DOCTOR OF MEDICINE

Photoallergic contact dermatitis in Europe

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A PROSPECTIVE, OPEN, MULTI-CENTRE PHOTOPATCH TEST STUDY OF PATIENTS SUSPECTED OF PHOTOALLERGY TO ORGANIC SUNSCREENS AND TOPICAL NONSTEROIDAL ANTI-INFLAMMATORY DRUGS USED WITHIN EUROPE

1. Introduction

While the phenomenon of contact allergy and photocontact allergy to organic sunscreens and topical Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) agents is well recognised,[1-24] their true incidence is unknown and in part will relate to a number of factors, including usage patterns and photoallergic potency. Although photoallergy to sunscreens and NSAIDs is likely to be uncommon, the population exposure of both new and established agents is considered to be on the increase. This, in the case of organic sunscreens, is not only due to conventional sun protection products but also cosmetic skin care agents which sometimes surprisingly contain sunscreens. Both oral and topical NSAID's have an increasing pattern of usage throughout the European Community (EC).

In the EC, sunscreens are deemed to be cosmetic products following a council directive in 1976. Currently, sunscreen manufacturers are guided by The European Cosmetic Toiletry and Perfumery Association (COLIPA). This is a trade association which encompasses 23 EC national associations and 21 major international companies. It is involved in ongoing research into increasing the safety of cosmetic products and has issued several guidelines on methods for evaluating different properties of sunscreens, such as their Sun Protection Factor (SPF) and potential for skin irritancy.

In 2006, the European commission adopted a recommendation which sets out to protect consumers by advising sunscreen manufacturers on several points including the claims that may be made regarding SPFs and clearer labelling of products. Although not legally binding, the commission expects industry to take steps to ensure the recommendations become more visible to consumers.[25] However, the

process of evaluating photocontact allergy in the pre-market phase is not covered by such directives and so is not routinely performed by industry.

In the post-market phase, testing for photocontact allergy is only usually performed by clinicians on patients in whom it is suspected clinically. Such investigation of suspected photoallergy by photopatch testing has in the past been beset by obsolete test agents, variable methodologies and differences between individuals in the interpretation of results. A number of multi-centre studies have been conducted with a range of conclusions and recommendations. [4,9,12,18] In 1997, the British Photodermatology Group (BPG) followed a number of similar publications which recommended an updated standard technique and sunscreen battery. [26] Within a decade, this battery contains agents which have already passed out of common use.

On behalf of the European Society for Photodermatology (ESPD) and the European Society of Contact Dermatitis (ESCD), a consensus methodology statement has emerged and to our knowledge has gained some acceptance across Europe. [27]

More recently, a UK Multi-centre Group published results focussing solely on a sunscreen series. [24]

Up to date information on the potency of individual photoallergic chemicals is considered to be poor. There is a need for relevant data in this area so that clinicians and patients, as well as industry, can benefit from a clearer picture of which agents we should suspect and therefore test. This would have the additional benefit of informing manufacturers of sunscreen ingredients most suitable for inclusion in commercial products.

Background to current study

A group of dermatologists and a photo-physicist with an interest in photocontact allergy and photopatch testing met in Amsterdam on the 16th of February 2007. At this meeting, several points of concensus were reached which provided a framework for proceeding with this Multi-centre European photopatch test study. The study is supported by the ESPD and the ESCD. It is hoped that the study may be repeated after a period of 5 years.

A single-centre photopatch test study to assess irritancy levels of the different concentrations of the test agents is currently being conducted (March-September 2007) in the Photobiology Unit, Dundee, U. K, supported by the sunscreen industry.

Commercial Support

Although direct project funding has not been forthcoming, a research fellow MD funding has been allocated to this project. Therefore, individual centres will receive photopatch test study agents free of charge.

2. Study Objectives

The objectives of this study are:

- To obtain an approximate incidence of contact and photocontact allergy to sunscreen constituents and topical NSAID's among a population of European patients who present with an exposed-site dermatitis.
- To determine the relative contact and photocontact allergic potential of each of the sunscreen constituents and topical NSAID's tested.
- To inform advisory bodies and providers of test batteries on which sunscreens and NSAIDs should be included in the routine photopatch test batteries.
- To inform sunscreen and cosmetic manufacturers and regulatory authorities which sunscreens would be most suitable for inclusion in commercial products.
- To assess the effectiveness of the concensus photopatch test methodology for detecting photocontact allergy across multiple European sites.

3. Study Design

This is an open, prospective, multi-centre photopatch test study which will commence on the 1st of January 2008. Patients will only be recruited from centres in Europe that perform photopatch tests on 20 or more patients per year as part of routine clinical care. Centres in the following countries have been identified as being potentially able to contribute patients:

Austria	Belgium	Denmark	France	Germany
Greece	Hungary	The Republic of Ireland		Italy
The Netherlands		Poland	Portugal	Spain
Sweden	Switzerland		The U.K. (Scotland and England)	

It is hoped that the target number of 1000 patients will be reached within 1 year. If it is not, a decision will be made at that point as to whether a further period of recruitment is necessary. A paper proforma will be used by all of the centres involved to ensure standardisation of the indications for testing, methodology, test agents and interpretation of results. The photopatch test series agents will be supplied by Chemotechnique Diagnostics (Vellinge, Sweden).

4. Inclusion and Exclusion criteria

Inclusion criteria

To be eligible for this study, patients must meet the following criteria:

- Male or female of 18 years of age or older.
- Have sufficient cognitive capacity to give written informed consent.
- Have an eruption on photo-exposed sites, which is to be further classified using one (or more) of the categories below:

Known photosensitivity disease	☐
History of sunscreen reaction	☐
Sun exposed site dermatitis during summer months	☐
Any sun exposed site dermatitis problem	☐

Exclusion criteria

To be eligible for this study, patients must *not* meet the following criteria:

- Be 17 years of age or younger
- Have had potent topical steroid applied to the photopatch test site on the back in the previous 5 days.
- Have skin disease activity on the back which is too active to allow testing.
- Be prescribed systemic immunosuppressant medication (e.g. prednisolone, methotrexate, azathioprine, ciclosporin)
- Be taking any photoactive medicine*. (This is a relative exclusion. Many centres may wish to go ahead despite such medication).

*e.g. thiazides
sulphonamide derivatives
amiodarone
fluoroquinolones
chlorpromazine
NSAIDs
quinine

Investigation of Those Photosensitivity Patients with Marked UV Sensitivity

Some centres may wish to conduct a UVA Minimal Erythema Dose (MED) prior to photopatch testing and if appropriate use a lower dose of UVA (e.g. 50% of the UVA MED) dose to irradiate the photopatch test site. For example, the MED dose series used in Dundee is 1 Jcm^{-2}, 1.5 Jcm^{-2}, 1.8 Jcm^{-2}, 2.2 Jcm^{-2}, 2.7 Jcm^{-2}, 3.3 Jcm^{-2}, 3.9 Jcm^{-2}, 4.7 Jcm^{-2}. It may be that in some patients with a severe photodermatosis, photopatch testing cannot be conducted. e.g., chronic actinic dermatitis (CAD).

5. Study Methods

Application of patches (Day 0)

- The study test agents will be applied to the patient using Finn chambers mounted on Scanpore tape (available from Bio Diagnostics Ltd, Upton Road, Upton-Upon-Severn, Worcestershire, WR8 0XL, U.K. [European Distributor list available at: www.epitest.fi/]).
- Number the reverse of each individual Finn chamber with the corresponding patch number prior to applying the test materials to the discs.
- The test substances come in 5 ml syringes. Apply the materials directly into the chamber, filling no more than half the chamber volume (a bar of about 5-6mm if the diameter is 2mm).
- Make up patches in duplicate, 1 set to be irradiated and 1 set as control.
- Avoiding the paravertebral groove, apply the patches to normal skin on the mid upper back. Both sides of the back may be used if space dictates.
- To facilitate even irradiation, ensure that the area to which the irradiated set is applied is relatively flat and that the patches are arranged in a group (3 rows of 4/5 rather than 2 rows of 6/7).
- Trace the patches onto a polythene “map” using a Pentel® permanent marker. Indicate any moles or blemishes as “land marks”.
- The patient should avoid strenuous exercise, keeping as cool as possible while the patches are on and avoid sun exposure to their back for the 4 or 5 days that they are in the study.
- According to local preference, centres may apply photopatch agents for either 24 or 48 hours prior to irradiation.* see note below After this time, all patches are removed and discarded. Label the patch test sites with a medium, black Staedtler Lumocolor® permanent pen.

**** Timing of readings***

- As photopatch testing in some Centres is structured in such a way that irradiation at 24 hours is impractical, **<u>two protocols will operate.</u> (Appendix 1)**
- In some centres, patches will be left in place for 24 hours and irradiation will then occur. This means that patch test site readings are at days 1,2,3 and 4 (or 0, 24, 48 and 72hours *after* irradiation).
- In other centres, patches will be left in place for 48 hours and irradiation will then occur. This means that patch test site readings are at days 2, 3, 4 and 5. (but also at 0, 24, 48 and 72hours *after* irradiation).

Irradiation of patches **(May be 24 or 48 hours after patch application – i.e. Day 1 or Day 2)**

- Randomise which of the two sets is irradiated without the reader being aware (i.e., he or she is blinded).
- The light sources to be used are standard fluorescent PUVA or R-UVA tubes.
- Irradiate one of the sets of patches while masking off and protecting the rest of the back with UV impermeable material. i.e. 4 layers of black/white polythene.
- To ensure even irradiance over the photopatch test site, the output should be measured at 20cm. To ensure that all centres are applying the same Jcm^{-2}, meters will be calibrated and a correction factor applied to the measured output of the test lamps. All centres are to send their dosage meters by post to the photobiology unit in Dundee (U.K) for calibration in the 3 months prior to the study start date.
- Manoeuvre the lamps to the correct position (20cm).
- Cover the photopatch test site until ready to irradiate.
- Allow the lamps a 2-3 minute warm-up time to stabilise.
- When ready, remove the cover from the photopatch test site and irradiate for the time required to administer 5 Jcm^{-2} (or 50% UVA MED if patient is abnormally photosensitive [see note above]).

Patch Readings **(At 0hrs, 24hrs, 48hrs, and 72hrs after irradiation)**
(at days 1, 2, 3 and 4 in patients who had patches applied for 24hrs and
at days 2, 3, 4 and 5 in patients who had patches applied for 48 hours)

- It would be best that a limited number of individuals who are trained in conducting the readings are involved in reading the results. These can be either experienced doctors or nurses/technicians.
- Readings of photopatch test sites must take place on the day of irradiation (0 hours) and 48 hours later. Optional readings (i.e. if possible but not essential) are made at 24 and 72 hours (to detect crescendo/decrescendo reactions) post-irradiation.

Recording of results

- A standardized paper proforma will be used by all centres to record patient details and the results of patch test readings (Appendix 2)
- The International Contact Dermatitis Research Group (ICDRG) scale will be used for recording the patch test reactions seen (Appendix 3).
- Where positive results occur, the COADEX recording system will also be used to help establish the rate of false-positive and irritant results (Appendix 3).

6. Collection of Results

It was decided at the preliminary meeting in Amsterdam that English is to be the language of recording of results, communication between centres and publishing. However, there were mixed views about the method of communication with the coordinating centre in Dundee, U.K. Therefore, it was decided that 2 methods could be used.

The first option would allow collation of all results from all centres in one country by a named representative who communicates with the photobiology unit in Dundee. The second option allows individual centres to communicate their results directly to the photobiology unit in Dundee. In either case, it is intended that there will be 3-monthly posting / faxing of completed profomas from countries / centres to Dundee, U.K.

The data from all the completed proformas will be entered onto a database in Dundee after all 1,000 patients have been tested. This data will be anonymised i.e. individual patients will not be identifiable. This will be followed by a period of analysis of the results. Although the results of local data can be presented at local meetings, the complete collected and analysed data is to be submitted for publication as one document. *Contact Dermatitis* will be the intended peer-reviewed scientific journal to which the study results will be submitted for consideration of publication.

7. Ethical considerations

An application for Ethical approval to cover the multiple sites in the U.K. will be made. Similarly, approval from the Medicines and Healthcare Regulatory Authority (MHRA) will be sought.

As regards other European centres, **if you are in doubt about the situation within your own country, it is advised that you discuss it with your Ethics regulatory authority.**

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9. Glossary of terms

- **BPG** (the British Photodermatology Group) – A group of clinicians and scientists in the U.K. who have an interest in aspects of dermatological photobiology.
- **COLIPA** (The European Cosmetic Toiletry and Perfumery Association) – a trade association encompassing 23 European national associations and 21 international companies which promotes safe and effective cosmetic manufacturing.
- **Contact allergy** – The allergic process seen when an exogenous allergen is applied to the skin.
- **ESPD** (the European Society for Photodermatology) - A group of clinicians and scientists across Europe who have an interest in aspects of dermatological photobiology.
- **ESCD** (the European Society of Contact Dermatitis) - A group of clinicians across Europe who have an interest in aspects of contact dermatitis.
- **Finn® chamber** – A small aluminium metal disc-shaped chamber of approximately 1cm diameter into which exogenous allergens to be used in photopatch testing are placed.
- **MED** (Minimal Erythema Dose) – The smallest dose of UV radiation required to produce barely perceptible reddening of the skin in a patient.
- **NSAID's** (Non-steroidal anti-inflammatory drugs) – A group of medications used for analgesia both topicaly and orally. e.g. diclofenac, ibuprofen.

- **Organic sunscreen** – A synthetic compound based on carbon atoms which is applied to the skin to protect against the effects of UV irradiation by reflecting or absorbing it.
- **Paravertebral groove** – The area of indented skin running down both sides of the spine on the back of a patient.
- **Photocontact allergy** – The allergic process seen when an exogenous allergen is applied to the skin and the area is subsequently UV irradiated.
- **Photopatch test** – the method used to determine whether photocontact allergy is present in a person by applying a small amount of potential exogenous allergen to the skin and subsequently exposing it to UV irradiation.
- **Proforma** – A standardised sheet of paper for recording the results of patient investigations on.
- **Scanpor® tape** – A hypo-allergenic adhesive tape on which Finn® chambers are mounted before being applied to the skin of the patient.
- **UVA (Ultraviolet A)** – The region of the electromagnetic spectrum between 315 and 400 nm wavelength used to irradiate photopatches.

Appendix 1 – Summary of study timings

i) Centres in which patches are applied for **24** hours before irradiation:

	Day 0	Day 1	Day 2	Day 3	Day 4
		0 hours after irradiation	**24 hours** after irradiation	**48 hours** after irradiation	**72 hours** after irradiation
Obtain patient history of photo-exposed eruption	**X**				
Check patient Inclusion / Exclusion criteria	**X**				
Obtain consent from patient	**X**				
Apply photopatches	**X**				
Perform UVA MED	**X**				
Remove patches & irradiate		**X**			
Read patch sites and record results		**X**	**Xa**	**X**	**Xa**

Xa = optional readings

ii) Centres in which patches are applied for **48** hours before irradiation:

	Day 0	Day 2	Day 3	Day 4	Day 5
		0 hours after irradiation	**24 hours** after irradiation	**48 hours** after irradiation	**72 hours** after irradiation
Obtain patient history of photo-exposed eruption	**X**				
Check patient Inclusion / Exclusion criteria	**X**				
Obtain consent from patient	**X**				
Apply photopatches	**X**				
Perform UVA MED	**X**				
Remove patches & irradiate		**X**			
Read patch sites and record results		**X**	**Xa**	**X**	**Xa**

Xa = optional readings

Appendix 2 – Study Proforma

Subject No:	**Diagosis (up to 3):**	**Indication for testing:**
Date Tested (dd/mm/yy):	1.	Known photosensitivity disease ☐
Age (years):	2.	History of sunscreen reaction ☐
Sex: Male ☐ Female ☐	3.	Exposed site dermatitis during summer months ☐
Length of patch application: 24 hrs ☐ 48 hrs ☐		Any exposed site dermatitis problem ☐

Patch No.	**MATERIALS**	Irradiation day (this will vary from centre to centre (48 hrs)	24 hrs	48 hrs	72 hrs	COADEX
1	Butyl-methoxy-dibenzoylmethane (Parsol 1789, Eusolex 9020)					
2	Homosalate					
3	Methylbenzylidene camphor (Eusolex 6300, 4MBC)					
4	Benzophenone-3 (2-hydroxy-4-methoxybenzophenone, Eusolex 4360, Escalol 567, Oxybenzone)					
5	Octyl methoxycinnamate (Ethylhexyl-methoxycinnamate, Parsol MCX, Escalol 557)					
6	Phenylbenzimidazol sulfonic acid (Eusolex 232, Novantisol)					
7	Benzophenone 4 (2-hydroxy-4-methoxybenzophenon-5-sulfonic acid, Sulisobenzone, Uvinyl MS40)					
8	Drometrizole trisiloxane (Mexoryl XL)					
9	Octocrylene					
10	Octyl salicylate					
11	Octyl triazone (ethylhexyl triazone, Univul T150)					
12	Isoamyl-p-methoxycinnamate					
13	Terephtalidene dicamphor sulphonic acid (Mexoryl SX)					
14	Tinosorb S					
15	Tinosorb M					
16	Univul A+					
17	Neoheliopan AP					
18	Uvasorb HEB					
19	Parsol SLX					
20	Ketoprofen 1%					
21	Etofenamate 2%					
22	Piroxicam 1%					
23	Diclofenac 5%					
24	Ibuprofen 5 %					
25	Control (WSP)					

1	Butyl-methoxy-dibenzoylmethane (Parsol 1789, Eusolex 9020)					COADEX
2	Homosalate					
3	Methylbenzylidene camphor (Eusolex 6300, 4MBC)					
4	Benzophenone-3 (2-hydroxy-4-methoxybenzophenone, Eusolex 4360, Escalol 567, Oxybenzone)					
5	Octyl methoxycinnamate (Ethylhexyl-methoxycinnamate, Parsol MCX, Escalol 557)					
6	Phenylbenzimidazol sulfonic acid (Eusolex 232, Novantisol)					
7	Benzophenone 4 (2-hydroxy-4-methoxybenzophenon-5-sulfonic acid, Sulisobenzone, Uvinyl MS40)					
8	Drometrizole trisiloxane (Mexoryl XL)					
9	Octocrylene					
10	Octyl salicylate					
11	Octyl triazone (ethylhexyl triazone, Univul T150)					
12	Isoamyl-p-methoxycinnamate					
13	Terephtalidene dicamphor sulphonic acid (Mexoryl SX)					
14	Tinosorb S					
15	Tinosorb M					
16	Univul A+					
17	Neoheliopan AP					
18	Uvasorb HEB					
19	Parsol SLX					
20	Ketoprofen 1%					
21	Etofenamate 2%					
22	Piroxicam 1%					
23	Diclofenac 5%					
24	Ibuprofen 5 %					
25	Control (WSP)					

ICDRG grading scale for allergic reactions	**COADEX system for assigning relevance to positive allergic reactions**
	C = Current relevance
? = Doubtful reaction; faint macular erythema only	O = Old or past relevance
+ = Weak (non-vesicular) positive reaction; erythema; infiltration, possibly papules	A = Actively sensitized
++ = Strong (vesicular) positive reaction; erythema, infiltration, papules, vesicles	D = Relevance not known
+++ = Extreme positive reaction; Bullous reaction	E = Exposed
- = Negative reaction	X = Cross-reaction

Appendix 3 – The ICDRG scale and COADEX system

ICDRG grading scale for allergic reactions

? = Doubtful reaction; faint macular erythema only

\+ = Weak (non-vesicular) positive reaction; erythema; infiltration, possibly papules

++ = Strong (vesicular) positive reaction; erythema, infiltration, papules, vesicles

+++ = Extreme positive reaction; Bullous reaction

\- = Negative reaction

The COADEX system for assigning relevance to positive allergic reactions

C = Current relevance – The patient has been exposed to allergen during the current episode of dermatitis and improves when the exposure ceases.

O = Old or past relevance – Past episode of dermatitis from exposure to the allergen.

A = Actively sensitised – Patient presents with a sensitisation (late) reaction.

D = Relevance not known – Not known whether the exposure is current or old.

E = Exposed – A history of exposure but not resulting in dermatitis.

X = The positive test is due to cross-reaction with another allergen.