Phototoxicity, Photoirritation, and Photoallergy Detection and Assessment

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Contents

Keywords

Centra UV-Messgerat® • Crescendo reaction model • Decrescendo reaction model • Fluorescent light tubes • High pressure UVA lamps • Minimal erythema dose • Photoallergic potential • Photodermatosis • Photointradermal test • Photopatch test • Photoprick test • Phototoxic and photoallergic reactions • Phototoxicity • Plateauing reaction model • Prick-test method • Scarified photopatch test • Solar simulator • Systemic phototest

Photosensitization includes the events triggered within the skin by the interaction of a molecule (called photosensitizer or chromophore) and wavelengths usually located in the ultraviolet (UV) light. It may be related either to phototoxicity, an inflammatory reaction depending on UV light dose and chromophore concentration, or to photoallergy, a specific immune reaction requiring a primary sensitization phase.

The in vivo testing of a compound's photosensitizing potential is needed in two circumstances:

- To check in a patient a compound suspected to be at the origin of an exogenous photosensitization
- The prospective evaluation of the photosensitizing potential of a drug before its commercialization

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Photosensitization tests combine compound introducing into the skin and further skin irradiation using an artificial light source. They are of three types: photopatch tests, photointradermal test, and systemic phototests. In photopatch tests, the compound is applied on the skin which eventually has been previously treated in order to increase penetration (abrasion of the horny layer or scarification). In photointradermal and photoprick test, the compound is intradermally injected in order to bypass the skin barrier. A prior measurement of the minimal erythema dose in UVB and UVA is necessary to help select the appropriate UV light doses. In photodermatoses exploration, one should also try to experimentally reproduce the light-induced eruption.

1 Material

1.1 Light Sources

Different types of sources are available (Anderson 1993; Beani 1987; Hölzle et al. 1987; Leroy et al. 1992).

- The *solar simulator* is the basic equipment. The Xenon arc lamp which emits a continuous spectrum, combined with a water filter to remove infrared ray and a WG305 Schott filter to eliminate shorter UV, is the common way to obtain a spectrum similar to that of solar light. Two devices are widely used in France: one from the CUNOW company, directly derived from equipment used in research and especially the Dermolum 3® (Müller, Moosining Germany). Interposition of cut-off filters or of a monochromator enables selecting the appropriate wavelengths.
- *High pressure UVA lamps* (UVAsun® 3000, Mutzhas, Munich RFA) are also essential; they emit very high UVA doses with a 330–460 nm spectrum (free from UVB), allowing in less than half an hour 100 J/cm^2 to be received by the skin placed at 30 cm of the lamp.
- *Fluorescent light tubes* emitting UVB (Philips TL12® or Sylvania F75®) or UVA (Philips TL09® OR Sylvania F85®); these tubes are either of small size for very localized irradiation or easily placed in a phototherapy cabin when bigger.
- *Slides projector with a Schott WG450 filter*: it is used for visible light irradiation, a rarely used test.

1.2 Diaphragms

Exposure time is set and irradiated area outlined through the interposition of a diaphragm between the light source and the skin.

Two types of diaphragm are necessary:

- A pierced plaque (usually 9 holes) 15–20 mm in diameter, covered by a second plaque which is moved manually or motorized. The movement of the front plaque uncovers the holes through which UVA or UVB light penetrates in preset geometrical or arithmetic progression doses. This computer-controlled device called sensitometer is integrated in the Müller solar simulator.
- A plaque with sufficient aperture to irradiate a large skin area, usually 5 × 10 cm^2.

1.3 Dosimeters

For better soundness, the measuring device should match the source spectrum. Two types of devices are widely used:

- The dosimeters Centra UV-Messgerat® (Osram, Munich) and IL9700® Research Radiometer (International Light, Newburyport, Massachusetts USA) which have two probes, one to measure UVB, the other UVA.
- Thermopiles (e.g., Kipp Zonen, 93270 Sevran France) which are connected to a voltmeter are sensitive to the whole spectrum (i.e., UV, visible, and infrared light). If they are calibrated for low energies, they can be connected to a monochromator.

1.4 Subject's Position

The selected skin area, usually the back, must be placed perpendicular to the light source and diaphragms; to facilitate positioning, a laterally and vertically motorized seat is helpful (Leroy and Dompmartin 1988).

2 Methodology

2.1 Minimal Erythema Dose (MED)

It is the lowest (A and/or B) UV dose which induces a visible erythema on the whole irradiated area. Its assessment uses a sensitometer. Irradiation by the solar simulator total spectrum results in the polychromatic (UVA and UVB) MED, also called MED_B, because the induced erythema is related almost exclusively to UVB. MED_A is provided either by a solar simulator-induced irradiation filtered by window glass or by a high pressure UVA source.

The tested area is the shoulder or the buttock. Reading is made 24 h after irradiation: MED_B in millijoule/cm^2 and MED_A in joule/cm^2. It should be made also immediately and 30 min after irradiation when early abnormal photosensitivity is suspected (e.g., solar urticaria).

The MED quantify the subject's actinic sensitivity which is related to his/her phototype. Accordingly, it is key parameter to select the UV light doses to be used in case of photosensitivity testing.

2.2 Photopatch Test (Syn: Photoepidermotest)

The investigated compound is applied as in any skin patch test, then the tested area is irradiated; the test is declared positive if a reaction appears only after irradiation. Until 1980, photopatch tests were not standardized, thus accounting for their poor reliability by these times (Hölzle et al. 1985). The first standardization attempts were proposed by the photopatch tests Scandinavian group (Thune 1988) followed by the German-Austrian-Swiss group (Hölzle et al. 1991) and the French group (Beani 1987; Jeanmougin M. et le Groupe de Recherche en Photobiologie Cutanée 1986). A consensus has finally been found although some points are debated.

- The *tested area* is usually the nontanned back skin.
- The *tested compound* (in petrolatum or alcohol) is applied in a Finn Chamber®, left in place for 24 h before irradiation and 48 h for the nonirradiated control.
- *Irradiation* takes place 24 h after application. However, this length of time may be inadequate, showing the difficulty of a fully standardized procedure because all photoallergens do not react in the same way. As example, for 6-methyl-coumarin the optimal time interval between application and irradiation is shorter, between 30 and 60 min (Jackson et al. 1980).

UVA irradiation is mandatory, as most photosensitizer's absorption spectrum is in UVA. The type of UVA source may affect the results; Przybilla et al. (1991) on a series of 27 compounds in 81 patients found a better efficiency with irradiation by TL09 type UVA fluorescent tubes than by high pressure UVA source. The UVA doses are chosen according to the expected type of reaction. Duguid et al. (1993) have shown, in patients with photoallergic positive patch tests obtained after 5 J/cm^2 irradiation, that irradiation between 0.7 and 1.9 J/cm^2 could elicit the same scores. Murphy (Murphy and White 1987), Cronin (1984), and English et al. (1987) have also shown that low doses (1–2 J/cm^2) are sufficient to elicit photoallergic reaction. In contrast, elicitation of a dose-dependent phototoxic reaction requires 10 or even 20 J/cm^2.

However, some molecules have their action spectrum in UVB. Consequently, to prevent any missing in detection, both UVA and UVB irradiation in parallel are now considered mandatory (Beani 1987; Jeanmougin M. et le Groupe de Recherche en Photobiologie Cutanée 1986; Jung 1981; Leroy et al. 1992; Przybilla et al. 1987). The UVB dose to be used is 0.75 MED_B, emitted by a solar simulator.

- Controls comprise skin irradiation without compound and skin irradiation with vehicle alone.
- *Photopatch tests interpretation*: reading is immediate following irradiation, then after 20 min, 24 h, 48 h, and 72 h and if possible later; in accordance with the international regulations regarding patch tests assessment, reactions are quantified:

+: erythema and flat papules or infiltration
++: erythema with papules and vesicles
+++: erythema with papules and blisters

A reaction limited to the irradiated area is universally considered positive (Gould et al. 1995). However, there is no consensus when both irradiated and nonirradiated areas are positive. The North American Contact Dermatitis group (Menz et al. 1988) and the Scandinavian group (Jansen et al. 1982) diagnose as photo-aggravated contact allergy a stronger reaction in irradiated area. Unless it is obvious, the "aggravation" assessment is subjective, however, and it seems difficult and unrealistic to grade the intensity of an erythema (The reader is advised to see ▶ Chap. 105, "Skin Barrier Function". The interpretation of these reactions is, therefore, uncertain.

- *Phototoxic and photoallergic reactions* must be distinguished: the former generates a well-defined erythema of early onset (24th hour) and straight of maximum intensity, sometimes associated with necrosis, whereas the latter evolves gradually and results in an eczema; biopsy may be useful to differentiate the reactions.

Hölzle et al. (1991) and Neuman et al. (1994) have refined the diagnosis through observation of intensity parameters over 4 days: erythema, infiltration, papules, vesicles, and blisters. Responses were classified into four types:

– The first type, called *decrescendo reaction model*, is similar to a contact toxic irritant reaction: a well-limited erythema, maximum on the first day, fading the following days. The absence of secondary inflammatory reaction suggests either a pharmacological effect of the compound or a phototoxic reaction. Further photo tests are needed before any conclusion is drawn. An example of this type of reaction is obtained with furosemide.
– The second type, named *combined reaction model*, shows an intense erythema on the first day which decreases the following days while on the second day an infiltration appears followed by papules and vesicles on the fourth day. It is interpreted as an initial phototoxic reaction followed by an allergic reaction. Examples of this type of reaction are found with tetrachlorosalicylamide, antiseptics, PABA, "*musk ambrette,*" or fragrance mixtures.
– The third type, the *plateauing reaction model,* shows a persistent erythema from the first up to the fourth day, often associated with an infiltration but rarely with vesicles or blisters. It is found preferentially with chlorpromazine and thioprofenic acid. Its meaning remains unknown.
– The fourth type, called *crescendo reaction model*, mimics an allergic reaction; erythema is not the prevailing sign, but papules and vesicles are present. Examples are given by fentichlor, 4-isopropyl-dibenzoyl-methane, 2-hydroxy-4-methoxy-benzophenone, and p-methoxyisoamylcinnamate.

This time-course based analysis aimed at differentiating pharmacological, phototoxic, and photoallergic reactions on clinical grounds, although potentially very useful, requires additional validation.

2.3 Scarified Photopatch Test

Before applying the tested molecule, control and irradiated areas are scarified diagonally with a small needle exerting a pressure strong enough to cut the epidermis without inducing bleeding (Kaidbey and Kligman 1978b; Kurumaji and Shono 1992). Then the irradiation and

interpretation procedures are not different from standard photopatch tests.

This method is interesting because it facilitates the penetration of compounds that have a low transcutaneous absorption capacity leading to false-negative reactions with standard photopatch tests (Kurumaji and Shono 1992). However, a recent study failed to show a better sensitivity in the diagnosis of drug-induced photosensitization (Conilleau et al. 2000).

2.4 Photointradermal Test

The epidermal barrier is bypassed in this technique. Epstein (1939) was the first to experiment it with sulfanilamide and obtained constant positive results. Schorr and Monash (1963) used it to confirm the phototoxic effect of dimethylchlotetracycline and tetracycline. Two key studies stand out in view of the number of tested drugs and the protocol used: the study by Kligman and Breit (1968), later improved by Kaidbey and Kligman (1978a), whose protocol is still the reference. It was recently used in a French study (Peyron and Pedailles 1986). Five intradermal injections, 0.1 ml of the compound diluted solution each, are carried out in the same subject; 15 min later, two sites are irradiated, one with 10 J/cm^2 UVA, the second one with 0.75 MED_B UVB. There are three controls: nonirradiated compound injected skin, UVA irradiated saline injected skin, and UVB irradiated saline injected skin. Reading takes place immediately, 6 h and 24 h later, as in common photopatch tests.

2.5 Photoprick Test

The prick-test method, widely used in IgE-mediated allergy testing for its low risk of systemic reaction, has recently been adapted to photobiological investigations under the name photoprick test (Bourrain et al. 1997).

The technique consists in three pricks made through a drop of the compound diluted in water covering 1 cm^2 skin (Stallerpoint®, Lab. Stallergène, Fresnes, France). The area is immediately irradiated 5 J/cm^2 UVA. A nonirradiated prick-test and a prick-test with the irradiated vehicle serve as controls. The same tests can be done in parallel with 0.75 MED_B UVB.

This method has the same purpose as photoscarification, but it is easy to implement and is safe as far as the risk of systemic reaction is concerned.

2.6 Systemic Phototest

It consists in performing photobiological tests after administration of a potential photosensitizer, usually a drug, by its usual oral or injected route (Beani 1987; Diffey and Langtry 1989; Emmett 1986; Ferguson 1995; Ferguson and Johnson 1990, 1993; Guidichi and Maguire 1985; Hölzle et al. 1987; Jonhson and Ferguson 1990; Leroy et al. 1992; Ljunggren and Bjellerup 1986; Meola et al. 1993; Schürer et al. 1992). It is imperative that the tested subject do not expose his (her) back to light over the whole test duration.

The two following methods are the most widely used:

- MED_A and MED_B assessment with immediate, early (5, 30, 30 min, and 4 h), and delayed (24, 48, and 72 h) reading: this is mainly used to identify phototoxicity (MEDs are lowered) although a protracted erythema may also (theoretically) indicate photoallergy.
- A phototest: a limited area (5 × 5 cm) on the back is irradiated with either infra-erythema UVB dose (0.5 or 0.75 MED_B) or 10 J/cm^2 UVA; immediate reading, then 30 min, 1 h, 4 h, 24 h, 48 h, and 72 h, and whenever possible one week after irradiation. Reactions may be phototoxic and/or photoallergic. They are differentiated on clinical grounds (aspect and time course), in some cases with the help of histological examination.

- The drug can be taken in a single dose, 2–3 times the therapeutic dose; because of frequent uncertainty regarding the drug pharmacokinetics, phototests are then repeated at different

times (1/2, 1, 2, 4, 6, and 8 h) after drug intake. Alternatively, the drug can be taken over a period of 5–7 days at usual doses before a single triggering irradiation is carried out when it is assumed that the skin is saturated with the substance.

- A last rarely used *variant* is to study a patient who still takes the drug: gradually increased UVB (5–100 mJ/cm^2) and UVA (1–15 J/cm^2) doses are given; an erythema arising at a dose lower than expected indicates phototoxicity. The test should be repeated 2 weeks or more after stopping the drug intake and by then the MED must have gone back to normal. The final proof will include a reintroduction test with an additional phototesting. This is often not possible in practice (Gould et al. 1995). In a recent optimization of this technique (Vousden et al. 1999), the MED was calculated before and after 5 days of drug intake, using several wavelengths delivered through a monochromator. A photosensitization index was defined as the ratio of MEDs before and after drug intake. This index would permit to compare the photosensitization potential of various compounds and to define their action spectrum.

3 Selection of the Appropriate Method

3.1 Detection and Quantification of a Compound Phototoxic or Photosensitizing Potential

The purpose of this type of study is to detect a phototoxic or photosensitizing potential of medicines before their commercialization. It is the natural complement of similar studies previously carried out *in vitro* or in animals. The test is performed in healthy phototype II to IV subjects. Exclusion criteria are those commonly used in research in man. In addition, any intake of potentially photosensitizing drug including oral contraceptive for the 3 months preceding the test must be avoided. The average number of volunteers is usually 30. The standard photobiological tests can only demonstrate a phototoxic potential. They are inappropriate for detecting a photoallergic potential since such reaction requires an earlier sensitization.

3.1.1 Detection of Phototoxic Power

Photopatch tests are the most widely used. Phototoxic reactions are dose dependent, therefore testing use increasing concentrations and progressive UV doses. However, in a prospective study, limitations of the method for compounds systemically taken have been shown (Jeanmougin M. et le Groupe de Recherche en Photobiologie Cutanée 1986). First, the responsible chromophore is often not the native drug but one of its metabolites. Second, the tested drug may not traverse the stratum corneum and thus fail to elicit a response of the viable tissue. Efficiency can be improved through additional procedures which facilitate the cutaneous penetration; however, such protocols are heavier and may raise ethical problems.

Detection is also possible through systemic administration of the drug. A comparison of both MED_A and MED_B before and after 5–7 days drug intake is a method usually preferred over the phototest kinetics observation following a single high dose. Drug administration is randomized between two groups, one taking the verum, the other one the placebo. In some studies additional subgroups are created in order to compare the photosensitizing potential of various drugs within each chemical class; this has been done within the fluoroquinolones (Ferguson and Johnson 1990, 1993) resulting in the following relative risk quantification (Scheife et al. 1993): Fleroxacin $\gg$ Lomefloxacin, Pefloxacin $\gg$ Ciprofloxacin $>$ Enoxicin, Norfloxacin, Floxacin.

For detection of phototoxic power, we lack comparative study of efficacy between systemic tests and photopatch tests.

3.1.2 Detection of a Photoallergic Potential: Photo-maximization Test

To detect a photoallergic potential, Kaidbey and Kligman (and 1980) proposed in 1980 a test in man adapted from the maximization test used for detection of potential contact sensitizers. They used a 150 W solar simulator polychromatic light for hypersensitivity induction and UVA light (solar simulator equipped with a WG345 filter) for elicitation .

The induction phase consists in six steps: (1) application of the compound under a 2.5 cm^2 patch kept for 24 h, (2) irradiation of a 0.8 cm diameter area of the patch with three MED polychromatic light as emitted by the solar simulator, (3) the test area is left uncovered for 48 h, (4) new patch application on the same area for 24 h, (5) the test area is left uncovered for 24 h, and (6) new irradiation as in step 1. This sequence was repeated six times. In fair skin subjects (phototype I and II), the second sensitizing irradiation is usually followed by an intense sometimes blistering inflammatory reaction.

The induced photosensitization is revealed 10–14 days after the last irradiation: a patch test is made on an area different from that used for sensitization and irradiated 4 J/cm^2 UVA (solar simulator with WG345 filter). Controls include a similar photopatch test with the vehicle only and a nonirradiated patch test. Readings are to be recorded 24 h and 48 h after irradiation. To differentiate phototoxic and photoallergic reactions, the authors recommend to reduce both the concentrations of the tested compound and the irradiation doses.

However interesting this method may be, it raises a major ethical issue, the risk of photosensitizing the volunteers.

3.2 Investigations in Photodermatoses

Obviously, the diagnosis of photodermatosis is established through the patient's interview and clinical examination but if there are no apparent lesions, the use of photobiological exploration becomes essential (Beani 1987; Emmett 1986; Epstein 1962; Goerz et al. 1995; Hölzle et al. 1987; Leroy et al. 1992; Meola et al. 1993; Selvaag and Thune 1996). Photopatch tests are commonly used but are weighty and time consuming when compared to the experimental reproduction of the lesions, which is the preferred test in the diagnosis. They should be used only if photosensitization is strongly suspected. It is necessary to use them appropriately as one cannot completely avoid the risk of inducing photosensitization by the tests themselves (Meola et al. 1993).

- Here the purpose of a photopatch tests is to look for a photoallergy to the compound, possibly at the origin of the disease, whereas identifying a phototoxic reaction would only suggest the compound is potentially photosensitizing without relation to the disease (the same remark applies to all the above mentioned photobiological tests). Making a difference between the two types of results requires low UV doses and low compound concentrations (British Photodermatology Group Workshop report 1997; Emmett 1986; Goerz et al. 1995; Jeanmougin M. et le Groupe de Recherche en Photobiologie Cutanée 1986; Menz et al. 1988; Schauder 1985) because photoallergic reactions are not dose dependent. Accordingly, the suggested UVA dose is only 5 J/cm^2; in case of doubtful reaction, the test should be made again but with still reduced UV doses. The tested compounds are selected according to the patient's history, and tests with standard compounds involving the most usual photosensitizers are also systematically carried out.
- Photopatch test's efficiency in finding the responsible agent is satisfactory in contact photoallergy but poor in systemic drug-induced photoallergy. For example, in the latter case a negative result does not mean nonresponsibility of the suspected drug and a positive result with a drug from the standard battery does not imply its involvement either.

The responsibility of the drug requires that the patient has been in contact with it and that in the patient's history photosensitization bursts match contacts with the drug. Illustration of the poor photopatch test's efficiency and how cautious should be the interpretation in case of suspected photoallergy is given by a recent paper (Conilleau et al. 2000) where among 15 patients suffering from drug photoallergy only three had photopatch tests positive to the suspected compound. This confirms a study from the German-Austrian-Swiss photopatch tests group (870 tested patients): 2,041 photopatch tests were positive but only 108 were considered as evidence of photoallergy with clinical relevance (Hölzle et al. 1991). This low specificity is also shown in a Mayo Clinic's study (Menz et al. 1988), in which only 14 out of 27 positive photopatch tests were confirmed as having clinical relevance.

While it is difficult to explain these false-positive photopatch tests of photoallergic type, possible explanations can be found to the false-negative results: compound low penetration capacity, unsuitable vehicle, inappropriate methodology (UV dose, irradiation time, etc.), and wrong interpretation. In fact, there is a lack of soundness in most investigations related to the diagnosis of drug-induced photoallergy. Especially, facilitated transcutaneous penetration in photopatch tests and the use of systemic tests should increase their reliability. But such tests cannot be used in routine and remain restricted to research laboratories.

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