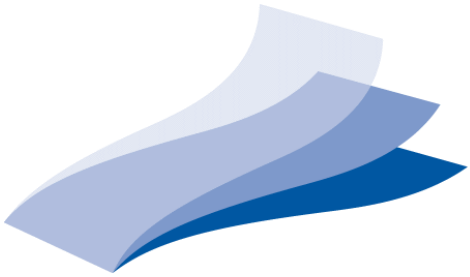

European Dermatology Forum

European Dermatology Guideline for the photodermatoses

2. Phototesting

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Conflict of interest:

The authors state no conflict of interest.

Abstract

Phototesting is used to establish a diagnosis in patients with suspected photodermatoses and to determine threshold dose and wavelength dependence. The phototest procedure comprises three steps. First, the threshold dose for erythema response is determined by MED testing. Small skin fields are irradiated with increasing UV doses using either a solar simulator, UVB fluorescent lamps, or, for a full and precise investigation, a xenon arc lamp with associated diffraction grating (a monochromator). The induced erythema is graded 22-26 hours after irradiation using an established 5-point scale. Additional readings should be made immediately, 7-8 hours, and 48 hours after irradiation when using a monochromator. Pathological reactions in response to the irradiation procedure are found in patients suffering from idiopathic solar urticaria, chronic actinic dermatitis and actinic prurigo. A separate grading system has been proposed for solar urticaria patients. The second step includes reproduction of photodermatosis by a provocation phototest procedure. Repeated irradiations, the most optimal being 4, are performed with polychromatic UVA and/or UVB on consecutive days to provoke the photodermatoses. Finally, photopatch testing is conducted to identify photoallergy. Sunscreen agents are currently the most common photoallergens. Allergens are applied in duplicate sets for 24-48 hours. One site is subsequently irradiated with broad-spectrum UVA fluorescent lamps usually in a dose of 5 J/cm^2 and one site remains as a control. The induced reaction is scored using the International Contact Dermatitis Research Group (ICDRG) scoring system before irradiation, immediately and 48 hours after irradiation, and if possible 72 and 96 hours after irradiation. The relevance of readings is recorded using the COADEX system.

Introduction

Phototesting of patients with suspected photodermatoses is essential to establish a diagnosis and to determine threshold dose and wavelength dependence. The phototest procedure comprises three steps: (i) determination of threshold doses for erythema, (ii) reproduction of photodermatosis by a provocation phototest procedure, and (iii) photopatch testing to identify photoallergy. Any topical or systemic immunosuppressive treatment should be withdrawn before testing to avoid false-negative results (Table 1). Exposure to the sun or sunbeds should not have occurred in the 4 weeks preceding phototesting. Screening for anti-nuclear antibodies and porphyrins are required to rule out lupus erythematosus and porfyria, and sometimes exclusion of a genophotodermatoses may be needed.

MED testing

The initial step in phototesting a patient with suspected photosensitivity is determination of the threshold dose for erythema response to simulated solar irradiation or UVB and UVA. Pathological responses to MED-testing are found in patients suffering from idiopathic solar urticaria, chronic actinic dermatitis and actinic prurigo. In patients with solar urticaria MED is normal but preceeded by whealing. In patients with chronic actinic dermatitis extremely small UV doses are needed to provoke MED, and in patients with actinic prurigo and persistent light reaction, the UV doses for MED may be reduced.

To determine the minimal erythema dose (MED), phototesting is conducted on the back, buttocks or inner aspect of the forearm. Small skin fields are irradiated with increasing UV doses. It is well known that a variation in erythema response exists depending on anatomical site. This variation is on average within 20% between the top and bottom of the back [1] and

the test sites are therefore usually placed either on the top or bottom of the back to secure minimal variation.

For routine screening, a xenon arc solar simulator that may be equipped with light guides that deliver increasing doses of simulated sunlight can be used for MED determination. For full investigation, a xenon arc lamp with associated diffraction grating (monochromator) is used with which discrete wavebands of 3-10 nm can be selected [1].

The use of fluorescent lamps such as Philips TL-12 emitting broad-band or TL01 emitting narrow-band UVB is simpler but less specific related to sunlight. To deliver increasing doses of UVB these lamps must be combined with (i) an template with several windows that is closed manually as the desired doses of irradiation have been achieved [2] (ii) an irradiation source with 10 apertures of 8 x 12 mm. One aperture is open and 9 apertures contain metal foil attenuators perforated with a grid of holes of different sizes allowing simultaneous delivery of 10 different doses [3], or (iii) a commercially available, disposable template (MED Test Patch, Chromo-Light, Copenhagen, Denmark) that lies directly on the skin with 6 windows of 1.2 x 1.2 cm allowing ultraviolet radiation to pass through density filters with a dose increment of 25% [4].

Lamps emitting UVA for MED testing include PUVA-type fluorescent lamps, narrow-band UVA1 (Philips TL10) and filtered solar simulators without UVB. The doses used are typically with greater steps than for UVB testing.

The induced erythema is graded 22-26 hours after irradiation using an established 5-point scale:

0 - no difference from surrounding skin

(+) just perceptiple erythema (diffuse mild erythema without defined borders)

\+ uniform erythema with sharply defined borders

++ bright red color with slight induration (edema) on palpation

+++ bright red color and pronounced induration (edema) raised above the surrounding skin

It is recommended that the dose to a (+) reaction is used as the minimal erythema dose since this dose can be determined with the greatest precision [5]. The readings should be made by the same observer working under identical lighting conditions and with the patient acclimatized to room temperature and seated on a high chair to avoid variations in erythema resulting from grading the erythema when the subject is lying down [1]. Determination of the MED can never be exact due to the dose steps when testing. The MED may lie from any dose greater than the preceding dose that caused no erythema in the series to the dose resulting in just perceptible erythema.

When testing with a monochromator, readings should be made immediately and around 7, 24, and 48 hours post-irradiation since erythema responses may peak at different time points. Immediately, urticaria, short-term erythema and immediate pigment darkening must be noted. After 7-8 hours, the erythema responses due to radiation of wavelength 290-305 nm may be maximal and fading by 24 hours [1], and delayed reactions for instance in xeroderma pigmentosum patients may not be apparent before 48 hours after irradiation [1]. It has been shown that in a given patient the UVB and UVA MEDs are correlated and if either the UVB or UVA MED is unusually low, a photosensitivity disorder should be suspected [6].

The dose to MED will depend on the patient's pigmentation and this can be adjusted for by reflectance spectroscopy (Optimize 555, Chromo-Light, Copenhagen, Denmark) thus predicting the expected normal MED level assuming normal sensitivity at any pigmentation.

MUD testing

For patients suffering from idiopathic solar urticaria, a standardized method for testing of these patients has been proposed [7]. Fifteen minutes after irradiation with causal wavelengths the reaction has developed to a maximum and the induced reaction can be graded visually according to 6-point scale: 0: no reaction; (+): just perceptible erythema (minimal urticaria dose; MUD); +: erythema localized to the irradiated area; ++: erythema spreading beyond the irradiated area; +++: wheal in some parts of the irradiated area; ++++: wheal in the entire area irradiated.

Provocative phototest

Provocative phototesting is used to reproduce the photodermatoses at the skin. The preferred season for testing is early spring when the susceptibility is highest. The test sites are larger than in MED testing, typically around 5 x 8 cm, and the location should be on currently uninvolved skin. This way it is more likely to reproduce the skin lesions as only few and scattered skin lesions may be evoked by provocative phototesting and these lesions might be missed in small fields.

Polychromatic UVA and/or UVB are most commonly used but testing with blue light may be employed in particular in patients suffering from solar urticaria. For PLE, it has been reported that testing the patients with both broad-band fluorescent UVA lamps and narrow-band fluorescent UVB lamps increases the probability of confirming the diagnosis [8]. Repeated irradiations on several consecutive days to simulate cumulative effects are often required to provoke the photodermatoses. The optimal number of irradiations for diagnostic phototesting

in PLE has been shown to be four irradiations [9]. Thus, all skin reactions that developed after 5 or 6 irradiations had been initiated during the preceding 4 irradiations. However, in very photosensitive patients with for instance solar urticaria or persistent light reaction the photodermatitis may occur after a single exposure.

Photopatch testing

Photopatch testing is used to diagnose photoallergy/photocontact dermatitis. A consensus methodology for Europe was published in 2004 [10].

Photoallergy should be suspected in any patient with an eczematous eruption predominantly affecting light-exposed sites or a history of dermatitis that worsens after sun exposure. The most common indication for phototesting in patients with photoallergy has been shown to be a history of reacting to a sunscreen [11]. Indications typically fall into five categories: (i) a history of sunscreen reaction (ii) exposed-site dermatitis during the summer months (iii) an exposed-site skin problem (iv) a known photosensitivity disease (v) chronic actinic dermatitis.

In advance of phototesting, the patients need to be informed of the risk of sensitization as recognized in routine patch testing and be aware of the possibility of strong provocation test results. Photopatch testing should not be performed when the dermatitis is active but only in skin that has been clinically normal for at least the previous 2 weeks and preferably longer.

Agents for testing:

An updated list of test agents has been proposed based on sunscreen agents and non-steroidal anti-inflammatory agents [10]. Sunscreen agents are currently the most common photoallergens and a large proportion of patients (59%) found to have photoallergy are

unaware of reacting to a sunscreen chemical [11]. If a patient suspects some of their own products as the cause for the dermatitis, these products should be included in the testing procedure.

Methodology:

Using Finn Chamber technique (Allerderm, Phoenix, AZ, USA), allergens are applied in duplicate sets (one site for irradiation, one as non-irradiated control) to the mid-upper back avoiding the paravertebral groove area. The sets are in position for either 24 or 48 hours after which the allergens and applicator chambers are removed and discarded. One study indicates that 48 hours gives greater sensitivity (Batchelor) whereas no difference between 24 or 48 h was found in another work [11].

Subsequently, one site is covered with a light-impermeable occlusive dressing and the other irradiated with a broad-spectrum UVA source. UVA is recommended but evidence for photoallergen wavelength dependency is lacking.

Broad-spectrum UVA fluorescent lamps are preferred for photopatch testing including those used in PUVA therapy because of their widespread availability, reproducible broad spectrum and beam uniformity. Mecury vapour, monochromator, and solar simulated sources are not recommended for photopatch testing [10].

Dose:

The UVA dose must be sufficient to trigger the photoallergic response without causing either a summation of an erythemal and subclinical chemical irritant response due to the irradiation itself, or a phototoxic reaction. The UVA dose of choice is 5 J/cm^2 [10]. In patients with other photosensitivity or photoaggravated disorders, photopatch testing may be difficult and in

some cases impossible. The UVA MED should be established prior to photopatch testing using the same light source as for photopatch testing and testing up to and including 5 J/cm^2.

Grading and interpretation of reading:

The induced reaction is scored using the International Contact Dermatitis Research Group (ICDRG) scoring system: ?+, doubtful reaction (faint erythema only); +, weak positive reaction (erythema, infiltration, possibly papules); ++, strong positive reaction (erythema, infiltration, papules, vesicles); +++, extreme positive reaction (intense erythema and infiltration and coalescing vesicles or bullae).

Grading of the results is conducted pre-irradiation, immediately after irradiation and 48h post-irradiation. It has been shown that further readings performed at 72h and 96h add value by detecting additional relevant responses [11]. Thus, a no reaction at a site after 48 h may turn into a positive reaction after 72 or 96 h [11]. Moreover, readings at 72 and 96h are useful to determine crescendo reactions where the reaction maintained or increased over time or decrescendo reactions where the strength of the reaction is weakened (24-96h).

The readings may show the following four patterns: (i) negative control and irradiated site (ii) negative control site and positive irradiated site (iii) positive control site and positive irradiated site (iv) positive control site and negative irradiated site.

The interpretation is: (i) negative (ii) photoallergic reaction, particular if strengthening over time (crescendo reaction type), or UVA-induced erythemal and irritant reaction weakening over time (decrescendo reaction type) (iii) contact reaction (crescendo reaction in both the irradiated and control panel), or photoaugmented contact reaction (contact reaction but at least one grade stronger in the irradiated panel, thus combined contact and photoallergy), or

photoinhibited contact reaction (contact reaction but at least one grade weaker in the irradiated panel), or irritant reaction (decrescendo reaction type) (iv) photoinhibition.
A reaction in skin irradiated alone indicates generalized UVA photosensitivity, which previous MED and provocative phototestings should have revealed. The possibility of technical errors should be kept in mind.

Relevance of reading:

The relevance of the readings are recorded using the COADEX system [10]:

Current relevance (the patient has been exposed to the allergen during the current episode of dermatitis and improves when the exposure ceases)

Old or past relevance (past episode of dermatitis from exposure to allergen)

Actively sensitized (the patient presents with a sensitization (late) reaction)

Do not know (relevance not known; not sure if exposure is current or old)

Exposed (i) cross-reaction (the positive test is due to cross-reaction with another allergen), or (ii) exposed (a history of exposure but not resulting in dermatitis from that exposure or history of exposure but a definite positive allergic patch test)

Concluding remarks:

In most cases, systematic phototesting involving MED test, provocative phototesting and photopatch testing will lead to a diagnosis in patients with photosensitivity disorders. This guideline is based on the current evidence for phototesting and periodic review will be required in particular of the allergens included in photopatch series in order to reflect the agents that are in commercial use.

Table 1. Types of systemic medication that should be withdrawn before phototesting. No topical treatment should be applied in the test areas 2 days prior to phototesting including sunscreens, lotions, cosmetics. Other medication including alternative medication and food (carrots, figs, celery, lime and chinin) should be considered if the MED test is not normal.

Medication	Time of withdrawal before phototesting
Antihistamines, NSAID, acetylsalicylic acid, morphine	2 days
Glucocorticosteroids, psoralens, chlorpromazine, extreme vitamin doses	1 week
Chloroquine, endoxane, imurel, methotrexate, cyclosporine	1 month

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