch testing batteries applied to their back.

Among interesting discussion points, there was a decision to include seven of the nine "newer" organic UV absorbers that are listed in Annex VII and which also had been used in the EMCPPTS. Although most of these led to very few PACD reactions in the EMCPPTS, there was consensus that they should be included because they have not been available for incorporation within sunscreens for a long duration, and their inclusion would lead to more information their photoallergenic potential being accumulated.

It can be seen that three agents that were not tested in the EMCPPTS were included. Firstly, the "older" organic UV absorber PABA was included mainly on the basis that its previous widespread usage in Europe means people may have retained sunscreens containing it in their possession. It is also possible that it continues to be incorporated in non-European sunscreens (e.g. those manufactured in Asian countries) meaning that there may still be exposure of people within Europe to it. It was also felt that its ability to cross-react to other "*para*-amino" compounds was of importance when attempting to determine the relevance of reactions observed when investigating patients by patch and photopatch testing.

The topical NSAID benzydamine and the topical antihistamine promethazine were also included despite not being tested in the EMCPPTS. These agents were included because topical formulations of both are available in several different European countries and several attendees from these countries reported investigating a continuing stream of patients with PACD to these agents.

Type of agent	Name of agent (INCI name for UV absorbers)	Test concentration and vehicle
"Older" organic UV absorbers	Butyl methoxydibenzoylmethane	10% pet
	Benzophenone-3	10% pet
	Benzophenone-4	2% pet
	Octocrylene	10% pet
	4-Methylbenzylidene camphor	10% pet
	Ethylhexyl methoxycinnamate	10% pet
	Isoamyl-*p*-methoxycinnamate	10% pet
	*PABA	10% pet
"Newer" organic UV absorbers	*Bis*-ethylhexyloxyphenol methoxyphenyl triazine	10% pet
	Methylene *bis*-benzotriazolyl tetramethylbutylphenol	10% pet
	Drometrizole trisiloxane	10% pet
	Terephthalylidene dicamphor sulfonic acid	10% water
	Diethylamino hydroxybenzoyl hexyl benzoate	10% pet
	Ethylhexyl triazone	10% pet
	Diethylhexyl butamido triazone	10% pet
Topical NSAIDs	Ketoprofen	1% pet
	Etofenamate	2% pet
	Piroxicam	1% pet
	*Benzydamine	2% pet
Topical antihistamine	*Promethazine	0.1% pet

Table 8.1. The composition of a new European Baseline photopatch test series.

(* = agent *not* tested in the EMCPPTS; pet = petrolatum)

8.3. The agents in an "additional" European photopatch test series

After discussion, 15 agents were considered appropriate for inclusion into an "additional" European photopatch test series, as given in Table 8.2. Among this series are the three "older" organic UV absorbers phenylbenzimidazole sulfonic acid, homosalate and ethylhexyl salicylate, which are listed in Annex VII and had been used in the EMCPPTS. A decision was agreed to include them in the "additional" photopatch test series because their photoallergenic potential was judged to be very low. This judgement was based on each of them leading to very few PACD and ACD reactions in the EMCPPTS, combined with very few previous reports of PACD and ACD appearing in the literature. A decision to include the "newer" organic UV absorber disodium phenyl dibenzimidazole tetrasulfonate in this series was made for the same reasons, although it has been available for a shorter duration.

The "newer" organic UV absorber polysilicone-15 was included in this series after an interesting discussion. Many attendees felt that its very high molecular mass, and by extension, decreased ability to penetrate the stratum corneum of the skin, would make it highly unlikely to be able to elicit PACD. Ultimately, the decision not to exclude it from either series was based on the fact that it has not been available for a long duration, necessitating the accumulation of further information. It was also proposed by some attendees that even although it is a large molecule, its breakdown products could lead to PACD and ACD.

The "older" UV organic absorber benzophenone-10 is not listed in Annex VII and was not used in the EMCPPTS. However, it was included in the "additional" series because it may still be found within other cosmetic products which are not

marketed as sunscreens, but is probably less commonly found than benzophenone-4 (which was included in the Baseline series).

Also included in the "additional" series were the two topical NSAIDs dexketoprofen and piketoprofen. These were not tested in the EMCPPTS but are available for topical use in certain European countries. There was a consensus that not enough is known regarding their photoallergenic potential and whether this differs from their parent molecule, ketoprofen. For this reason, several attendees felt that they should be made commercially available, such that further PPT studies incorporating these (and possibly ketoprofen, benzophenone-3, octocrylene and fenofibrate) can be undertaken.

The two topical NSAIDs ibuprofen and diclofenac were included in the "additional" series despite leading to very few PACD and ACD reactions in the EMCPPTS. The main reason influencing this decision was their continued high usage within topical preparations in Europe, particularly diclofenac which is the active ingredient in Solaraze® gel used to treat actinic keratoses, often on photo-exposed sites such as the scalp.

As intonated above, the medication fenofibrate was included in the "additional" series and should remain commercially available for testing primarily for its possible use in studies of its potential for cross-reacting with ketoprofen and benzophenone-related agents. In the case of the medication CPZ, attendees felt it should remain commercially available due to its continued widespread usage as an anti-psychotic, which could lead to sporadic cases of possible PACD requiring investigation.

It was thought that although European legislation has prohibited use of the veterinary additive olaquindox, it may still be used in China, hence its retention as a

test agent. Likewise, there was uncertainty among attendees that some antiseptics had been completely removed from usage in other countries, hence the retention of two such agents.

Type of agent	Name of agent (INCI name for UV absorbers)	Test concentration and vehicle
"Older" organic UV absorbers	Benzophenone-10	10% pet
	†Phenylbenzimidazole sulfonic acid	10% pet
	†Homosalate	10% pet
	†Ethylhexyl salicylate	10% pet
"Newer" organic UV absorbers	†Polysilicone-15	10% pet
	†Disodium phenyl dibenzimidazole tetrasulfonate	10% pet
Topical NSAIDs	Dexketoprofen	1% pet
	Piketoprofen	1% pet
	†Ibuprofen	5% pet
	†Diclofenac	5% pet
Medications	Fenofibrate	10% pet
	Chlorpromazine (CPZ)	0.1% pet
Veterinary additive	Olaquindox	1% pet
Antiseptics	Triclosan	2% pet
	Trichlorocarbanilide	1% pet

Table 8.2. The composition of an "additional" European photopatch test series.

(† = agent tested in the EMCPPTS)

8.4 Agents excluded from either photopatch test series

After discussion, 30 agents were not considered appropriate for inclusion in either of the two photopatch test series outlined above. These agents are given in Table 8.3 and include agents which were felt to be of historical interest or very low current clinical photoallergenic potential in Europe. Of note among these agents are the two PABA esters and four camphor derivatives which are listed in Annex VII. There was a consensus decision to exclude them on the basis of the apparent discontinuation of their usage in sunscreen products. In the case of the two PABA esters, the inclusion of PABA itself in the European Baseline series was thought to be adequate as a "screening" agent to pick up PACD and ACD reactions to this class of agents.

In the case of carprofen, although the outbreak of photoallergy occurred in Dundee as described in Chapter 2, it is not used in humans. The few cases that have been reported in pharmaceutical workers appear to be very sporadic in nature. If cases of suspected PACD to carprofen arise, testing the agent "as is" initially would seem appropriate. Further testing could then be considered if appropriate, using the methodology presented in Chapter 2 as a template.

In the case of CPE, it was excluded on the basis that it has been removed from the European marketplace. As with carprofen, if possible future cases of PACD did arise to CPE in the future, they could be investigated using the "as is" and subsequent methodology presented in Chapter 3 as a template.

Type of agent	Name of agent (INCI name for UV absorbers)
"Older" organic UV absorbers	TEA salicylate
	2-ethoxyethyl-*p*-methoxycinnamate
	Menthyl anthranilate
	¶Camphor benzalkonium methosulfate
	¶Benzylidene camphor sulfonic acid
	¶Polyacrylamidomethyl benzylidene camphor
	¶3-Benzylidene camphor
	¶PEG-25 PABA
	¶Ethylhexyl dimethyl PABA
Topical NSAIDs	Tiaprofenic acid
	Carprofen
	Suprofen
Medications	Sulphanilamide
	Diphenhydramine
	Chlorproethazine (CPE)
	Flutamide
	Fluoroquinolone antibiotics
Fragrance ingredients	Sandalwood oil
	6-Methylcoumarin
	Musk ambrette
Veterinary additive	Quindoxin
Antiseptics	TCSA
	TBSA
	Bithionol
	Fenticlor
	Buclosamide
	Chlorhexidine
	Hexachlorophene
Miscellaneous agents	Wood tar
	Thiourea

Table 8.3. Agents excluded from the photopatch test series'.

(¶ = currently listed in Annex VII)

8.5 The future of the European PPT series'

For reasons stated in previous Chapters, the two European PPT series' decided upon will need continued scrutiny and periodic updating over time to ensure they remain relevant. In the case of some of the "newer" organic UV absorbers, if they are made available for widespread PPT but continue to lead to very few cases of PACD and ACD, removal from these series may be justifiable. Other agents, such as fragrance ingredients and antiseptics may need removal if legislation in other parts of the world moves towards that adopted in Europe, prohibiting their usage. Until then, the formation of these series, aided by work contained within this thesis, will enable clinicians to more effectively use PPT to investigate possible cases of PACD and deliver tangible benefits to patients.