

INVESTIGATIVE REPORT

Successful Photopatch Testing with Ketoprofen Using One-Hour Occlusion

Victoria MARMGREN^{1,2}, Monica HINDSÉN¹, Erik ZIMERSON¹ and Magnus BRUZE¹

¹Department of Occupational and Environmental Dermatology, Skåne University Hospital, Malmö, Lund University, Lund, and ²Department of Dermatology, Southern Älvsborg Hospital, Borås, Sweden

The standard procedure for photopatch testing includes 24-h occlusion of the allergen, followed by irradiation at 5 J/cm² ultraviolet A (UVA). Due to the timing, a separate visit to the clinic is needed for UV irradiation. The aim of this study was to determine whether a reduction in occlusion time from 24 h to 1 h, in order to simplify the testing procedure, influences test results when photopatch testing with ketoprofen. A total of 22 patients with a known or suspected photo-allergy to ketoprofen were simultaneously photopatch-tested with ketoprofen using both 1 h and 24 h occlusion. One side of the patient's back was irradiated with 5 J/cm² UVA, and the other side was covered. Measurements were made after 3 days on both irradiated and non-irradiated sides. A total of 20 controls were photopatch-tested with ketoprofen using 1 h occlusion. All of the patients showed positive reactions on the irradiated side. No positive reactions were observed on the non-irradiated side. All controls were negative. In conclusion, 1 h occlusion time is sufficient to establish photo-contact allergy to ketoprofen. No adjustments in UVA or ketoprofen dose were needed. Limiting occlusion time to 1 h could simplify the photopatch test procedure by eliminating one visit to the clinic. These results apply only to ketoprofen; further studies are needed to determine whether a similar approach can be used with other components of photopatch test series. *Key words:* photo-allergy; 24 h, occlusion time; UVA; benzophenone; NSAID; topical treatment.

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Victoria Marmgren, Southern Älvsborg Hospital, Brämhultsv. 53, SE-501 82 Borås, Sweden. E-mail: victoria.marmgren@vgregion.se

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) that is widely used in Europe. In Sweden it is used orally, rectally and topically. Topical gels (Siduro[®], Ipex Medical AB, Solna, Sweden; Orudis[®], Sanofi-Aventis AB, Bromma, Sweden; and Zon[®], Antula Helthcare AB, Stockholm, Sweden) are over-the-counter drugs¹. These preparations are very popular for treatment of localized inflammation and pain because they are fairly easy to use and are thought to cause fewer side-effects

than oral medication. It is well-known, however, that topical ketoprofen is responsible for more photo-related skin reactions than other topical NSAIDs. Over the years there have been many reports of photo-contact allergy to ketoprofen from different countries (1–12). Also, in Sweden, ketoprofen is one of the main drugs causing photosensitization (9).

During the last 4 years more than 50 patients who developed skin reactions after using topical ketoprofen-containing gel have been referred to the Department of Occupational and Environmental Dermatology, Malmö University Hospital. The vast majority of patients had had quite severe reactions, sometimes mimicking other conditions such as deep vein thrombosis. These conditions had, however, been ruled out prior to referral. When photopatch-tested with the standard procedure, most of the patients developed vigorous vesicular-bullous reactions to ketoprofen (11).

The Scandinavian Photo Contact Derm Research Group and the corresponding European group have published guidelines on photopatch testing, in which components of the photopatch test series and ultraviolet A (UVA), as the radiation source of choice, were suggested (13, 14). According to these guidelines the occlusion time for a potential photosensitizer is 24 h (13, 14) or 48 h (14), the timing being a matter for discussion, with different clinics using different protocols. In our clinic we use 24 h as the standard occlusion time for photopatch testing. The British Photodermatology Group describes, in a report from 1997 (15), three protocols in use in the UK. The occlusion time is 24 h according to one protocol and 48 h according to two others. Batchelor & Wilkinson (16) compared 24 h with 48 h occlusion, and suggested that the latter is perhaps more sensitive. Nonetheless, all of these approaches mean that an additional visit to the clinic is required for irradiation of the test site.

The aim of this study was to investigate whether a reduction in occlusion time during photopatch testing

¹Until recently ketoprofen was available as an over-the-counter drug. In July 2010 the decision was made by European Committee for Medicinal Products for Human Use (CHMP) that due to fotosensitizing capacity of ketoprofen the prescription will be mandatory. The article was written before this information had become official.

with ketoprofen can be made, such that the test sites can be irradiated sooner after patch test application without affecting the test results.

MATERIALS AND METHODS

Patients

Since 2005, 22 patients (11 men and 11 women, mean age 49.5, range 17–68 years) with known or suspected photo-contact allergy to ketoprofen have participated in the study. Patients who were referred to our clinic with suspected photo-contact allergy to ketoprofen, but who had not yet been tested, were automatically included in the study (11 patients). Patients who were tested earlier (2000 to 2003) and showed positive photopatch reactions to ketoprofen were contacted and invited to participate (11 patients). This approach was approved by the Regional Ethical Review Board in Lund, Sweden. Informed consent was obtained from each patient in group 2 (those tested earlier).

Test preparations

A stock preparation of ketoprofen in petrolatum at 10.0% w/w was further diluted to the desired concentrations with petrolatum (2.5% and 1.0% w/w). Solutions of ketoprofen in ethanol at the following concentrations (2.5%, 1.0%, 0.1%, 0.01%, 0.001% and 0.0001% w/v) were used for photopatch testing. The original ketoprofen preparation was obtained from Sigma (Aldrich, Stockholm, Sweden). Ethanol 99.5% v/v was obtained from Kemetyl AB (Haninge, Sweden). Petrolatum (Vaselinum Album), USP/NF, was provided by Apoteket AB (Gothenburg, Sweden).

Light source

The light source used was UV440DT IP20 luminare (ESSHÅ Elagentur AB, Värnamo, Sweden) equipped with 4 Philips PL-L 36W UVA tubes (Philips AB, Sundsvall, Sweden).

The metering device, which was used to ensure that the correct UVA dose was given, was a Delcomp UV-meter (PUVA Combi Light, Leuven, Belgium).

Photopatch testing and substances

All 22 patients in our study were photopatch-tested with ketoprofen using both 24 h and 1 h occlusion. Patches with test preparations were placed on the patient's back in 22 cases and

on the upper arm in 11 cases. Photopatch testing was performed using small Finn Chambers Ø8 mm (Epitest Ltd, Tuusula, Finland), secured with Scanpore tape (Norgesplaster A/S, Vennesla, Norway). The test sites were irradiated with UVA.

Two different approaches were used depending on whether photo-contact allergy to ketoprofen had already been shown or was only suspected (Table I).

In the following description, the word "standard" is used to indicate that the occlusion time is 24 h, and the word "study" refers to 1 h occlusion.

Group 1 (patients with suspected photo-contact allergy to ketoprofen)

Patients in this group were tested with our standard photopatch test series together with ketoprofen in serial dilutions (referred to as "standard patches 24 h") attached to the left side of the back, and ketoprofen patches alone (referred to as "study patches 1 h") attached to the left upper arm. Identical sets of "standard" and "study" patches were applied to the right side of the back and to the right upper arm to serve as non-irradiated controls.

The procedure is illustrated in Fig. 1a. Concentrations and vehicles are set out in Table I.

Group 2 (patients with known photo-contact allergy to ketoprofen)

Patients in this group were tested with two sets of patches containing serial dilutions of ketoprofen in ethanol applied to the right side of the upper back ("standard patches 24 h") and to the left side of the upper back ("study patches 1 h"), respectively. Single patches with the highest tested concentration of ketoprofen for each respective group (1.0% w/v for "standard patches 24 h" and 2.5% w/v for "study patches 1 h") were attached to the back in a lower position, to serve as non-irradiated controls. Patients who had shown strong positive reactions to ketoprofen previously were not tested with 1.0% ketoprofen.

The procedure is illustrated in Fig. 1b. Concentrations and vehicles are described in Table I.

Controls

Controls were used to investigate whether phototoxicity could explain the positive results. Twenty dermatitis patients investigated for a suspected allergic contact dermatitis with epicutaneous testing were simultaneously photopatch-tested with ketoprofen. Controls were tested with ketoprofen 2.5% and 1% w/w in petrolatum with 1 h occlusion, followed by UVA irradiation at 5 J/cm².

Table I. Overview of the photopatch testing procedure with 1 h and 24 h occlusion, including control patches

	Group 1 (Suspected photo-contact allergy)				Group 2 (Known photo-contact allergy)			
	Study patches 1 h	Standard patches 24 h ^c	Control patches 1 h	Control patches 24 h	Study patches 1 h	Standard patches 24 h ^d	Control patches 1 h	Control patches 24 h
Location	Left side of the upper back ^a	Left upper arm ^b	Right side of the upper back ^a	Right upper arm ^b	Left side of the upper back ^b	Right side of the upper back ^b	Left side of the back ^b	Right side of the back ^b
Concentration of ketoprofen, %	2.5, 1.0 w/w	1.0, 0.1, 0.01, 0.001, 0.0001 w/v	2.5, 1.0 w/w	1.0, 0.1, 0.01, 0.001, 0.0001 w/v	2.5, 1.0, 0.1, 0.01, 0.001 w/v	1.0, 0.1, 0.01, 0.001, 0.0001 w/v	2.5 w/v	1.0 w/v
Occlusion time, h	1	24	1	24	1	24	1	24
UVA irradiation	Yes	Yes	No	No	Yes	Yes	No	No

^aKetoprofen preparations in petrolatum.

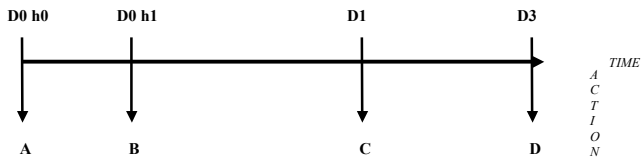
^bKetoprofen preparations in ethanol.

^cStandard patches consist of photopatch test series including ketoprofen in serial dilutions.

^dStandard patches consist of ketoprofen in serial dilutions only.

UVA: ultraviolet A.

- a) Suspected photocontact allergy**
- A. Patches with serial dilutions of ketoprofen in ethanol and the standard photopatch test series are applied to the left side of the back ("standard patches 24 h") and to the right side of the back ("control patches 24 h").
patches with dilutions of ketoprofen in petrolatum are applied to the left upper arm ("study patches 1 h") and to the right upper arm ("control patches 1 h").
 - B. Removal of the "control patches 1h" and the "study patches 1 h". The site for "control patches 1h" is covered with black cloth and the site for "study patches 1 h" is irradiated with UVA 5 J/cm² (without cleaning).
 - C. Removal of the "control patches 24 h" and the "standard patches 24 h". The site for "control patches 24 h" is covered with black cloth and the site for "standard patches 24 h" is irradiated with UVA 5 J/cm² (without cleaning).
 - D. Test reading



- b) Known photocontact allergy**
- A. Patches with dilutions of ketoprofen in ethanol are applied to the right side of the upper back ("standard patches 24 h") and to the left side of the back ("study patches 1 h")
single patch with ketoprofen in ethanol is applied to right side of the back ("control patch 24 h") and to the left side of the back ("control patch 1 h").
 - B. Removal of the "control patch 1h" and the "study patches 1 h". The site for "control patch 1 h" is covered with black cloth and the site for "study patches 1 h" is irradiated with UVA 5 J/cm².
 - C. Removal of the "control patch 24 h" and the "standard patches 24 h". The site for the "control patch 24 h" is covered with black cloth and the site for "standard patches 24 h" is irradiated with UVA 5 J/cm².
 - D. Test reading.

Fig. 1. Photopatch test procedure for patients with (a) suspected and (b) known photo-contact allergy to ketoprofen (Group 1) (D=day, h=hour).

Statistical analysis

In theory there should be complete concordance between the results of photopatch testing with 1 h occlusion and 24 h occlusion. However, it is not possible to prove this correlation statistically. To reach a confidence interval of 0.83–1.0 a total of 20 patients must be tested using both methods (occlusion for 1 h and 24 h, respectively) and positive concordant results demonstrated.

To compare the number of positive reactions in test patients and controls the Fisher's *t*-test (two-sided) was used.

RESULTS

All patients who were positive on earlier photopatch test occasions showed positive results at re-testing during our study. Positive photopatch test reactions to ketoprofen, with morphology consistent with the allergic nature of the reactions, was demonstrated in all patients with suspected photo-contact allergy. A plane erythema was read as a (+) reaction, erythema with a slight infiltration covering the whole test area

and possibly a few papules was read as a + reaction, a ++ reaction included many papules and possibly a few vesicles, and a +++ reaction included many vesicles or a bullae.

Of the 22 patients tested, 20 showed positive test results on the site tested with the standard method using 24 h occlusion. Two patients showed doubtful reactions (Table II), both had a known photo-allergy to ketoprofen, where patient N14 had previously reacted with +++ for ketoprofen 1.0% w/v and patient N22 with + for the same concentration.

All of the patients who tested positive to ketoprofen with standard photopatch testing, and two patients with doubtful reactions, were positive when tested with 1 h occlusion. None of the 20 dermatitis patients who served as controls was positive (*p* < 0.001).

With 1 h occlusion the strength of the reactions was +++ in 17 cases, ++ in two cases, + in two cases and one patient showed a doubtful reaction when tested with 1.0% ketoprofen (Table II). In both groups (24 h and 1 h) there were positive reactions down to 0.001%, and in one case in the 24 h group a positive reaction was seen at 0.0001% w/v dilution of ketoprofen.

Thirteen patients were tested with 1.0% ketoprofen with both 24 h and 1 h occlusion. In this group 10 +++

Table II. Results of the photopatch testing with ketoprofen using 1 h and 24 h occlusion in 22 individuals. Results are presented for the irradiated test sites only, readings 3 days after the application. Non-irradiated controls gave no positive reactions and are not presented in the table

	Ketoprofen, 24 h occlusion					Ketoprofen, 1 h occlusion*				
	1	0.1	0.01	0.001	0.0001	2.5	1	0.1	0.01	0.001
N1	+++	+++	+++	++	+	+++	+++	NT	NT	NT
N2	+++	+++	-	-	-	+++	+++	NT	NT	NT
N3	+++	+++	+++	-	-	+++	+++	NT	NT	NT
N4	+++	+++	+++	-	-	+++	+++	NT	NT	NT
N5	+++	+++	++	-	-	+++	+++	NT	NT	NT
N6	+	+	+	-	-	++	+	NT	NT	NT
N7	+++	+++	+	-	-	+++	+++	NT	NT	NT
N8	+++	++	++	++	-	+++	+++	NT	NT	NT
N9	+++	+++	+	-	-	+++	+++	NT	NT	NT
N10	+++	+++	++	-	-	+++	+++	NT	NT	NT
N11	+++	+++	++	-	-	+++	+++	NT	NT	NT
N12	NT	+++	++	-	-	+++	+++	+++	+++	+++
N13	NT	+++	+	-	-	+++	+++	+++	+	-
N14	NT	(+)	(+)	-	-	+++	+++	+	-	-
N15	NT	+++	-	-	-	+++	++	(+)	-	-
N16	NT	+	++	-	-	++	+	-	-	-
N17	NT	++	-	-	-	+++	+++	++	-	-
N18	NT	+	-	-	-	+++	+++	++	(+)	-
N19	NT	+++	++	-	-	+++	+++	+++	++	-
N20	NT	++	-	-	-	+++	+++	(+)	-	-
N21	+++	+	-	-	-	++	(+)	-	-	-
N22	(+)	-	-	-	-	++	++	-	-	-

*Patients N1–11 (group 1, suspected photo-contact allergy) are tested using ethanol as the vehicle and only two dilutions of ketoprofen applied to the upper arm when tested with 1 h occlusion. Patients N12–22 (group 2, known photo-contact allergy) are tested with ketoprofen dilutions in ethanol for 24 h occlusion and with ketoprofen dilutions in petrolatum for 1 h occlusion. NT: not tested.

reactions were present after 24 h occlusion and 9 +++ reactions after 1 h occlusion. In one case a +++ reaction in 24 h group became a doubtful ((+)) reaction when occlusion was 1 h. At the same time, one doubtful reaction at 24 h testing changed into a ++ reaction with the 1 h protocol.

Twelve patients were tested with 0.1% with both 24 h and 1 h occlusion. In this group three of the reactions that were positive in the 24 h group became negative in the 1 h group, two +++ and one ++ reaction became doubtful in the 1 h group. Patients N14, N17 and N18 showed a trend towards stronger reactions in the 1 h group for this concentration.

DISCUSSION

The success of the patch-testing procedure depends on several factors of significance, such as the dose of the sensitizer, the patch-test technique and the occlusion time (16–20). With one and the same test technique the concentration can be used as a parameter of dose, provided that the same volume/amount of sensitizer is always applied to the patch unit and that there is no spreading outside the test unit. In addition to these factors of significance for the patch-test, there is one more factor of obvious significance for the photopatch test, namely the quality and quantity of UV radiation. Furthermore, the time interval between occlusion and irradiation of the patch-test area is likely to be an important factor for the photo-allergic response. For the patch-test a longer occlusion time means that more molecules of the sensitizer can migrate from the patch unit into the skin, up to the time-point where all molecules have left the test unit. Thus, for substances with a slow release, a longer occlusion time means there is a higher likelihood of a positive patch-test response. This also applies to the photosensitizer when it comes to the availability of the tested molecule(s) in the skin. The UV radiation may transform the tested substance or its skin metabolite into a sensitizer. However, with regard to the photosensitizer, the chemical responsible for the photo-allergic response is always a different chemical from the tested substance. Consequently, factors such as the kinetics of penetration of the tested substance and possible metabolism in the skin are, in our opinion, probably more important for photopatch testing compared with patch-testing. For example, if a substance is rapidly released from the patch unit and also rapidly migrates through the skin before UV radiation, a few molecules may be present in the superficial skin layers to become “photo-activated” and elicit a positive photopatch test. In theory, a short occlusion time followed by UV radiation might suffice to provide the required number of the real photo-sensitizers to elicit a positive photopatch test.

In 1982 the Scandinavian Photo Contact Derm Research Group suggested a list of allergens, including

concentrations and vehicle, type of radiation source and time for reading the results (13). More recently, a consensus methodology for European photopatch testing has been suggested (14). UVA is used as a radiation source, but, until recently, the dosage has not been evidence-based. The study published in 1993 by Duguid et al. (19) showed that doses of 5 J/cm², down to as little as 1.0 J/cm² are sufficient for photo-elicitation, but in order to avoid false negative test results 5 J/cm² should remain the standard (14). In 1996, Hasan & Jansen (20) concluded that lowering the UVA dose below 5 J/cm² (doses used in the study were 1 J/cm² and 2.5 J/cm²) could lead to the loss of significant photo-contact test reactions, but increasing the dose to between 20–40 J/cm² and 80 J/cm² did not give a significantly higher number of positive reactions. Regarding the occlusion time, different protocols exist (13–16), but the one currently used in our clinic requires 24 h between the application of allergen and removal of the patches/UVA irradiation. In practice this means that a tested patient has to visit the clinic on one day exclusively for irradiation (Table III). If the radiation could be performed not long after application of the patch test this would save both time and money for the patient and the clinic.

The UVA dose used in this study was 5 J/cm², which is the same as is routinely used for photopatch testing in our clinic. As the number of molecules of a sensitizer/photo-sensitizer depends on the dose and the occlusion time, a shorter occlusion time could be compensated for by a higher dose if necessary (21). Ketoprofen concentrations tested in our department are normally 2.5% (i.e. gel as is), 1.0%, 0.1%, 0.01%, 0.001% and 0.0001% w/w in ethanol. For testing with 1 h occlusion, we removed the lower concentrations in some cases and tested with only 2.5% and 1.0% w/w in petrolatum. The occlusion time was decreased to 1 h from the previous 24 h.

Eleven patients included in the study had a known photo-allergy to ketoprofen, verified previously by conventional photopatch testing, and the rest were suspected to be photo-allergic. All of the patients were tested using the standard procedure during the study, and all but two showed positive reactions. In most cases reactions were strong, +++ for the highest tested concentration, while there were no reactions on the non-irradiated side. None of the 20 dermatitis patients who were tested with ketoprofen using 1 h occlusion

Table III. Comparison of the standard and shortened procedure for photopatch testing with ketoprofen, occluded for 24 h and 1 h, respectively

"24 h"-procedure (standard)	"1 h"-procedure
Day 0: Application of patches	Day 0: Application of patches, removal after 1 h and UVA irradiation of the test site
Day 1: Removal of patches.	
UVA irradiation of the test site	
Day 3: Reading	Day 3: Reading

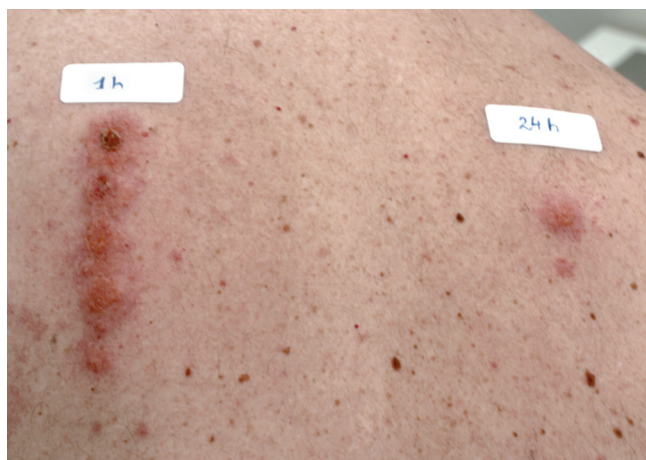


Fig. 2. The back of a patient (group 2, known photo-contact allergy) photopatch tested with ketoprofen in serial dilutions, using 1 h and 24 h occlusions (labels).

had a positive test reaction. This suggests the presence of photo-contact allergy at the time of study.

While testing with only 1 h occlusion we could confirm that all of the tested patients developed rather strong positive reactions (Fig. 2). It was evident that 2.5% and 1.0% ketoprofen occluded for 1 h gave responses equivalent to 1.0% and 0.1% ketoprofen occluded for 24 h, respectively (Table I). The best concordance between the two groups occurred for a 1.0% concentration, although the vehicle was different. This makes 1.0% the concentration of choice, though the role of the vehicle is not completely clear. However, according to our experience, testing with petrolatum and ethanol gives equivalent results.

It is interesting that even the patient with negative/doubtful results at the standard photopatch testing with ketoprofen 1.0% showed a ++ positive reaction to this dose at testing with 1 h occlusion. In theory, reactions that strong may be due to phototoxicity. However, factors mitigating against this are: negative controls, the pattern of the reactions in the dilution series and the morphology of the reactions. If we assume that such strong reactions are caused by highly irritant, but short-lived, reaction products that are formed in the skin on application of ketoprofen, then we should expect that controls also develop positive reactions after 1 h occlusion. However, no such reactions were observed. Thus, we cannot exclude the possibility that ketoprofen might have some phototoxicity in humans; however, taking all these facts into consideration we believe that the reactions are photo-allergic in nature.

Because a photo-allergic reaction follows a certain immunological pathway, it may be more difficult to elicit the reaction with only 1 h occlusion. It is possible that, besides the increased concentration of allergen, the radiation dose may have to be increased. Thus, far fewer investigations have been performed on the patch-test methodology (21, 22). The significance of occlusion time with phototoxic chemicals has been studied. The

optimal occlusion time for psoralen was found to be 1 h, while the corresponding time for coal-tar was 24 h (17, 23).

Considering the high concordance between test results for the standard test procedure and our new modified test procedure we have shown that photopatch testing with ketoprofen using 1 h occlusion gives reliable test results and may be used instead of 24 h occlusion. The obvious advantage of this method is that the procedure becomes easier and more cost-efficient for both the patient and the physician (Table III). At present it is not possible to adjust the photopatch test procedure to each individual component in the photopatch test series. Therefore, if a clinician needs to pursue testing to determine more about a patient's photo-contact allergy status, he or she will have to use a standard approach to testing and follow the guidelines. However, in those, albeit rare, situations when ketoprofen needs to be tested as a single allergen, or, if testing with ketoprofen is part of a research study, 1 h occlusion presents clear advantages. Further research is required to determine whether a similar approach can be used with other components of photopatch test series.

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