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Thoughts on the interpretation of positive photopatch test reactions

Background: Positive photopatch test reactions are classified according to the International Contact Dermatitis Group. The various reaction patterns are interpreted to represent patterns such as contact allergy, photocontact allergy, photoaugmentation, and photoinhibition. **Objective:** To investigate whether there are any weaknesses in the interpretation of reaction patterns. **Materials & Methods:** A dermatitis patient with photoallergic contact dermatitis due to ketoprofen was photopatch tested with serial dilutions of ketoprofen in ethanol. The reaction patterns for the various concentrations were used as a basis for discussion on weaknesses regarding the present interpretations of positive photopatch test reactions. **Results:** The reaction patterns to the ketoprofen photopatch at various concentrations were interpreted as (i) contact allergy, (ii) contact allergy with photoaugmentation, (iii) contact allergy and photocontact allergy, and (iv) photocontact allergy. **Conclusion:** The present interpretation of positive photopatch test reactions is unreliable and therefore insufficient regarding appropriate advice for patients.

Key words: photopatch testing, interpretation, photoallergic contact dermatitis, ketoprofen

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To arrive at a diagnosis of photoallergic contact dermatitis, as is the case for allergic contact dermatitis, a three-step procedure is required of which the first step is to establish photocontact allergy [1]. Presently, the only way to do this is by photopatch testing. Recommendations on how to perform photopatch testing in a standardized way, including interpretation of positive test reactions, have been published since the late 1970s [2-10]. Based on the morphology of the photopatch test reactions, the reactions are classified according to the International Contact Dermatitis Group (ICDRG) [11]. The photopatch testing should always be performed with a duplicate set of potential photosensitizers, including a baseline photopatch test series, as well as, depending on the history and clinical features, other chemicals and products such as personal sunscreens. All products are tested in duplicate, one of which is tested on an unirradiated area (often on one side of the back), covered by a UV-impermeable material immediately after the removal of the patches. A duplicate (on the other side of the back) is irradiated with UVA, most often 5 Joules/cm² [2-10]. Depending on the distribution of positive reactions on the unirradiated and irradiated sites, the interpretation of the reactions is virtually the same irrespective of the pattern, excluding irritant and unclear reactions (table 1). When there is at least one positive reaction, one of five reaction patterns (table 1) may be ascribed to the tested chemical. Occasionally, supplementary investigations, including testing with controls, are needed to distinguish between a phototoxic and photoallergic reaction [2-10].

Examples of interpretations in photopatch-tested dermatitis patients

In table 2, examples of interpretation of five different sets of positive photopatch test reactions are presented.

Problems with the present interpretation of positive photopatch reactions

The present interpretation of positive photopatch reactions is insufficient and may be misleading for the management of patients with contact dermatitis, allergic and/or photoallergic (tables 2, 3). The five examples in table 2 originate from a single patient who was photopatch tested on one occasion with a dilution series of ketoprofen, starting at 1.0% w/v with consistent application of 15 µL [12] applied to a small Finn chamber with a diameter of 8 mm (dose: 30 µL/cm²).

According to the photopatch test reactions shown in table 3, the patient had four out of five possible reaction patterns. Depending on the concentration (dose/cm²), the photopatch tested patient was shown to have: (i) contact allergy, (ii) contact allergy with photoaugmentation,

Table 1. Interpretation of positive photopatch test reactions classified according to the International Contact Dermatitis Group.

Unirradiated site	Irradiated site	Interpretation
+	+	Contact allergy
++	++	Contact allergy
+++	+++	Contact allergy
+	+++	Contact allergy and photocontact allergy
+	++	Contact allergy with photoaugmentation
++	+++	Contact allergy with photoaugmentation
+++	++	Contact allergy with photoinhibition
++	+	Contact allergy with photoinhibition
-	+	Photocontact allergy
-	++	Photocontact allergy
-	+++	Photocontact allergy

Table 2. Examples of interpretation of five different sets of positive photopatch test reactions.

Example	Unirradiated site	Irradiated site	Interpretation
1	+++	+++	Contact allergy
2	++	+++	Contact allergy with photoaugmentation
3	+	+++	Contact allergy and photocontact allergy
4	-	++	Photocontact allergy
5	-	++	Photocontact allergy

Table 3. Results of photopatch testing using a dilution series of ketoprofen in ethanol in the same dermatitis patient on one test occasion.

Ketoprofen in ethanol, concentration: w/v	Unirradiated site	Irradiated site	Interpretation
1.0	+++	+++	Contact allergy
0.1	++	+++	Contact allergy with photoaugmentation
0.01	+	+++	Contact allergy and photocontact allergy
0.001	-	++	Photocontact allergy
0.0001	-	++	Photocontact allergy

(iii) contact allergy and photocontact allergy, and (iiii) photocontact allergy to ketoprofen. Clearly, the present system of interpretation of positive photopatch reactions is imprecise.

Weaknesses in interpretation

The weaknesses in interpretation are discussed under the following four subheadings, based on the intensity of the test reactions at the unirradiated and irradiated sites.

1. Same degree of test reactivity at unirradiated and irradiated sites (+++ / +++ ; ++ / ++ ; + / +)

These reaction patterns are interpreted as representing contact allergic reactions (*tables 1-3*). It is very likely that the ++ and + reactions on both test sites (*table 1*) represent contact allergy while one should be sceptical when it comes to +++ reactions. The reason for this is that a +++ reaction represents the highest possible intensity of a test reaction, irrespective of whether it is allergic or photoallergic. Thus, for a strong photocontact allergy, as in the case presented in *table 3*, the +++ reaction for the irradiated site has already been achieved at a dose 100 times lower than that for both +++ reactions at the unirradiated and irradiated sites. Regarding the case in *table 3*, the “contact allergy” was not apparent at a photopatch test concentration 1,000-fold lower than the concentration eliciting +++ reactions on both the unirradiated and irradiated sites. However, does it really matter whether the test reaction is diagnosed as contact allergic or photocontact allergic? Indeed, for the management of dermatitis, it is of utmost significance to know whether a patient has photocontact allergy or not. Testing for cross-reactivity and simultaneously over-represented allergies differs depending on the nature of the allergy. Furthermore, the avoidance of UV irradiation is not important for contact allergy but might be decisive for photocontact allergy in order to exclude dermatitis. Can the misinterpretation exemplified in *table 3* be avoided? One way to avoid misinterpretation is to test all individuals with +++ / +++ reactions with a decreasing dilution series of the sensitizer to at least 1,000-fold less than the dose (concentration) that elicited the +++ / +++ reactions. The 1,000-fold dilution is based on the reactions of the patient in *table 3* and the dilution range may vary depending on the sensitizer/photosensitizer involved, as the gradients of the dose-response curves for elicitation of a positive reaction will likely be different.

2. One-grade difference in the degree of test reactivity for positive reactions at unirradiated and irradiated sites (+ / ++ ; ++ / +++ ; +++ / ++ ; ++ / +)

As presented in *table 1*, these reaction types represent either photoaugmentation when the degree of reactivity is higher at the irradiated site or photoinhibition in the opposite situation, with a higher degree of reactivity on the unirradiated site. Obviously, photoaugmentation and photoinhibition have been demonstrated *in vitro* and *in vivo* in various species using UVA doses other than that used

for photopatch testing. In one study, photoaugmentation and photoinhibition were demonstrated for a single contact sensitizer; no defined doses of the sensitizer were used [13]. Furthermore, using petrolatum as a vehicle [11] for hydrophilic substances implies possible solubility problems with uneven distribution of the sensitizer in the vehicle. Presently, these reaction types must be questioned due to the variation in test response when the same test preparation is tested with the same dose and test methodology multiple times on the same test occasion. Variation in the degree of patch test reactivity has been shown to be common for both metals and a fragrance ingredient [14, 15]. Thus, the combinations with different degrees of test reactivity at the unirradiated and irradiated sites should never automatically be interpreted as photoaugmentation or photoinhibition unless further testing is performed. If the pattern is consistent when tested several times with the same test method and dose/cm², of course an interpretation of photoaugmentation or photoinhibition is justified. However, from a statistical point of view (McNemar's test, 2-sided), such testing requires the pattern to be repeated six times in order to be evaluated as significant, provided that the opposite pattern does not occur. In the event of the opposite pattern occurring, the need for a higher number of prevailing reaction patterns increases to support the interpretation of photoaugmentation or photoinhibition. Clearly, it is not feasible to test multiple times to confirm photoaugmentation or photoinhibition.

Can photoaugmentation and photoinhibition therefore manifest during photopatch testing? I believe that this is an area to be further explored scientifically. Although a single UVA dose during photopatch testing may be too low to have an immunological impact, it may have a chemical impact. Theoretically, a photopatch-tested substance may be metabolized in the skin to form the hapten, and subsequently a contact allergic reaction. This metabolite, as the hapten, may also be formed upon photooxidation in the skin, hence more molecules of the hapten may be generated on the irradiated site than on the unirradiated site, thus creating a reaction pattern consistent with photoaugmentation. A similar situation, at least theoretically, may occur as a result of altered metabolism in the skin due to a contact allergen, in which photooxidation in the skin degrades the substance to a non-sensitizer (non-metabolite).

From a clinical point of view, does it really matter whether a photopatch-tested individual has positive reactions representing photoaugmentation or photoinhibition? It is hard to see how photoinhibition in a patient would have any clinical implications in the management of dermatitis besides treatment with UV radiation of an allergic contact dermatitis due to an unavoidable sensitizer. On the other hand, photoaugmentation may justify an avoidance of UV irradiation by using protective textiles or sunscreens if the photoaugmented contact sensitizer is widespread.

3. A “+ reaction” on the unirradiated site and a “++ reaction” on the irradiated site

This combination is considered to represent both contact allergy and photocontact allergy, although the contact

allergy would most likely not be considered upon repeated photopatch testing with a lower dose. In any case, I do not doubt that both types of allergy to a substance may be present in the same individual. However, there is also an additional interpretation. The contact allergic reaction may be a false positive and due to a photoallergic reaction resulting from the unintentional UV irradiation when taking off the test patches and before covering the site to be unirradiated with a UV-impermeable material. The patient in *table 3* had a contact allergic and photocontact allergic reaction to a ketoprofen concentration of 0.01%, with 15 µL applied to a small Finn chamber with a diameter of 8 mm. At a 10-fold dilution, the contact allergic reaction disappeared, while the concentration most likely could be lowered 1,000-fold to 0.00001% and still elicit a positive photopatch test result. If one presumes that the UVA dose is related to the number of molecules of photosensitizer in order to elicit a positive photopatch test result, a test concentration of 0.01% would allow lowering of the UVA dose from 5 J/cm² to 5 mJ/cm². Is such a low level of unintentional UVA irradiation to the “unirradiated” site possible before covering the site with UVA-impermeable material? Ketoprofen and many other photosensitizers exhibit a higher level of absorption in the UVB region than the UVA region. Could an unintentional one-minute UVB dose contribute to a positive photopatch test, incorrectly interpreted as a contact allergic reaction? Obviously, this is another area that requires further scientific exploration in order to define the range of unintentional UVA and UVB irradiation on the “unirradiated” site during photopatch testing performed in different departments and during different seasons.

4. A negative reaction on the unirradiated site and a “+ reaction” on the irradiated site

According to *table 1*, this reaction pattern represents photocontact allergy. This is probably the case, at least for substances for which photocontact allergy but not contact allergy has been demonstrated. On the other hand, if the substance contains a compound for which contact allergy has been unambiguously demonstrated, then the possibility of a false negative reaction on the unirradiated site must be considered [14, 15]. Repeated photopatch testing with the same concentration as well as both higher and lower concentrations may help resolve the problem. As mentioned before, this is of utmost significance for the management of a patient in order to establish whether he/she has a contact or photocontact allergy.

Suggestions

As discussed and exemplified in this paper, the recommended interpretations of positive test reactions upon photopatch testing can give rise to incorrect and insufficient information on which allergy the patient has contracted. Improved knowledge is needed within certain areas to enable different interpretations or to define combinations of negative and positive reactions which can be problematic.

Suggestions on possible supplementary investigations to enable improved interpretation of initial photopatch test reactions are given below:

(i) In patients with “+++ reactions” on both the unirradiated and irradiated sites, a second photopatch test should be performed with dilutions of the “sensitizer/photosensitizer” to investigate the dose response curves for possible contact allergic and photocontact allergic reactions.

(ii) In patients with positive reactions on both the unirradiated and irradiated sites, interpreted as photoaugmentation or photoinhibition, simultaneous and multiple photopatch tests should be performed with the same methodology. To ensure the same dose of test preparation applied, a vehicle enabling the substance to be dissolved and applied onto the test chamber with a micropipette should be used [16].

(iii) In patients with various photocontact allergies, investigations to determine a direct relationship between the UVA dose on the one hand and the number of molecules (dose/cm²) on the other should be performed [17]. In the event of such a relationship, within which range does it exist?

(iv) In photopatch-tested patients, the amount of unintentional UVA and UVB irradiation on the “unirradiated” site during the photopatch test procedure should be determined in different settings and during different seasons. ■

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