

Frequency of sensitization to methyl aminolaevulinate after photodynamic therapy

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Background: Allergic contact dermatitis to methyl aminolaevulinate (MetvixTM) after topical application in photodynamic therapy (PDT) has previously been described in case reports.

Objective: To compare the frequency of sensitization to Metvix[®] cream in a group of patients previously treated at least five times with Metvix-PDT with the frequency observed in an unexposed control group.

Methods: Twenty patients treated five times or more with Metvix-PDT and 60 controls with no prior exposure to Metvix[®] were patch tested with Metvix[®] cream and Metvix[®] placebo cream. Subsequently, the patients were interviewed to determine the relevance of a positive patch test reaction to Metvix[®].

Results: Of 20 patients treated with Metvix-PDT, 7 were sensitized to Metvix[®] cream, giving a sensation risk of 35%. In the control group, 1 of 60 became sensitized after a single exposure to Metvix[®] cream (1.7%). There was no reaction to the placebo cream. The positive patch tests to Metvix[®] were considered relevant in four of seven patients (57%).

Conclusions: This study demonstrates a considerable risk of sensitization after Metvix-PDT. We suggest that the patients are interviewed to detect late or persistent local reactions after PDT. These reactions are often considered to be local infections but may represent allergic contact dermatitis, and therefore, patients should be offered patch testing with Metvix[®] cream.

Key words: 5-aminolaevulinic acid; allergic contact dermatitis; methyl aminolaevulinate; Metvix[®]; photodynamic therapy; sensitization risk. © 2009 John Wiley & Sons A/S.

Conflicts of interest: The authors have declared no conflicts.

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Background

Photodynamic therapy (PDT) with topical application of the photosensitizers methyl aminolaevulinate (methyl 5-amino-4-oxo-pentanoate, CAS 33320-16-0; MetvixTM, PhotoCure ASA, Oslo, Norway) or 5-aminolaevulinic acid (5-ALA) is widely used in the treatment of actinic keratosis, Bowen's disease, and superficial basal cell carcinoma. The procedure of PDT involves gentle curettage and application of a photosensitizer under occlusion for 3 hr, followed by exposure to red light. The photosensitizer is absorbed by lesional skin and converted intracellularly to protoporphyrin IX, which after red or blue light activation results in the production of cytotoxic oxygen species that cause selective cell destruction.

Both 5-ALA and Metvix[®] are used in PDT, but Metvix[®] has the advantage of a shorter application time, less pain during treatment (1), and greater affinity for tumour cells (2). The methylation of 5-ALA to methyl aminolaevulinate may enhance the risk of sensitization and thereby increase the risk of type IV allergic reactions (3).

Various side-effects of PDT have been reported. Most frequently, not only local irritation and inflammation but also urticarial reactions (4) and allergic contact dermatitis have been reported in case reports and case series (5–9). The risk of developing contact allergy to methyl aminolaevulinate in PDT-treated patients has earlier been estimated to 1% after an average of seven treatments (7).

In the present study, we investigated the frequency of contact sensitization to Metvix[®] in a group of 20 patients exposed at least five times to Metvix[®] during PDT and compared this with an unexposed control group.

Materials and Methods

Subjects

Twenty patients previously treated with Metvix-PDT and 60 unexposed controls, all more than 18 years of age, were recruited at the Department of Dermatology at Aarhus University Hospital from January 2007 to January 2008. The 20 patients were asked to participate in the study when they attended follow-up visits after PDT or routine examination for skin cancer. The inclusion criteria were at least five exposures to Metvix-PDT. Any history of local adverse skin reactions to Metvix-PDT was unknown prior to inclusion.

The control group was recruited from consecutive eczema patients patch tested with the European baseline series and without prior exposure to Metvix-PDT. Informed consent was obtained from all participants. Exclusion criteria were patients on systemic immunosuppressive treatment, sunbathing, or ultraviolet B/ultraviolet A therapy in the month before patch testing. Pregnant and breast-feeding women were also excluded from the study.

Drugs, patch test, and prick test

Patients were patch tested with Metvix[®] cream (methyl aminolaevulinate 160 mg/g, 16%) 'as is', and 50% and 20% dilutions of Metvix[®] cream in petrolatum, and Metvix[®] vehicle as is. Metvix[®] vehicle was provided by the manufacturer (Photo-Cure ASA, Oslo, Norway). 5-ALA cream (20% in a basic cream, purchased from Glostrup Pharmacy, Glostrup, Denmark) was tested as is. Pure methyl aminolaevulinate was not available. The standard patch test procedure using patch test materials from Chemotechnique (Vellinge, Sweden) and Pharmacia (Hillerød, Denmark) and small Finn Chambers[®] (Epitest Ltd Oy, Tuusula, Finland) on Scanpor[®] tape (Alpharma AS, Oslo, Norway) was used. Patch test readings were performed on D3 and D7 and scored according to guidelines (10). Prick test with Metvix[®] cream as is was performed in the patient group previously exposed to Metvix[®].

Ethics

The project was approved by the Danish Regional Committee for Biomedical Research Ethics and the Danish Data Protection Agency.

Statistical analysis

Sample size calculation: The expected risk for sensitization was chosen as 20% in the Metvix-treated group and 0.1% in the control group. Because of the small expected numbers, the risks in the two groups were compared by Fisher's exact test and the corresponding power calculations were based on a simulation study. The power calculation showed that 20 patients treated with Metvix-PDT and 60 controls should be enrolled in the study to obtain a power of 80% with a significance level of 5%.

Comparisons between groups were performed by Fisher's exact test. All computations were performed with the software package STATA version 10.0. The significance level was 5%.

Results

The demographic data and the patch test results of the 20 patients earlier treated with Metvix-PDT are shown in Table 1. Three women and 17 men, age 46–88 years, with an average age of 71 years were included. The patients had been treated for actinic keratosis and/or superficial basal cell carcinoma and had received 5–21 PDT treatments with an average of 9. Six patients had + to +++ reactions to Metvix[®] cream on both D3 and D7 readings. In five of seven patients, the patch test reactions to Metvix[®] cream were present in all dilutions of Metvix[®], indicating that Metvix[®] is a strong sensitizer (Fig. 1). One patient had a follicular (F) reaction on both D3 and D7 readings, interpreted as an allergic reaction. The control group consisted of 39 women and 22 men, age 19–78 years, with an average age of 45 years. A single patient responded with maximum +2 for Metvix[®], although no prior exposure to Metvix[®]. One patient in the control group was excluded because of an angry back reaction. The patient had doubtful positive reactions for nickel and chromate on D3 and exacerbations of eczema on his back and face, making D7 readings impossible (11).

Thirty-five per cent of the patients were sensitized to Metvix[®] and only 1.7% of the controls ($P < 0.0001$, Fisher's exact test; Table 2). The patients were interviewed after patch testing to determine the relevance of the positive patch test, and the patient records were investigated for reports on local reactions after PDT treatment. In four of seven patients (57%) with positive patch tests to Metvix[®], there were notes reporting strong local skin reactions. Furthermore, one patient twice had signs of local skin infections after Metvix-PDT; however, patch test to Metvix[®] cream

Table 1. Patch test and prick test data of 20 patients earlier exposed to Metvix[®] photodynamic therapy

Patient number	Age (years)	Sex	Number of treatments	Diagnosis	Metvix [®] 1:1	Metvix [®] 1:2	Metvix [®] 1:5	Relevance	Metvix [®] prick test
1	51	M	10	AK/BCC	n	n	n		—
2	67	M	7	AK/BCC	n	n	n		—
3	75	M	5	AK	n	n	n		—
4	70	M	6	AK/BCC	F	n	n		(+) 2 mm
5	62	M	9	AK	n	n	n		—
6	70	M	11	AK	++	++	++	Yes	Dermographism
7	46	M	10	BCC	n	n	n		—
8	69	M	6	AK	n	n	n		—
9	70	F	5	AK/BCC	+++	+++	+++		—
10	71	M	5	BCC	n	n	n		—
11	66	F	7	AK	n	n	n		—
12	82	M	7	AK/BCC	++	++	++		—
13	72	F	10	AK/BCC	n	n	n		—
14	87	M	9	AK/BCC	n	n	n		—
15	86	M	13	AK	n	n	n		—
16	80	M	5	AK	+	n	n	Yes	—
17	71	M	5	AK/BCC	n	n	n		NT
18	88	M	7	AK	n	n	n		—
19	68	M	21	AK/BCC	++	+	++	Yes	—
20	61	M	13	AK/BCC	++	++	++	Yes	—

—, no reaction; AK, actinic keratosis; BCC, basal cell carcinoma; F, follicular; n, negative; NT, not tested.

was negative. All tests with Metvix[®] vehicle were negative, indicating that the positive reactions to Metvix[®] cream are an allergic response to the active ingredient methyl aminolaevulinate. Although the patient group and control group are not comparable by age, sex, and diagnoses, we find this difference unlikely to have any major influence on the results.

Patch tests with Metvix[®] and 5-ALA can be difficult to interpret as local irritations are often present at early readings on D2 and D3 (4). In both patient and control groups, positive readings (F to +++) on both D3 and D7 were considered specific, and doubtful and weak readings were considered non-specific and insignificant when present only on D3.

Furthermore, we investigated cross-allergy between the chemical-related Metvix[®] and 5-ALA. Three of the 20 patients prior treated with Metvix[®] had also been exposed to 5-ALA and were excluded in the investigation of cross-allergy between Metvix[®] and 5-ALA. Results are shown in Table 3; one of five patients with positive

Metvix[®] patch test also had a positive patch test to 5-ALA, although no prior exposure to 5-ALA. None of the patients was positive for 5-ALA alone. However, no statistically significant difference was observed between the Metvix[®] patch test-positive and the Metvix[®] patch test-negative patients with respect to positivity in patch test to 5-ALA. There is no indication of cross-allergy between Metvix[®] and 5-ALA in this study. Prick tests with Metvix[®] cream gave no positive reactions (≥ 3 mm; Table 1).

From January 2002 to the end of January 2008, 1402 PDT treatments on 500 patients with an average of 2.8 PDT treatments per patient were carried out at the department. Fifteen patients had a positive patch test to Metvix[®], giving a 3.0% calculated risk of sensitization. Sensitization occurred in 1.0% of PDT treatments. Only a minority of the 500 Metvix-PDT-treated patients have been offered a Metvix[®] patch test; therefore, the true number of patients with allergic contact dermatitis towards Metvix[®] is probably higher.

Table 2. Metvix patch test results^a

	Positive		Total (N)
	n	Proportion [% (95% exact CI)]	
Metvix group	7	35 (15–59)	20
Control group	1	1.7 (0.0–8.9)	60
Total	8		80

CI, confidence interval.

^a $P < 0.0001$ Fisher's exact test.

Table 3. Investigation of cross-allergy between Metvix and 5-ALA patch test results^a

	Positive	Negative	
Metvix patch test positive	1	4	5
Metvix patch test negative	0	12	12
	1	16	17

5-ALA, 5-aminolaevulinic acid.

^aCross-allergy comparison of Metvix and 5-ALA: $P = 0.294$ (Fisher's exact test).

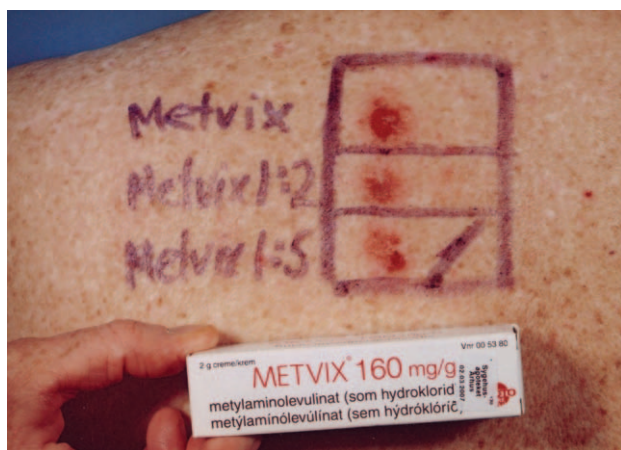


Fig. 1. Patch test reactions at D7 with Metvix[®] cream (1:1, 1:2, 1:5), Metvix[®] vehicle 1:1 and 5-aminolaevulinic acid cream 1:1.

Discussion

This study demonstrates a considerable risk (35%) of sensitization in patients who had received five or more Metvix-PDT treatments. A dermal safety study provided by PhotoCure to assess the sensitization potential of Metvix[®] cream demonstrated that Metvix[®] cream is a sensitizer. Metvix[®] cream was applied continuously on the back of 156 healthy subjects during a 3-week induction phase (Ronald Marks, Cutest Systems Ltd, unpublished data). Because of local reactions, 38% withdraw before a scheduled Metvix[®] patch test would be performed 14 days later. Of those patch tested with Metvix[®], approximately half were sensitized. The high frequency of sensitization was assumed to be because of the extreme exposure. In this study, we demonstrate that also during normal clinical use, a high frequency of sensitization to Metvix[®] cream is seen among patients who have been treated several times with Metvix-PDT. Severe or moderate local clinical reactions with redness, crusting, and scaling few days after treatment are often considered to be local infection or simply a good response to the treatment. However, in our experience, some of these cases may represent allergic contact dermatitis. Therefore, we suggest that all patients with repeated strong inflammatory reactions after PDT are offered patch testing with Metvix[®] to avoid unnecessary side-effects. Our study also demonstrates that these patients allergic to Metvix[®] can be offered 5-ALA-PDT, as there is no significant cross-allergy between 5-ALA and Metvix[®], in agreement with other reports (6, 7). However, there is no indication that patients with Metvix-PDT allergic reactions have inferior treatment results to PDT. We have experienced that patients, even with moderate clinical reactions

and with confirmed allergic contact dermatitis to Metvix[®], want to continue Metvix-PDT because of the good treatment results. Allergic contact dermatitis is not an absolute contraindication of continued Metvix-PDT treatment to areas not involving the face. To minimize the symptoms, potent local steroids or systemic prednisolone could be used (7). Estimates of sensitization risk to Metvix[®] have earlier been published to be 1% by Hohwy et al. in 2007 and 0.4% by Jungersted et al. in 2008. In both reports, the estimates of sensitization risk were based on total number of patients with positive Metvix[®] patch tests divided by the total number of Metvix-PDT-treated patients. A similar calculated estimate on the data from our department showed a risk of 3.0%. The risk of sensitization was found in 1.0% of PDT treatments compared with 0.3% in the study by Hohwy et al. Differences in the estimates may be caused by differences in the frequency of patch testing PDT-treated patients. Signs of allergic contact dermatitis may be overlooked when symptoms appear late after PDT treatments.

In this study, we have not investigated the association between the number of Metvix-PDT treatments, size of treatment area, or body site and the development of sensitization to Metvix[®] cream. It would be interesting to investigate a larger group of patients treated with Metvix-PDT with respect to frequency and size of areas treated. Our study indicates a considerable risk of sensitization after Metvix-PDT, and local signs of infections or inflammation after treatment may represent allergic contact dermatitis. However, further investigations are necessary to clarify whether allergic contact dermatitis to Metvix[®] influences the response to Metvix-PDT and the clearance of carcinomas and premalignant cells.

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